ASSESSMENT OF PATIENTS HOSPITALIZED FOR COVID-19 WITH AND WITHOUT DIABETES MELLITUS REGARDING SEVERITY AND OUTCOME OF THE DISEASE: A RETROSPECTIVE OBSERVATIONAL STUDY

AVALIAÇÃO DE PACIENTES INTERNADOS POR COVID-19 COM E SEM DIABETES MELLITUS QUANTO À GRAVIDADE E EVOLUÇÃO DA DOENÇA: UM ESTUDO OBSERVACIONAL RETROSPECTIVO

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ABSTRACT

BACKGROUND: Outcome of coronavirus disease 2019 (COVID-19) is related to comorbidities and possibly to previous use of medications. OBJECTIVE: Evaluate inpatients with COVID-19 for the presence of previous DM and inhospital glycemic control and their outcomes. DESIGN AND SETTING: Retrospective observational study in a Public University Hospital. METHODS: Data obtained from medical records. Study approved by ethics committee. Patients were divided in 4 groups: euglycemic (no previous DM), controlled and uncontrolled DM (according to mean capillary blood glucose) and inhospital hyperglycemia (IHH - no previous DM but inhospital hyperglycemia). RESULTS: Included 208 patients [no previous DM (67.8%), IHH (23.4%)]. Inhospital uncontrolled DM and IHH were more prone to intensive care unit (ICU) admission, orotracheal intubation (OIT) and death. Multivariable regression showed that increasing mean plasma glucose during hospitalization increased the odds of ICU admission [odds ratio, OR = 1.03, 95% confidence interval, CI = 1.02-1.05; P < 0.001], OIT [OR = 1.03, 95% CI = 1.02-1.04; P < 0.001] and death [relative risk, RR = 1.007, 95% CI = 1.003-1.011; P < 0.001]. Previous statin use decreased the odds of ICU admission [OR = 0.11, 95% CI = 0.04-0.35; P < 0.001] and OIT [OR = 0.15, 95% CI = 0.05-0.46; P = 0.001], but not death. CONCLUSION: Hyperglycemia proved to be a stronger predictor of worse prognosis in COVID-19 than DM per se. Our data also indicate that prior statin use may serve as a protective factor, a finding that warrants verification through additional research.

KEYWORDS: COVID-19; Coronavirus; SARS-CoV-2; Hyperglycemia.

RESUMO

FUNDAMENTO: O desfecho da doença por coronavírus 2019 (COVID-19) está relacionado a comorbidades e possivelmente ao uso prévio de medicamentos. OBJETIVO: Avaliar pacientes internados com COVID-19 quanto à presença de DM prévio e controle glicêmico hospitalar e seus desfechos. TIPO E LOCAL: Estudo observacional retrospectivo em Hospital Universitário Público. MÉTODOS: Dados obtidos de prontuários médicos. Estudo aprovado por comitê de ética. Os pacientes foram divididos em 4 grupos: euglicêmico (sem DM prévio), DM controlado e não controlado (de acordo com a glicemia capilar média) e hiperglicemia hospitalar (HIH - sem DM prévio, mas com hiperglicemia hospitalar). RESULTADOS: Incluídos 208 pacientes [sem DM prévio (67,8%), HHI (23,4%)]. DM não controlado hospitalar e HIH foram mais propensos a internação em unidade de terapia intensiva (UTI), intubação orotraqueal (OIT) e óbito. A regressão multivariada mostrou que o aumento da glicemia plasmática média durante a hospitalização aumentou as chances de internação na UTI [odds ratio, OR = 1,03, intervalo de confiança de 95%, IC = 1,02-1,05; P < 0,001], OIT [OR = 1,03, IC 95% = 1,02-1,04; P < 0,001] e óbito [risco relativo, RR = 1,007, IC 95% = 1,003-1,011; P < 0,001]. O uso prévio de estatinas diminuiu as chances de internação na UTI [OR = 0,11, IC 95% = 0,04-0,35; P < 0,001] e OIT [OR = 0,15, IC 95% = 0,05-0,46; P = 0,001], mas não diminuiu mortalidade. CONCLUSÃO: A hiperglicemia provou ser um preditor mais forte de pior prognóstico na COVID-19 do que o DM per se. Nossos dados também sugerem uso prévio de estatina como fator de proteção, o que deve ser confirmado em estudos futuros.

PALAVRAS-CHAVE: COVID-19; Coronavirus; SARS-CoV-2; Hyperglycemia.

1. INTRODUCTION

Just over three years after the first cases of coronavirus disease 2019 (COVID-19) emerged and a lot of knowledge has been acquired, many questions remain unclear. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has a wide spectrum of clinical manifestations, from asymptomatic patients to upper respiratory tract involvement causing mild respiratory symptoms or even severe viral pneumonia with respiratory and multiple organ failure and eventually death[1,2].

In COVID-19, mortality rate varies according to patients' characteristics. In fact, epidemiological data reveal advanced age (older than 60 years) and the presence of comorbidities such as hypertension, diabetes mellitus (DM), obesity and coronary artery disease as risk factors for severe forms of the disease[1,3].

A descriptive study suggested that DM and/or acute uncontrolled hyperglycemia were associated with an increased hospital length of stay, more frequent lower respiratory tract involvement and higher mortality due to COVID-19.[4] Furthermore, in patients admitted for COVID-19 with pre-existing type 2 DM, good glycemic control during hospitalization has been associated with lower mortality.[4] The connection between an elevated risk of complications, mortality, and hyperglycemia in hospitalized patients, whether they have diabetes or not, has been well-established for quite some time. This phenomenon is evident in both admission glucose levels and the overall glucose levels during their hospitalization[5-8]. This risk can be reduced, though not eliminated, by improved glycemic control[9,10]. Inpatient hyperglycemia is defined as blood glucose ³ 140 mg/dL and can affect patients with or without a prior diagnosis of DM[5]. In noncritically ill patients, the target of blood glucose levels of 100 to 180 mg/dL has a potential to ameliorate adverse outcomes[5].

Endothelial dysfunction is the common denominator of most comorbidities that determine poor prognosis in COVID-19. Reports suggested that COVID-19 affects other organs beyond the lung, most importantly the heart and kidney[11]. Considering tissue tropism of SARS-CoV-2 for Angiotensin-converting enzyme (ACE) 2-expressing cells, another major organ of the body is an important target of infection: the vascular endothelium. Expression of ACE2 is abundant on vascular endothelial cells of both small and large arteries and veins[12]. SARS-CoV-2 may thus cause endothelial dysfunction either directly through endothelial cell infection, or indirectly through the infection of other susceptible cell types, which cause hyperinflammation and aberrant antiviral responses[11]. It seems then plausible that patients with preexisting endothelial dysfunction are vulnerable to a more severe disease course given the crucial role of endothelial cells for vascular homeostasis and organ perfusion[12].

Since the beginning of the pandemic, in March 2020 (World Health Organization, WHO)[13], much has been suggested about the association between DM, hyperglycemia and prognosis in COVID-19 and additional data can help delineate care protocols for better outcomes. The objective of the present study was to evaluate COVID-19 patients admitted in a Public University Hospital for the presence of previous DM as well as the development of inhospital hyperglycemia (IHH) and their outcomes such as intensive care unit (ICU) admission, need for orotracheal intubation (OIT), development of nosocomial infections, total length of stay and death. In addition, we aimed at exploring these and other possible outcome determinants such as previous use of ACE inhibitors (ACEi), angiotensin receptor blockers (ARBs), metformin and statins.

2. MATERIAL AND METHODS

This was a retrospective observational study approved on June 26, 2020 (CAAE 31831820.6.0000.5243), and all data obtained by medical records. The patients reached signed the written informed consent, while, of those whose contact was not possible, the ethics committee of Hospital Universitário Antônio Pedro da Universidade Federal Fluminense (HUAP/UFF) waived consent.

Patients

Sample size was calculated from the population covered by our hospital (12% of the population of Rio de Janeiro State) and the total number of registered COVID 19 cases in our State at the end of 2020 (400,000 cases). From a population of 48,000 registered COVID-19 cases with 16% proportion of admissions and 95% confidence level, the sample size was 206. We reviewed the medical records of all patients admitted to HUAP/UFF between March and December 2020 with a suspected diagnosis of COVID-19. Only those with a confirmed diagnosis of COVID-19 by reverse transcription polymerase chain reaction (RT-PCR) for SARS CoV2 were included.[14] Inclusion criteria were in hospital admission and positive RT-PCR for SARS CoV2.

Methods

The research team performed retrospective review of the medical records after patients' discharge from hospital. This review included data regarding past medical history, comorbidities and chronically used medications such as anti-hypertensive drugs, glucose lowering oral and injectable and lipid lowering agents. Furthermore, we registered laboratorial data, as first fasting glucose levels upon admission and last glycated hemoglobin (HbA1c) up to three months before admission. The researchers also reviewed clinical and laboratorial data for total hospitalization period, highlighting need for insulin use and dose, glucose levels (plasma glucose [PG] and capillary blood glucose [CBG]). In hospital hyperglycemia (IHH) was defined as a mean capillary blood glucose during hospitalization > 180 mg/dL (and not only two CBG > 140 mg/dL to assure patients remained for a significant

length of stay above glycemic targets (100 - 180 mg/dL).

To this study, we considered "previous diabetes" for any patient reporting this diagnosis as well as any patient using oral antihyperglycemic medication and/or insulin prior to admission or with an A1c during the hospitalization that confirmed the diagnosis. In addition, we considered the reports of chronic kidney disease in conservative treatment as well as dialysis, history of previous cerebrovascular or cardiovascular events, coronary artery bypass graft surgery and/or percutaneous coronary angioplasty or angina.

The primary endpoint was death and secondary endpoints included ICU admission, need for OIT and development of nosocomial infections.

Statistical analysis

Data were analyzed using SPSS 23.0 for Windows (SPSS, Inc., Chicago, Illinois, United States) and R version 3.6.1 (available in www.r-project.org). The Kolmogorov-Smirnov test assessed normality of numeric variables and the only numerical variable with normal distribution was body mass index (BMI). For this reason, we presented the numerical data as median (p25-p75) and used non-parametric tests for the analysis. We conducted an exploratory data analysis to identify factors linked to adverse outcomes in patients admitted for COVID-19. Our objective was to evaluate patients admitted for COVID19 for the presence of previous DM as well as the development of in hospital hyperglycemia (IHH) [4 groups: euglycemic (no previous DM), in hospital controlled and in hospital uncontrolled DM and IHH (the last two defined by mean capillary blood glucose of the whole admission >180mg/dL)] and their outcomes. Through Fischer´s exact test, it was possible to do comparison of categorical variables (such as presence of comorbidities, intensive care unit (ICU) admission, need for orotracheal intubation (OIT), development of nosocomial infections and death) between groups. The Mann Whitney and Kruskal wall tests made the comparison of numerical variables (such as age, BMI, plasma glucose, capillary blood glucose and total length of stay) between groups. In addition, we aimed at exploring these and other possible outcome determinants such as previous use of ACE inhibitors (ACEi), angiotensin receptor blockers (ARBs), metformin and statins. We applied the same statistical approach to these variables. The effect of possible independent variables on the response variables were analyzed using logistic regression model for ICU admission and OIT and Cox proportional hazards model for death; forward selection was used to determine the multiple/multivariate final model for each response. Consider p values < 0.05 as significant.

3. RESULTS

Between March and December 2020, we assessed 498 medical records for eligibility and 208 were eligible and included in this study. Among the ineligible, were not admitted 18 patients and in 272 inclusion criteria were not met.

Enrolled patient characteristics

Among the 208 included patients, 67.8% had no previous history of DM (no DM; n = 141). In hospital hyperglycemia (IHH) was noted in 23.4% of no DM group (n = 33/141). In patients with previous DM 43.3% were also hyperglicemic during hospitalization (inhospital uncontrolled DM; n = 29/67) (Figure 1).

Figure 1. Patient inclusion and exclusion algorithm. COVID = coronavirus disease. Patients divided in 4 groups: euglycemic (no previous diabetes mellitus, DM), controlled and uncontrolled DM and inhospital hyperglycemia (IHH), the last two defined by mean capillary blood glucose of the whole admission >180mg/dL).

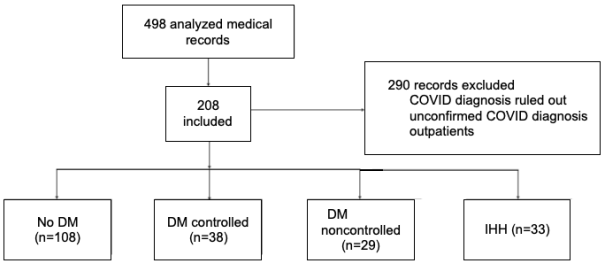

Table 1. Demographics and comorbidities of inpatients with coronavirus disease 2019 (COVID-19)
BMI = body mass index; DM = diabetes mellitus; IHH = inhospital hyperglycemia; numeric variables presented as median (p25-p75).

	No DM (n = 108)	DM controlled (n = 38)	DM uncontrolled (n = 29)	IHH (n = 33)	P value
Age (years)	62 (46.3-72)	65.5 (58-73.5)	67 (59-73)	66 (57-74.5)	0.12
Female (n,%)	55 (50.9)	23 (60.5)	12 (41.4)	12 (36.4)	0.18
BMI (kg/m²)	25.9 (20.3-29.4)	28 (25-31.2)	27.9 (22.3-33.8)	26.6 (22.6-31.9)	0.39
Hypertension (n,%)	47 (43.5)	34 (89.5)	28 (96.5)	22 (66.7)	**< 0.001**
Cardiovascular disease (n,%)	13 (12)	7 (18.4)	10 (34.5)	5 (15.2)	**0.041**
Cerebrovascular disease (n,%)	2 (1.9)	4 (10.5)	1 (3.5)	4 (12.1)	**0.046**
Chronic renal failure (n,%)	12 (11.1)	7 (18.4)	9 (31)	3 (9.1)	**0.04**
Malignancy (n,%)	51 (47.2)	13 (34.2)	8 (27.6)	15 (45.5)	0.188

Median age, BMI and proportion of females was not different between groups. Hypertension was more common among patients with DM (inhospital controlled and inhospital uncontrolled). These data as well as distribution of cardiovascular, cerebrovascular

disease, chronic renal failure and malignancy between groups is shown in Table 1. Only a few patients in each group had a previous history of chronic obstructive pulmonary disease, inflammatory diseases or were transplant recipients so these variables were not included in further analysis (data not shown but available upon request).

Glycemic control data

In patients with DM (n = 67), median HbA1c at admission or in the previous 90 days was 7.6 (6.0-9.3)% (n = 11).

Plasma glucose (PG in mg/dL) at admission was higher in individuals with inhospital uncontrolled DM when compared to inhospital controlled DM, IHH and euglycemia groups [180 (146.3-240.5) versus 108.5 (82-158.3) versus 110 (96-148.5) versus 98 (83-111); P < 0.001]. Inhospital uncontrolled DM also had higher mean PG and mean capillary blood glucose (CBG) during hospitalization than the other groups [200 (167-224) versus 120 (88-155) versus 144.5 (117.3-175.8) versus 93 (80.5-108); P < 0,001 and 197 (186-221.5) versus 144 (101.5-167.5) versus 149 (121-181.2) versus 100.5 (90-120); P < 0,001; respectively]. These data as well as mean insulin dose during hospitalization are shown in Table 2.

Table 2. Glycemic control at admission and during hospitalization for coronavirus disease 2019 (COVID-19)

	No DM (n = 108)	DM controlled (n = 38)	DM uncontrolled (n = 29)	IHH (n = 33)	P value
Admission PG (mg/dL)	98 (83-111)	108.5 (82-158.3)	180 (146.3-240.5)	110 (96-148.5)	< **0.001**
Mean PG during hospitalization (mg/dL)	93 (80.5-108)	120 (88-155)	200 (167-224)	144.5 (117.3-175.8)	< **0.001**
Mean CBG during hospitalization (mg/dL)	100.5 (90-120)	144 (101.5-167.5)	197 (186-221.5)	149 (121-181.2)	< **0.001**
Mean insulin during hospitalization (Units/Kg/day)	-	0.1 (0.06-0.18)	0.24 (0.13-0.39)	0.09 (0.05-0.28)	**0.006**

PG = plasma glucose; CBG = capillary blood glucose; DM = diabetes mellitus; IHH = inhospital hyperglycemia; numeric variables presented as median (p25-p75).

Outcomes data

Duration of hospitalization, bloodstream and urinary tract infection were not different between groups. However, patients with hyperglycemia (inhospital uncontrolled DM and IHH) were more prone to be admitted in ICU, need OIT, had longer mechanical ventilation duration, higher risk of mechanical ventilator associated pneumonia and death (Table 3).

Table 3. Primary and secondary outcomes in coronavirus disease 2019 (COVID-19).

	No DM (n = 108)	DM controlled (n = 38)	DM noncontrolled (n = 29)	IHH (n = 33)	P valor
Duration of hospitalization (days)	14.5 (7-26.8)	12 (7.5-21.3)	17 (12-26)	17 (10.5-22.5)	0.377
ICU admission	47 (43.5%)	19 (50%)	21 (72.4%)	26 (78.7%)	**0.001**
Orotracheal intubation	27 (25%)	16 (42.1%)	19 (65.5%)	20 (60.6%)	< **0.001**
MV duration (days)	6 (1.3-12)	10 (3.3-12.8)	12 (8-18)	14 (7.3-20.8)	**0.033**
Ventilator Associated Pneumonia	6 (5.6%)	6 (15.8%)	10 (34.5%)	8 (24.2%)	< **0.001**
Bloodstream infection	4 (3.7%)	4 (10.5%)	3 (10.3%)	4 (12.1%)	0.238
Urinary tract infection	4 (3.7%)	2 (5.3%)	1 (3.5%)	4 (12.1%)	0.282
Death	28 (25.9%)	14 (36.8%)	17 (58.6%)	18 (54.5%)	**0.001**

ICU = intensive care unit; MV = mechanical ventilation; DM = diabetes mellitus; IHH = inhospital hyperglycemia; numeric variables presented as median (p25-p75).

We performed logistic regression for univariable and multivariable analyses to identify factors associated with increased or decreased chances for ICU admission, OIT and increased or decreased risk for death (Table 4).

Odds of ICU admission were higher for older individual (odds ratio, OR = 1.02, 95% confidence interval, CI = 1.00-1.04, P = 0.01), higher PG at admission (OR = 1.01, 95% CI = 1.00-1.02, P = 0.004), inhospital hyperglycemia (inhospital uncontrolled DM and IHH) [OR = 3.75, 95% CI = 1.93-7.31, P < 0.001), higher mean PG during hospitalization (OR = 1.02, 95% CI = 1.01-1.03, P < 0.001), higher mean CBG during hospitalization (OR = 1.02, 95% CI = 1.01-1.03, P < 0.001) and hypertension (OR = 1.82, 95% CI = 1.03-3.22, P = 0.04). Odds of OIT were higher for previous DM (OR = 2.06, 95% CI = 1.14-3.73, P = 0.017), higher PG at admission (OR = 1.01, 95% CI = 1.00-1.02, P = 0.001), inhospital hyperglycemia (inhospital uncontrolled DM and IHH) [OR = 3.98, 95% CI = 2.13-7.45, P < 0.001), higher mean PG during hospitalization (OR = 1.02, 95% CI = 1.01-1.03, P < 0.001) and higher mean CBG during hospitalization hospitalization (OR = 1.02, 95% CI = 1.01-1.02, P < 0.001). Finally, risk of death was higher for older individual (OR = 1.03, 95% CI = 1.01-1.05, P = 0.003), previous DM (OR = 1.85, 95% CI = 1.02-3.36, P = 0.04), inhospital hyperglycemia (inhospital uncontrolled DM and IHH) [OR = 3.18, 95% CI = 1.72-5.89, P < 0.001), higher mean PG during hospitalization (OR = 1.02, 95% CI = 1.01-1.03, P < 0.001) and higher mean CBG during hospitalization

hospitalization (OR = 1.01, 95% CI = 1.01-1.02, P < 0.001) (**Table 4**).

Table 4. Logistic Regression Analysis for outcomes and demographic variables, comorbidities, previous medications and laboratorial data.

	ICU admission		Orotracheal intubation		Death	
	OR (CI 95%)	P value	OR (CI 95%)	P value	OR (CI 95%)	P value
Age	1.02 (1.00 - 1.04)	**0.01**	1.01 (0.99 - 1.03)	0.12	1.03 (1.01 - 1.05)	**0.003**
Female	1.05 (0.61 - 1.81)	0.87	1.14 (0.65 - 1.99)	0.65	0.67 (0.38 - 1.19)	0.17
BMI	1.02 (0.94 - 1.11)	0.65	1.02 (0.93 - 1.11)	0.7	0.95 (0.87 - 1.04)	0.27
Previous DM	1.33 (0.74 - 2.4)	0.348	2.06 (1.14 - 3.73)	**0.017**	1.85 (1.02 - 3.36)	**0.04**
DM duration	0.79 (0.55 - 1.13)	0.2	0.77 (0.50 - 1.17)	0.22	0.90 (0.70 - 1.17)	0.45
HbA1c at admission	1.53 (0.85 - 2.75)	0.16	1.43 (0.71 - 2.86)	0.31	1.35 (0.71 - 2.54)	0.36
PG at admission	1.01 (1.00 - 1.02)	**0.004**	1.01 (1.00 - 1.02)	**0.001**	1.01 (0.99 - 1.01)	0.09
Inhospital hyperglycemia (DM noncontrolled and IHH)	3.75 (1.93 - 7.31)	**<0.001**	3.98 (2.13 - 7.45)	**<0.001**	3.18 (1.72 - 5.89)	**<0.001**
Mean PG during hospitalization	1.02 (1.01 - 1.03)	**<0.001**	1.02 (1.01 - 1.03)	**<0.001**	1.02 (1.01 - 1.03)	**<0.001**
Mean CBG during hospitalization	1.02 (1.01 - 1.03)	**<0.001**	1.02 (1.01 - 1.02)	**<0.001**	1.01 (1.01 - 1.02)	**<0.001**
Mean insulin during hospitalization	2.22 (0.39 - 12.59)	0.37	4.88 (0.77 - 30.88)	0.09	1.85 (0.45 - 7.67)	0.39
Hypertension	1.82 (1.03 - 3.22)	**0.04**	1.54 (0.86 - 2.79)	0.15	1.23 (0.68 - 2.21)	0.5
Cardiovascular disease	1.54 (0.73 - 3.26)	0.26	1.46 (0.70 - 3.07)	0.31	1.33 (0.64 - 2.78)	0.45
Cerebrovascular disease	1.03 (0.30 - 3.48)	0.96	1.32 (0.39 - 4.49)	0.65	1.46 (0.43 - 4.94)	0.55
ACE inhibitor	0.59 (0.23 - 1.54)	0.28	0.70 (0.25 - 1.92)	0.49	1.00 (0.38 - 2.65)	0.99
ARB	1.48 (0.82 - 2.66)	0.2	1.19 (0.65 - 2.15)	0.57	1.09 (0.60 - 1.99)	0.78
Statin	0.51 (0.24 - 1.07)	0.07	0.51 (0.22 - 1.15)	0.11	0.54 (0.24 - 1.22)	0.14

ICU = intensive care unit; BMI = body mass index; DM = diabetes mellitus; PG = plasma glucose; IHH = in hospital hyperglycemia; CBG = capillary blood glucose.

Multivariable regression showed that increasing mean PG during hospitalization increased the odds of ICU admission [OR = 1.03, 95% CI = 1.02-1.05; P < 0.001] and OIT [OR = 1.03, 95% CI = 1.02-1.04; P < 0.001] and the risk of death [relative risk, RR = 1.007, 95% CI = 1.003-1.011; P < 0.001]. On the other hand, previous history of statin use decreased the odds of ICU admission [OR = 0.11, 95% CI = 0.04-0.35; P < 0.001] and OIT [OR = 0.15, 95% CI = 0.05-0.46; P = 0.001], but not death.

4. DISCUSSION

Since the initial identification and description of COVID-19 cases, numerous questions have arisen, and our understanding of its epidemiology, pathophysiology, and treatment is continuously developing. From the beginning of the pandemic, one of the priorities is to determine patients at higher risk of developing severe forms and fatal outcome. This was particularly important in early vaccination strategy programs and still is in countries struggling with vaccine shortage where an order of priority for immunization of the most vulnerable needs scientific justification. In this sense, results of the present study reinforce not only the role of DM but also and mainly in-hospital hyperglycemia as determinants of unfavorable outcomes in patients hospitalized for COVID-19. Furthermore, and partially unexpectedly, our results point to a possible protective role of previous use of statins.

Type 2 DM is described as one of the most frequent comorbidities among patients hospitalized with COVID-19 and an independent predictor of worse prognosis[9,15] and this was confirmed by our results. In fact, in our study DM determined an increased risk of ICU admission, OIT, longer mechanical ventilation duration and death. Type 2 DM is associated with a low-grade chronic inflammation induced by the excessive visceral adipose tissue. This inflammatory status disrupts glucose homeostasis and peripheral insulin sensitivity. Chronic hyperglycemia and inflammation hinder the immune response making it ineffective with decreased mobilization of polymorphonuclear leukocytes, chemotaxis, phagocytic activity, and glycation of immunoglobulins[5,8,16-18]. Our study findings, up to this point, have not yielded any unexpected or previously undisclosed results. However, logistic, and multivariate regression analyses allowed a better discrimination of the "real villain" which seems to be hyperglycemia, much more than DM per se.

In the present series, hyperglycemia revealed to be an independent contributor to unfavorable outcomes. This has been previously suggested by many studies since the beginning of the pandemic, when DM emerged as a major risk factor for SARS and adverse outcomes in patients with COVID-19[8,19]. However, most studies focused on the previous diagnosis of DM and did not evaluate glycemic control during hospitalization as ours[10]. This is one of the strengths of this study that evaluated the presence of

comorbidities and the in-hospital glycemic control not only in patients with DM but also in those previously euglycemic. This approach allowed for the identification of a group of patients who were previously euglycemic, and therefore theoretically without increased risk, that developed in-hospital hyperglycemia. And like dysglycemic DM patients, this group had an increased risk of being admitted in ICU, needing orotracheal intubation, having longer mechanical ventilation duration, with higher risk of mechanical ventilator associated with pneumonia and death. Which remains to be elucidated is if in patients with in-hospital dysglycemia, hyperglycemia determines this poor outcome or is merely a marker of greater/uncontrolled inflammatory response and illness severity[5,8,9,17].

Numerous studies indicate that COVID-19 patients with diabetes mellitus (DM) and/or uncontrolled hyperglycemia have a greater than two-fold increased likelihood of ICU admission and face up to three times higher mortality rates when compared to patients without DM and/or uncontrolled hyperglycemia.[20] Hyperglycemia is also associated with poor outcomes because of the capacity of increasing inflammatory cytokine levels[18,21]. Indeed, several preclinical and clinical studies have suggested that this condition may induce susceptibility and the development of more aggressive infectious diseases. Although the precise mechanisms that link glycemia to the exacerbated infections remain elusive, hyperglycemia is known to induce a wide array of changes in the immune system activity[17,22]. Our multivariate regression analysis showed that hyperglycemia, in both DM and non-DM patients, was the factor with the greatest influence on unfavorable outcomes. Therefore, a previous diagnosis of DM and the presence of other comorbidities such as hypertension, obesity, cardiovascular and cerebrovascular disease interfered with lesser importance, with hyperglycemia itself being the most important factor for admission to the ICU, orotracheal intubation and death.

Studies also have tried to understand the mechanisms that lead to hyperglycemia in patients infected with COVID, as it seems that the infection resulted in increased values of glycemia. Among them, we can mention the greater production of hormones that generate insulin resistance, such as cortisol, catecholamines and glucagon, because of the response to the stress generate by the infection[27]. Furthermore, literature shows that the virus reduces the effectiveness of the insulin production by pancreatic B cells[28]. Besides that, the use of corticosteroids in more severe patients, as well as the use of parenteral nutrition, common in patients admitted to the ICU, also end up causing hyperglycemia[27].

Another important aspect of our study was the evaluation of the previous use of some medications as possible interfering factors in prognosis of COVID. Since ACE2 is utilized by SARS-CoV-2 for cell binding and entry, there has been a suggestion of a potential increased risk of a worse prognosis in patients taking ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs), which are medications known to affect ACE2 levels[12].Therefore, studies have shown that the effects of ACE inhibitors or ARBs seem to play an important role in the severity of COVID 19 by regulating the pro-inflammatory and anti-inflammatory reactions. Current data indicates that drugs that reduce pro inflammatory activity of the ACEi and, particularly ARBs, may be beneficial for the outcome, both by reducing organ inflammation and by triggering mechanisms that counteract a possible increase in viral entry related to increased ACE2 cell expression. As with other drugs, the potential effects of ARBs and ACEi may differ in different patients, depending on other external factors, including combinations with other treatments, patient comorbidities and even gender or age[29]. It was also suggested that in patients infected with coronavirus who were in conditions of greater inflammation or who had factor that generated a greater inflammatory state, such as older age, hyperglycemia and obesity, the use of ACEi seemed to have a protective effect regarding the length of hospitalization[30,31].

Indeed, data from cardiological societies around the world support the continued use of ACEi and ARBs in patients with hypertension hospitalized with COVID-19, a strategy yielding better survival rates compared with hypertensive patients not on these drugs[23,31,32,33]. In our study, previous use of ACEi or ARBs has not shown to predict worse outcomes, nor did it confer any protection. Furthermore, the previous use of metformin and other anti-hypertensive classes such as calcium channel blockers, beta-blockers and thiazides did not interfere with the prognosis of patients hospitalized for COVID either.

Although controversies remain regarding the direct infection of endothelial cells by SARS-CoV-2, it appears that endothelial dysfunction is responsible for microvascular complications in severe COVID-19. Indeed, recent studies suggests that endothelial dysfunction is the common link between risk-determining comorbidities in COVID-19 such as type 2 DM, hypertension, obesity, and cardiovascular diseases.[11] It is still to be clarified if SARS-CoV-2 cause endothelial dysfunction directly by downregulating cellular ACE2 or indirectly by impairing normal endothelial crosstalk, potentiating immunothrombosis, and impairing the antiviral response[24]. We observed a higher proportion of CVD in those patients with previous DM who developed hyperglycemia during hospitalization when compared with patients with DM who remained euglycemic and patients without DM (Table 1). Even if it is merely speculative, this could suggest that these patients had previously worse endothelial dysfunction and, therefore, would be more prone to a poor outcome in COVID-19. In any case, a more robust finding of the present study derives from the multivariate analysis that revealed the previous use of statins as a protective

factor in COVID-19 (admission to the ICU and OIT outcomes). There is a possibility that statins may improve the clinical course in patients with COVID-19 at to some extent by preventing or decreasing the likelihood of myocardial injury and cardiovascular events and that statins may modulate the immune response, improving endothelial function and decreasing oxidative stress and inflammation[25]. Statins have known anti-inflammatory properties and may modulate host immune response in COVID-19[26]. The mechanisms involved in the systemic endotheliitis in COVID-19 include the activation of the renin angiotensin system and angiotensin II type 1 receptor, the increase of reactive oxygen species (ROS), the activation of NF-kB reducing nitric oxide (NO) production and the activation of several cytokine receptors, such as TNF-a and IL-6[24]. In turn, endothelial dysfunction itself impairs organ perfusion by disrupting the balance between vasoconstriction and dilatation, increases inflammation and leads to a pro-thrombotic state in both larger and smaller vessels by favoring tissue factor production and platelet activation[24]. In this setting, statins might be helpful by reducing oxidized LDL levels and NADPH oxidase activity, which decreases reactive oxygen species (ROS), by affecting the NF-kB transcription or by improving the coupling of endothelial NO synthase. Statins also prevent the expression of tissue factor, toll like receptor 4, high-affinity receptor and cofactor for factor (F) VII/VIIa in endothelial cells protecting against blood coagulation and platelet activation. Furthermore, they can reduce macrophages action associated with the cytokine release syndrome in COVID 19[24,34].

Even though a study that analyzed data from hospitalized COVID patients demonstrated that maintenance of statin use ended up being associated with 35% reduction in mortality compared to those patients who did not maintain their use during hospitalization and necessity of mechanical ventilation.[35.] Despite this corroborates the positive results found in our study regarding the use of medication, this should not be recommended to patients without traditional indications for the use of this medication. However, on the other hand, it can serve as a great motivation to encourage prescription by physicians and adherence to treatment by patients when indicated by the cardiovascular risk profile. Studies designed specifically for this purpose will need to clarify whether the use of statins during hospitalization has any beneficial effects on COVID-19 outcomes.

One of the main limitations of the present study is the lack of information on pre-admission glycemic control, since HbA1c data was available in only a small number of patients. Although this was precious information that would allow for a better exploration of the relationship between dysglycemia and unfavorable outcomes in COVID, it does not invalidate the findings of the present study, since we explored in-hospital glycemic control through PG and CBG. We even consider the latter as one of the strengths of our work, since several previous studies did not address in-hospital glycemic control, but only the previous diagnosis of DM[2,15,16].

5. CONCLUSION

Although prognosis of COVID-19 was poor in patients with a previous diagnosis of DM, in-hospital hyperglycemia *per se* proved to be a stronger predictor of worse prognosis outcomes, in both DM and non-DM patients. What remains to clarify is whether in-hospital hyperglycemia is a determinant of this poor prognosis or whether it is just a marker of greater systemic inflammatory response in more severely ill patients. Our data also suggest previous use of statin as a protective factor in COVID-19, requiring confirmation in studies.

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