Open Access

Article Type: Research Article
Volume 1, Issue 1 - 2023

SCIBASE Journals

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Impact of In-Hospital Hyperglycemia on the Outcome of Patients with COVID-19

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Article information

Received: Jul 05, 2023
Accepted: Jul 24, 2023
Published: Jul 25, 2023

SciBase Epidemiology and Public Health - scibasejournals.org

Citation: Amaral Ritter J, Pitrez Mocellin L, Vargas Barcelos AL, Busanello J. Impact of In-Hospital Hyperglycemia on the Outcome of Patients with COVID-19. SciBase Epidemiol Public Health. 2023; 1(1): 1001.

Abstract

Purpose: To investigate the relationship between in-hospital hyperglycemia and clinical outcomes in hospitalized patients affected by Coronavirus Disease 2019 (COVID-19).

Methods: Retrospective longitudinal study carried out at the Hospital Santa Casa de Uruguaiana, through document analysis of the medical records of patients hospitalized with COVID-19 in the study setting, between the months of August 2020 and August 2021. For the analyses, the admitted patients were divided into two groups, according to the classification of blood glucose. The effects of hyperglycemia on clinical outcomes were verified using bivariate and multivariate analysis, with Odds Ratio (OR) and 95% confidence intervals (95%CI). Adjusted logistic regression models were built with three input levels of covariates. The main outcomes were the need for ventilatory support, admission to an Intensive Care Unit (ICU) and death.

Results: The study consisted of 54 individuals (57% male), with a mean age of 56.5±2.2 years. Blood glucose values ranged from 74 to 569 mg/dL and there was no record of hypoglycemia. Overall, 42.6% of the sample had blood glucose levels above 140 mg/dL. Higher blood glucose values were associated with a greater need for ventilatory support among individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients with blood glucose above 140 mg/dL were predisposed to the need for oxygen (OR: 10.476, p=0.032), and this risk was 24 times higher after adjusting for possible confounders (OR: 24.337; p=0.014). However, no association was found between hyperglycemia and ICU admission or death, even in adjusted models.

Conclusion: In-hospital hyperglycemia is associated with an increased risk of severe respiratory involvement among adult and elderly patients hospitalized with COVID-19. However, high glycemic values were not predictors of composite outcomes, such as ICU admission and/or death.

Keywords: Hyperglycemia; Severe acute respiratory syndrome; SARS-CoV-2; COVID-19; Hospitalization.

Introduction

Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), began in Wuhan, China [1], and is considered one of the most important epidemics of the century [2]. According to the World Health Organization (WHO), globally, COVID-19 infection has exceeded 689.7 million cases and 6.8 million deaths [3]. In Brazil, the disease affected approximately 37.6 million cases; of these, 700,000 resulted in death [4]; and these estimates only increased.

The specific mechanisms and risk factors underlying a more severe clinical manifestation remain unknown. However, since the onset of the disease, numerous predictors of worsening COVID-19 have been identified in observational studies. In certain population groups, mortality and morbidity rates increase significantly, such as men [5], elderly people [6] or individuals with comorbidities, especially diabetes mellitus [7], systemic arterial hypertension [8] and obesity [9].

The relationship between the diagnosis of diabetes and the favoring of some infections is well documented [10]. Influenza and pneumonia seem to occur with greater severity among the population that has diabetes [11,12] and, in the current context, the results complement these findings. The occurrence of COVID-19 in individuals diagnosed with diabetes seems to reflect a higher rate of morbidity and mortality compared to those who do not have this chronic condition [13]. Furthermore, diabetes and persistent hyperglycemia have been reported as significant predictors of worse outcomes in this setting [14,15].

However, the available evidence is controversial. The literature suggests that the worst outcomes of COVID-19 infection are closely related to the presence of diabetes [16,17]; however, new studies argue that persistent hyperglycemia is a predictive factor for disease worsening, regardless of the diagnosis of diabetes [18-20]. Thus, the association between the glycemic profile during hospitalization and the characteristics of the SARS-CoV-2 infection remains uncertain. Therefore, the aim of this study was to investigate the relationship between in-hospital hyperglycemia and clinical outcomes in hospitalized patients affected by COVID-19.

Materials and methods

Study design and sample

This is a retrospective longitudinal study, carried out at Hospital Santa Casa de Uruguaiana, in the state of Rio Grande do Sul, Brazil. This study is linked to the larger project entitled "Clinical and epidemiological profile of patients with COVID-19 and factors related to death and hospital care".

Data collection was carried out through document analysis of the medical records of patients hospitalized in the study setting, with COVID-19 diagnoses, between August 2020 and August 2021. Clinical data available in the system were obtained, including demographic information (gender and age), history of previous disease (diabetes and systemic arterial hypertension), in-hospital blood glucose, need for ventilatory support, transfer to another institution, hospital discharge, death and length of stay (in clinical inpatient unit, intensive care unit and total time of hospitalization).

The sample attend to the inclusion criteria: hospital care for a confirmed case of COVID-19, established by a rapid test and, subsequently, by the detection of viral RNA of SARS-CoV-2 in nasopharyngeal swab samples (RT-PCR) (ICD- 10 U07.1 or ICD-10 U07.2); age equal to or greater than 18 years. Those who remained under observation for less than 24 hours and were released for treatment or home isolation, transferred to another hospital or who died were excluded from the study.

For this study, data from critical and non-critical patients, over 18 years old, affected by COVID-19, treated at the emergency room of this institution and who had blood glucose data available, were used.

Disease severity

Disease severity (critical or non-critical) was assessed from admission to hospital discharge or death. Individuals who progressed to any of the outcomes during hospitalization were classified as critically ill: (1) respiratory failure requiring ventilatory support; (2) organic failures requiring monitoring and treatment in an intensive care unit (ICU); and (3) death [21].

Glycemia

The blood glucose values verified during hospital care, through the capillary blood glucose test or by blood collection and laboratory analysis, were considered. In-hospital blood glucose was classified considering the guidelines of the American Diabetes Association (ADA) [22] and the Brazilian Society of Diabetes (SBD) [23], in accordance with the proposal by the American Association of Clinical Endocrinologists (AACE) [24], being defined as: hypoglycemia, when <70 mg/dL; normoglycemia, when >70 mg/dL and <140 mg/dL; and hyperglycemia, when >140 mg/dL. For the analyses, the patients were divided into two groups: Group 1: individuals with blood glucose levels below 140 mg/dL; group 2: Individuals with blood glucose levels equal to or greater than 140 mg/dL [23,25].

Clinical outcomes

Composite outcome was used to verify the association between blood glucose and the risk of progression to critical cases or death. The composite endpoint consists of progression to any of the following outcomes: hospital discharge, need for ventilatory support, transfer to the ICU, and death.

Statistical analysis

All variables were tested for normality using the Kolmogorov-Smirnov test. Descriptive statistics were used to characterize the study sample. Quantitative variables were described as mean and Standard Deviation (SD) and categorical variables were described as frequencies and percentages. Differences between groups were verified using Student's t test, when quantitative variables, and Pearson's chi-square test, when categorical variables. All estimates were stratified according to blood glucose classification.

Associations between exposure variables and clinical outcomes were verified using bivariate analysis with Odds Ratio (OR) and 95% confidence intervals (95%CI). To assess the effects of hyperglycemia on clinical outcomes, multivariate logistic regression was performed, presented by Odds Ratio (OR) and 95%CI. Fitted models were constructed with three input levels of covariates. The first model was adjusted for gender and age; in the second model, the previous variables were maintained in the model and diabetes mellitus and arterial hypertension were included; and the third model included the previous variables plus the length of stay in the Clinical Inpatient Unit (CIU) and in the intensive care unit. All adjustment variables were cho-

sen according to the literature [26] and variables that obtained p<0.1 in the crude analysis were included.

All analyzes were performed using Stata software (version 14.0, Stata Corporation, College Station, TX, USA). The established significance level was 0.05 for the developed analyses.

Results

During the study period, 422 subjects met the eligibility criteria. However, only 12.8% (n=54) of this population had blood glucose data recorded, as shown in Figure 1.

The study included 54 individuals (57% male), with a mean age of 56.5±2.2 years. Blood glucose values ranged from 74 to 569 mg/dL and there was no record of hypoglycemia. Arterial hypertension was the most frequent comorbidity (46.3%, n=25), followed by diabetes (29.6%, n=16). The mean length of stay was 5.9±0.6 days. During hospitalization, most of the sample required ventilatory support (79.6%, n=43), with predominance among individuals with glycemic values equal to or greater than 140 mg/dL (p=0.012). Overall, 18 (33.3%) individuals were transferred to the ICU and 12 (22.2%) resulted in death. The characteristics of the sample, according to the classification of in-hospital blood glucose values, are shown in Table 1.

Table 1: Characteristics of study participants according to in-hospital blood glucose classification. Uruguaiana, Rio Grande do Sul, Brazil, 2022. (n=54).

Variables	All (n=54)	Group 1 (n=31)	Group 2 (n=23)	p
Sex, n (%)				0.075
Male	31 (57.4)	21 (67.7)	10 (48.5)	
Female	23 (42.6)	10 (32.3)	13 (56.5)	
Age, years, mean (±SD)	56.6 (±2.2)	54.8 (±3.3)	59.0 (±2.9)	0.354
Glucose, mg/dL, mean (±SD)	174.1 (±14.1)	111.2 (±3.9)	259.0 (±22.8)	<0.001
Comorbidities, n (%)				
Systemic arterial hypertension	25 (46.3)	11 (35.5)	14 (60.9)	0.064
Diabetes mellitus	16 (29.6)	5 (16.1)	11 (47.8)	0.012
Disease severity, n (%)				0.503
Critical	23 (42.6)	12 (38.7)	11 (47.8)	
Non-critical	31 (57.4)	19 (61.3)	12 (52.2)	
Period of hospitalization				
Total length of stay, days, mean (±SD)	5.9 (±0.6)	6.1 (±0.8)	5.7 (±0.9)	0.739
Length of stay in CIU >7 days, n (%)	13 (24.1)	8 (25.8)	5 (21.7)	0.730
Length of stay in the ICU >5 days, n (%)	11 (20.4)	7 (22.6)	4 (17.4)	0.640
Clinical outcomes				
Need for ventilatory support, n (%)	43 (79.6)	21 (67.7)	22 (95.7)	0.012
ICU admission, n (%)	18 (33.3)	10 (32.3)	8 (34.8)	0.846
Death, n (%)	12 (22.2)	8 (25.8)	4 (17.4)	0.462

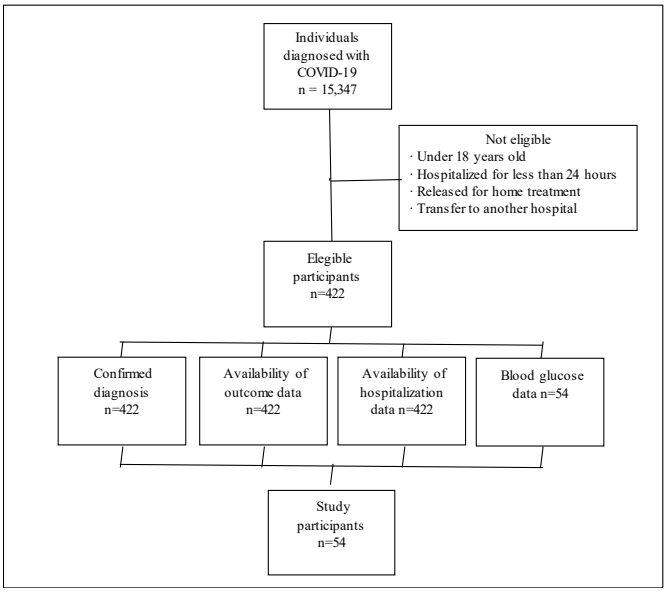

Figure 1: Flowchart of eligible participants. Uruguaiana, Rio Grande do Sul, Brazil, 2022.

Group 1: Participants with glucose levels below 140 mg/dL; Group 2: Participants with glucose levels equal to or greater than 140 mg/dL; SD: Standard Deviation; BMI: Body Mass Index; CIU: Clinical Inpatient Unit; ICU: Intensive Care Unit.

Mean glucose was log-transformed and presented as geometric mean and standard deviation.

Table 2 presents the bivariate analysis performed to verify associations between exposure variables and clinical outcomes. It was observed that blood glucose values above 140 mg/dL represent a greater chance of needing ventilatory support during hospitalization (OR: 10.476, p=0.032). Hospitalization longer than 7 days in a clinical inpatient unit seems to reflect a greater risk of transfer to the intensive care unit (OR: 8.000, p=0.003) and death (OR: 8.400, p=0.004); while hospitalization for more than 5 days in the ICU seems to increase the chances of death among this population (OR: 7.400; p=0.008).

Table 2: Bivariate analysis with odds ratio (OR) and 95% confidence interval (95%CI) of exposure variables, including different in-hospital blood glucose levels, for clinical outcomes. Uruguaiana, Rio Grande do Sul, Brazil, 2022 (n=54).

Variables	Need for ventilatory support (n=43)			ICU admission (n=18)			Death (n=12)		
	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p
Glucose <140 mg/dL	1.0	-	-	1.0	-	-	1.0	-	-
Glucose ≥140 mg/dL	10.476	1.232; 89.116	0.032	1.120	0.358; 3.508	0.846	0.605	0.158; 2.324	0.464
Male	1.385	0.353; 5.441	0.640	0.795	0.251; 2.551	0.697	0.952	0.259; 3.495	0.941
Age >60 years	0.864	0.228; 3.275	0.830	0.795	0.251; 2.521	0.697	3.600	0.927; 13.971	0.064
Systemic arterial hypertension	1.670	0.426; 6.549	0.462	0.636	0.201; 2.012	0.442	1.867	0.509; 6.851	0.347
Diabetes mellitus	0.677	0.167; 2.740	0.585	0.354	0.086; 1.455	0.150	1.250	0.316; 4.940	0.750
Length of stay in CIU >7 days	1.547	0.289; 8.286	0.610	8.000	1.991; 32.142	0.003	8.400	1.997; 35.336	0.004
Length of stay in the ICU >5 days	-	-	-	-	-	-	7.400	1.706; 32.094	0.008

OR: Odds Ratio; 95%CI: 95% Confidence Interval; BMI: Body Mass Index; CIU: Clinical Inpatient Unit; ICU: Intensive Care Unit.

Table 3: Multivariate logistic regression with odds ratio (OR) and 95% confidence interval (95%CI) to verify the relationship between in-hospital blood glucose and clinical outcomes. Uruguaiana, Rio Grande do Sul, Brazil, 2022 (n=54).

Variables	Need for ventilatory support (n=43)			ICU admission (n=18)			Death (n=12)		
	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p
Glucose <140 mg/dL	1.0	-	-	1.0	-	-	1.0	-	-
Glucose ≥140 mg/dL	10.476	1.232; 89.116	0.032	1.120	0.358; 3.508	0.846	0.605	0.158; 2.324	0.464
Model 1: *adjusted for sex and age*									
Glucose <140 mg/dL	1.0	-	-	1.0	-	-	1.0	-	-
Glucose ≥140 mg/dL	11.642	1.283; 105.606	0.029	1.239	0.379; 4.056	0.723	0.498	0.119; 2.082	0.339
Model 2: *adjusted for variables in model 1 plus systemic arterial hypertension and diabetes mellitus*									
Glucose <140 mg/dL	1.0	-	-	1.0	-	-	1.0	-	-
Glucose ≥140 mg/dL	19.974	1.664; 239.727	0.018	1.788	0.487; 5.570	0.381	0.519	0.113; 2.382	0.399
Model 3: *adjusted for variables in model 2 plus length of stay in CIU and ICU*									
Glucose <140 mg/dL	1.0	-	-	1.0	-	-	1.0	-	-
Glucose ≥140 mg/dL	24.337	1.904; 311.010	0.014	3.235	0.522; 20.058	0.207	0.537	0.092; 3.126	0.489

OR: Odds Ratio; 95%CI: 95% Confidence Interval; BMI: Body Mass Index; CIU: Clinical Inpatient Unit; ICU: Intensive Care Unit.

The results of the multivariate logistic regression to verify the relationship between in-hospital blood glucose and clinical outcomes are shown in Table 3. In the first model, adjustments were made for gender and age, and patients with blood glucose above 140 mg/dL showed they were more likely to use ventilatory support during hospitalization (OR: 11.642, p=0.029). In the second model, the previous variables and chronic health conditions were added: diabetes and high blood pressure. In this model, the presence of hyperglycemia also represented a higher risk of respiratory failure (OR: 19.974, p=0.018). In the third model, all the above variables plus hospitalization time greater than 7 days in the ICU and 5 days in the ICU were considered. When compared to normoglycemic individuals, patients with blood glucose above 140 mg/dL had a 24 times greater risk of needing ventilatory support during hospitalization (OR: 24.337, p=0.014). However, no associations were found between hyperglycemia and the need for ICU admission or death, even after adjustments for possible confounders.

Discussion

The present study investigated the relationship between in-hospital hyperglycemia and clinical outcomes in hospitalized patients affected by COVID-19 admitted to Hospital Santa Casa de Uruguaiana. The results showed that blood glucose levels greater than 140 mg/dL were independently associated with an increased risk of needing ventilatory support among patients admitted due to SARS-CoV-2 infection at this institution.

It is not surprising that hyperglycemia has been associated with worse outcomes in patients with COVID-19 and without a diagnosis of diabetes. The association of in-hospital hyperglycemia with length of stay, morbidity and mortality, especially in critical illnesses, is widely reported [27,28]. Previous studies have already shown the association between high glycemic values and higher mortality rates in Severe Acute Respiratory Syndrome (SARS-CoV-1) and Middle East Respiratory Syndrome (MERS) [29,30].

Our findings are relevant and are in line with evidence available in the literature. The relationship between in-hospital hyperglycemia, independent of diabetes, and progression to severe COVID-19 has been widely documented [26,31,32]. Recent studies demonstrate that, in patients without diabetes, hyperglycemia at the time of diagnosis of COVID-19 is an independent predictor of mortality and favors the occurrence of unfavorable outcomes, such as ICU admission, use of mechanical ventilation and death [20,33].

A nationally representative retrospective cohort conducted in Turkey included 12,000 patients with confirmed SARS-CoV-2 infection but no previous diagnosis of diabetes, and observed that glucose levels greater than 140 mg/dL increased mortality by 2 .7 times and the rate of ICU admission and/or mechanical ventilation by 2.3 times compared to normoglycemia [33]. The same has been verified in observational studies conducted in European countries, such as Italy and France [19,34].

Several studies have been carried out in order to explain the interaction between blood glucose and the outcomes of SARS-CoV-2 infection, especially among the Chinese population. In a study carried out by Zhang et al. [35], 461 adult patients with COVID-19 were included, and the results indicated that hyperglycemia (any glucose level greater than 140 mg/dL during hospitalization) was positively associated with higher inflammatory levels and progression to COVID-19 serious. Additionally, Wang et al. [15], when evaluating 605 adult individuals, found that glycemic values above 126 mg/dL were predictors of mortality among this population.

Another large retrospective longitudinal study was carried out by Bode et al. [18]. The authors analyzed approximately 1122 adult individuals affected by COVID-19, admitted to 88 hospitals in the United States, in order to describe the clinical characteristics of the infection in this population. The main results highlighted persistent hyperglycemia as an independent risk factor for higher rates of hospital complications, such as the need for ventilatory support, mainly the use of mechanical ventilation, ICU admission and death. Additionally, the large study by Carrasco-Sanchez et al. [36] served as a complement to the previously described evidence. In this study, researchers included more than 11,000 Spanish patients and observed that hyperglycemia is related to poor prognosis and mortality in patients infected with SARS-CoV-2, especially with regard to the use of ventilatory support [36] Studies carried out with different populations have found similar results [37-41].

The mechanism of interaction between glucose metabolism and SARS-CoV-2 remains unclear. Recent studies assess the existence of a bidirectional relationship between hyperglycemia and COVID-19. The most common speculations suggest that SARS-CoV-2 uses Angiotensin-Converting Enzyme 2 (ACE2) receptors for entry into cells [42] and, as these receptors are also present in more organs responsible for glucose homeostasis, it is it is possible that the occurrence of COVID-19 causes persistent hyperglycemia when affecting them [43]. In addition, hyperglycemia in the course of the disease, often observed in severe acute conditions, can also be explained by metabolic stress, an important characteristic of infection by this agent [44].

Elevation of plasma glucose damages organs essential for the homeostatic maintenance of the body, including, in addition to cardiovascular, renal and neuronal complications, pulmonary microangiopathy, compromising alveolar gas exchange, already affected by COVID-19 [2]. In addition, hyperglycemia is also associated with a reduction in the metabolic capacity of erythrocytes to capture and diffuse oxygen to tissues, a process secondary to hemoglobin glycation, modifying the tertiary molecular structure of this oxygen-carrying protein [11,13]. In short, impaired gas exchange in response to higher blood glucose levels seems to reflect worse outcomes in SARS-CoV-2 infection, especially in the use of ventilatory support.

In addition to the available evidence on the glycemic impact of SARS-CoV-2 infection, systematic reviews with meta-analyses, including prospective studies on the interrelationship of diabetes and COVID-19, indicate greater morbidity and mortality in individuals who had diabetes and were hyperglycemic [45,46]. Other studies suggest that, although diabetes does not increase the risk of SARS-CoV-2 infection, its presence is closely related to worse outcomes, especially among individuals with poor glycemic control [46,47].

The idea that individuals with chronic health conditions represent an extremely high risk group for adverse outcomes during eventual infections has been widely discussed [48,49]; therefore, its association with worse outcomes in COVID-19 is not surprising. However, it is important to recognize that most of the available data on the role of diabetes in SARS-CoV-2 infection derives from observational studies, making it difficult to properly address pathogenic inferences [50]. In this scenario, the identification and understanding of risk factors for the progression of the disease caused by SARS-CoV-2 are essential, as they provide important evidence for defining conducts during clinical management.

Despite the consistency of our results with the findings of other studies, some methodological issues need to be reconsidered. Much of the research on the subject used different criteria to identify patients without a diagnosis of diabetes and also delimited different cutoff points for the definition of hyperglycemia. Therefore, the definition of the methods used, especially for identifying non-diabetic patients and defining hyperglycemia levels, may differ from the studies available in the literature.

However, part of our findings differ from those reported by other authors. Associations commonly observed in other studies were not significant in our study. Worse health outcomes have been consistently associated with male gender [5], elderly [6] and individuals with chronic health conditions such as diabetes [7], hypertension [8] and obesity [9]. Furthermore, hyperglycemia was not associated with the need for ICU admission or death, diverging from most data available in the literature [25-28]. This inconsistency in the results reinforces the need for further studies on glycemic values and clinical outcomes in SARS-CoV-2 infection in different contexts and populations.

Limitations

This study had limitations that must be addressed. A study performed with a database constructed from pre-existing records is subject to several biases and residual confounding factors. The accuracy of data collection was a potential limiting factor, since it depends on the professional who completes the medical record in the system during the service. The possibility of having patients diagnosed with diabetes, but without the diagnosis referred to at the time of admission, was also not ruled out. The lack of information regarding the use of medication, lifestyle, complementary laboratory tests and anthropometric data favored the fragility of the associations. As a result of the

method of data collection, the diagnosis of diabetes may have been missed in a significant proportion of patients. Also, the lack of recording of glycemic values at the time of hospital care limited the sample size. Additionally, the study population was relatively small, with a limited number of results, represented by very wide confidence intervals, which consequently causes a risk of overfitting the regression models. To try to reduce the risk of developing overfitted models, the number of variables in the multivariate analyzes was restricted.

Strengths

Despite all limitations, our study had strengths. A retrospective longitudinal study allows associations to be suggested and expands the possibilities of analyzing the variables. In addition, data from the reality of patients with COVID-19 hospitalized at Hospital Santa Casa de Uruguaiana were reported. In this context, our results are essential, as they allow the verification of the weaknesses presented during the assistance and enable the notification of these aspects, in order to promote the improvement of the service provided to users of the health system.

Conclusion

In conclusion, available evidence suggests that in-hospital hyperglycemia is associated with an increased risk of severe respiratory involvement among adult and elderly patients hospitalized with COVID-19. However, further investigations are needed to explore unexpected associations and elucidate the effects of hyperglycemia on morbidity, mortality, and length of stay among this population, especially in the presence of chronic health conditions.

Declarations

Ethical standards: This study was approved by the Research Ethics Committee of the Federal University of Pampa (Unipampa), with registration number 30837520.2.3004.5324, under opinion number 4.062.712, on May 25th 2020, in accordance with CNS resolution 466/12 , with an informed consent form waived.

Competing interests and funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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