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Clinical outcomes in patients with diabetes and stress hyperglycemia that developed SARS-CoV-2 infection

Desenlaces clínicos de los pacientes con diabetes e hiperglucemia de estrés que presentaron infección por SARS-CoV-2

Diabetes and stress hyperglycemia in SARS-CoV-2 infection

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Introduction. Diabetes and stress hyperglycemia (SH) have been related with poorer clinical outcomes in patients infected by SARS-CoV-2 and at risk for severe disease.

Objective. To evaluate clinical outcomes in three groups of patients (with diabetes, without diabetes and stress hyperglycemia [SH]) with SARS-CoV-2 infection.

Materials and methods. A retrospective cohort study was conducted in Cali-Colombia. Patients aged ≥18 years with a diagnosis of SARS-CoV-2 infection managed in the emergency room, hospitalization or intensive care unit (ICU) between March 2020 and December 2021 were included. Immunocompromised patients and pregnant women were excluded. Patients were classified in three groups: without diabetes, with diabetes and SH. A comparison between the groups was performed.

Results. A total of 945 patients were included (59.6% without diabetes, 27% with diabetes and 13.4% with SH). Fifty-five-point three percent required ICU management, with a higher need in patients with SH (89.8%) and diabetes (67.1%), with no difference between these groups (p=0.249). A higher chance of death was seen in SH vs. without diabetes (adjOR= 8.12, 95% CI 5.12-12.88, p<0.01). Frequency of acute respiratory distress syndrome, need for invasive mechanical ventilation, use of vasopressors and inotropes, the need for *de novo* renal replacement therapy and mortality was higher in patients with metabolic alterations (diabetes and SH).

Conclusions. Diabetes and SH are associated to worse clinical outcomes and mortality in patients with COVID-19. These patients should be identified early

and considered as high risk at moment of COVID-19 diagnosis that allow to mitigate adverse outcomes.

Keywords: SARS-CoV-2; COVID-19; diabetes mellitus; hyperglycemia; intensive care units; mortality.

Introducción. La diabetes y la hiperglucemia de estrés (HE) se han relacionado con peores desenlaces clínicos en pacientes infectados por SARS-CoV-2 y con riesgo de enfermedad grave.

Objetivo. Evaluar los resultados clínicos en tres grupos de pacientes (con diabetes, sin diabetes e hiperglucemia de estrés [SH]) con infección por SARS-CoV-2.

Materiales y métodos. Se realizó un estudio de cohorte retrospectivo en Cali-Colombia. Se incluyeron pacientes ≥18 años con diagnóstico de infección por SARS-CoV-2 atendidos en urgencias, hospitalización o unidad de cuidados intensivos (UCI) entre marzo de 2020 y diciembre de 2021. Se excluyeron pacientes inmunocomprometidos y mujeres embarazadas. Los pacientes fueron clasificados en tres grupos: sin diabetes, con diabetes e HE. Se realizó una comparación entre los grupos.

Resultados. Se incluyeron un total de 945 pacientes (59,6% sin diabetes, 27% con diabetes y 13,4% con HE). El 55,3% requirió manejo en UCI, con mayor necesidad en pacientes con HE (89,8%) y diabetes (67,1%), sin diferencia entre estos grupos (p=0,249). Se observó una mayor probabilidad de muerte en HE vs. sin diabetes (adjOR= 8,12, 95% IC 5,12-12,88, p<0,01). La frecuencia de síndrome de distrés respiratorio agudo, necesidad de ventilación mecánica invasiva, uso de vasopresores e inotrópicos, necesidad de terapia de reemplazo renal *de novo* y la mortalidad fue mayor en pacientes con alteraciones metabólicas (diabetes e HE).

Conclusiones. La diabetes y la HE se asociaron a peores resultados clínicos y mortalidad en pacientes con COVID-19. Estos pacientes deben ser

identificados tempranamente y considerados de alto riesgo al momento del diagnóstico de COVID-19 que permitan mitigar los desenlaces adversos.
Palabras clave: SARS-CoV-2; COVID-19; diabetes mellitus; hiperglucemia; unidades de cuidados intensivos; mortalidad.

In December 2019, the world saw how COVID-19 infection started taking thousands of lives (1), being the COVID-19 epidemic declared a public health emergency by the World Health Organization (WHO) on the 30th of January, 2020, and characterized as a pandemic since March 11th, 2020 (2). In Colombia, according to the Instituto Nacional de Salud (INS), the number of confirmed cases was 6,305,562 with a total number of 141,746 deceased patients (3).

The mechanisms of glycemic disturbances in COVID-19 include a number of complex and interrelated etiologies, including impairments in both glucose disposal and insulin secretion, stress hyperglycemia, preadmission diabetes, and steroid-induced diabetes. Additionally, factors that have been identified such as preexisting diabetes, poor glycemic control (age, sex, comorbidities, obesity, inflammation, procoagulative state), COVID-19 severity (SARS-CoV-2 β-cell tropism, cytokine storm, stress) that contributes to new-onset diabetes show a bidirectional relationship between type 2 diabetes, hyperglycemia, and COVID-19 (4).That is why diabetes has shown to be a risk factor to develop severe COVID-19, with a higher risk of related adverse outcomes (5-8).

Severe hyperglycemia is common in critically ill patients and is often seen as a marker of disease severity (9). Stress hyperglycemia (SH) negatively affects the outcomes of patients with and without diabetes hospitalized due to infections. Evidence suggest that SH alters the immune response against infection, increases the release of pro-inflammatory chemokines, generates abnormalities in the coagulation system, increases oxidative stress and induces greater bronchial hyperreactivity and promotes fibrosis in the airway (10).

As for the greater risk in patients with metabolic alterations of glucose such as diabetes and SH in the current SARS-CoV-2 pandemic scenario, there are further studies needed in different population groups that allow to establish the expected clinical outcomes for each one. The objective of this study was to evaluate the clinical outcomes in patients with diabetes and SH that developed SARS-CoV-2 infection.

Materials and methods

Design and setting

A retrospective cohort study was conducted in Fundación Valle del Lili (FVL), in Cali-Colombia. FVL is a non-profit university hospital that serves as a reference center for all the Colombian southwest, affiliated to Universidad ICESI Faculty of Health Sciences. In Colombia, the prevalence of diabetes is around 10% according to International Diabetes Federation (IDF) in 2021 (11) and taking data of the high-cost account, the incidence of diabetes in men is 2.98 per 100,000 inhabitants and 3.77 per 100,000 inhabitants for women. The highest proportion of newer cases occurs between 55 and 69 years of age, accounting for 43.77% of incidence (12). In the country, the majority of COVID-19 cases occurred in the age group that comprises between 30-39 years of age, 52.52% corresponded to women, 97.01% were mild cases, the death rate was 2.5 per 100 cases and the three main comorbidities were hypertension (HTN), diabetes and kidney disease (6,416, 3,901 and 2,226 cases, respectively) (13).

Ethics statement

The Institutional Review Board–Comité de Ética en Investigación Biomédica at FVL approved this study (IRB/EC 1566), and it was conducted after the Declaration

of Helsinki and Resolution 8430/1993 from the Colombian Ministry of Health. There was no process of written consent, given that the data was gathered through clinical records and the data bases from the clinical and microbiology laboratories.

Patients and data

The selected population were patients treated between March 2020 and December 2021. Patients aged ≥18 years, from both sexes, that were admitted to the hospital and were managed either in the emergency room, hospitalization or in the intensive care unit (ICU) were eligible.

SARS-CoV-2 infection cases. SARS-CoV-2 cases were patients with clinical and/or epidemiological criteria and a viral antigen detection test and/or presence of SARS-CoV2 antibodies, or patients with a positive viral real-time RT-PCR test assay regardless of clinical or epidemiological criteria (according with the WHO definitions). The clinical criteria were acute onset of fever and cough (influenza-like illness), or acute onset of 3 or more of any signs or symptoms (fever, cough, weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, nausea, diarrhea, anorexia). The epidemiological criteria were contact of a probable, confirmed or linked case to a COVID-19 cluster.

SARS-CoV-2 infections were diagnosed with nasopharyngeal swabs using the CDC 2019-nCoV Real-Time RT-PCR Diagnostic Panel protocol (CDC, Atlanta, Georgia, USA), VIASURE® SARS-CoV-2 Real-Time PCR Detection Kit (Certest Biotec S.L., Zaragoza, Spain), Allplex™ 2019-nCoV Assay (Seegene Inc, Seoul, South Korea), or AccuPower® SARS-CoV-2 Multiplex Real-Time RT-PCR Kit (Bioneer Corporation, Daedeok-gu, South Korea. IgG and IgM antibodies against SARS CoV-2 measurement through chemiluminescence assay (Abbott

ARCHITECT Assays, Chicago, Illinois). All diagnosis tests were performed in the hospital and cases were obtained from the clinical records and laboratory databases.

Exclusion criteria. Immunocompromised and pregnant patients were excluded.

Cases classification. Patients included were classified in three groups: without diabetes, with diabetes (known diagnosis, or HbA1c value >6.5%) and with SH (defined as blood glucose levels >180 mg/dL and HbA1c <6.5% or blood glucose levels >180 mg/dL, without HbA1c measurement during the hospitalization. This cut-off point to define stress hyperglycemia is based on the fact that this is chosen by some scientific associations to define it (14). It is also the maximum upper limit for the initiation of insulin therapy in the hospital setting. And some studies show that there are worse clinical outcomes associated with this level of blood glucose (15,16).

Variables and outcomes

Demographic, clinical, laboratory tests, treatment (need of insulin, required insulin dose, glycemic control during hospitalization and development of diabetic ketoacidosis) and complications variables were collected retrospectively from the clinical records of all patients. Old age was defined as ≥65 years old; cardiovascular event as the group of coronary disease, heart failure (HF) and arrythmias; chronic kidney disease (CKD) as a glomerular filtration rate (GFR) <60 mL/min/1,73m^2 calculated by CKD-EPI equation (17); HTN as a patient with a known diagnosis following the criteria given by the Eight Joint National Committee (JNC 8) (18) or the use of anti-hypertensive medication. Body mass index (BMI) was determined by weight and height at hospital admission (kg/m^2).

The clinical outcomes evaluated during the follow-up while the patient was hospitalized: in-hospital stay (ICU and general hospitalization), sequential organ failure assessment (SOFA) score, acute respiratory distress syndrome (ARDS), need for invasive mechanical ventilation (IMV), use of vasopressor and/or inotrope support, *de novo* renal replacement therapy (RRT) and death. The information related to these outcomes was collected in a database retrospectively after reviewing the medical records.

Statistical analysis

A descriptive analysis of data was performed. The data distribution was evaluated with the Shapiro-Wilk test. The numerical variables comparison between the groups was done with the Mann-Whitney's U test or t-student, corresponding to the data distribution, while for categorical variables, the chi-squared test was used.

To measure the association, odds ratios (OR) were calculated with corresponding 95% confidence intervals (CIs) through logistic regression for qualitative variables. For outcomes involving quantitative variables, beta coefficients were obtained using linear regression. Graphic representations of serum glucose levels for each group of interest were also provided. Statistically significant differences were considered if the p-value was <0.05. It is important to note that these analyses were further refined by adjusting for potential confounding factors. Specifically, the models were adjusted for heart disease, chronic kidney disease, hypertension, and the use of angiotensin II receptor blockers (ARB).

Study data were collected and managed using REDCap electronic data capture tools hosted at Fundación Valle del Lili (19,20). All analyses were performed using STATA (version 14.0, StataCorp LP, CollegeStation, TX).

Results

We included a total of 945 patients with confirmed diagnosis of COVID-19, from which 563 did not have diabetes (59.6%), 255 had diabetes (27%) and 127 presented SH (13.4%). Patient selection flow chart in figure 1.

Population characteristics

Table 1 presents the demographic and clinical characteristics of patients at hospital admission. Ages ranged between 18 and 99 years, the youngest population belonged to the group without diabetes ($p<0.001$). Most were men (63.1%), even though there was no significant difference regarding sex; neither was their difference in BMI in the different patient groups, with a median of 27.1 kg/m^2 (IQR: 24.4-30.5 kg/m^2).

There were cardiovascular comorbidities in 10.2% of patients, being more frequent in patients with diabetes than the other groups (15.7%, $p<0.001$). HTN was greater in the diabetes group (63.9%, $p<0.001$), just like CKD (17.3%, $p<0.001$). There were no differences in relation to smoking, cerebrovascular events, chronic obstructive pulmonary disease (COPD) and neoplasms among groups.

Patients with diabetes and SH presented a higher increase in the neutrophil/lymphocyte ratio (NLR), serum concentration of C-reactive protein (CRP), D-dimer and ultra-high sensitivity cardiac troponin-I compared to the group without diabetes.

When evaluating the population with diabetes (n=225), we found that metformin was the most used medicine for outpatient management, used in 43% of cases. A 25.9% used insulin at the moment of admission (median

insulin dose was 34 IU/day [IQR: 20–50 IU/day]), 9.8% received DPP-4 inhibitors, 4.7% SGLT2 inhibitors, 2.7% sulfonylureas and 1.9% GLP-1 receptor agonist. The median HbA1c was 7.2% (IQR 6.5%-8.42%).

Clinical outcomes during hospitalization

Median in-hospital stay was 11 days (IQR: 5-23 days) for patients with diabetes while it was 17 days for SH (IQR: 10-29 days) with a statistically significant difference ($p<0.001$). A 55.3% of the population required ICU management. The need for ICU transfer was higher in patients with SH (89.8%) and diabetes (67.1%) than in the group without diabetes (42.3%) as well as ICU stay (12 and 11 days vs. 6 days respectively, $p <0.001$)(table 2).

Patients with diabetes and SH had higher chances of ARDS, IMV need, vasopressor and inotrope support, and *de novo* RRT requirement compared to normoglycemic patients (table 3). We found higher likelihood of death in patients with the previously mentioned abnormalities, differences that kept on showing in the logistic regression model.

Clinical outcomes in ICU

Considering the sample size for each group, adjustments were made solely for heart disease, chronic kidney disease, hypertension, and the use of angiotensin II receptor blockers (ARB). The choice of these specific variables aimed at balancing the need for adjustment with the importance of maintaining parsimony.

Figure 2 presents the clinical outcomes from the 523 patients that required ICU management. Patients with diabetes had higher probabilities of developing ARDS (OR: 3.35, 95% CI 2.44-4.60), IMV requirement (OR: 4.20, 95% CI 3.02-

5.84), vasopressor (OR: 4.53, 95% CI 3.17-6.46) and inotrope support need (OR: 5.14, 95% CI 2.86-9.22), and RRT (OR: 5.38, 95% CI 3.42-8.46) than those with normoglycemia. Patients with SH had higher probabilities of developing ARDS (OR: 7.93, 95% CI 4.74-13.29), IMV requirement (OR: 16.23, 95% CI 10.16-25.94), vasopressor (OR: 10.98, 95% CI 7.10-16.98) and inotrope support need (OR: 8.96, 95% CI 4.79-16.76), and RRT (OR: 4.44, 95% CI 2.56-7.68) than those with normoglycemia. Differences that kept true after adjusting for the logistic regression model (figure 3). We found that the presence of diabetes and SH significantly increases the risk of death when compared with those with normoglycemia (OR: 3.16, 95% CI 2.08-4.81; and OR: 8.16, 95% CI 5.12-12.88).

BMI, age, and sex effect

When adjusting the effect of BMI on mortality for those with diabetes vs. without diabetes, we found that the presence of diabetes increases the risk of death independent of BMI. In patients with obesity, the absence of diabetes behaved as a protective factor (OR: 0.40, 95% CI 0.16-0.97, p=0.042).

The analysis of the impact of age reported that the risk of death is directly related to age. When diabetes was present, mortality increases independent of age. Observing a trend that it is worse in those with diabetes and old age (OR: 42.85, 95% CI 10.18-180.42, p<0.001). In patient from 18-49 years of age the risk was higher than in the 50-64 years old group (OR: 12.07, 95% CI 1.91-76.23, p=0.008; OR 8.74, 95% CI 1.81-42.08, p=0.007, respectively). Sex category when adjusted to diabetes compelled a significantly higher risk of death to men (OR: 4.54, 95% CI 2.42-8.53, p<0.001). Nonetheless, both sexes

had a higher chance of death when diabetes was present independent of sex. In patients with SH vs without diabetes, we discovered that those with SH have a higher risk of dying independent of BMI, and in patients with obesity the lack of SH behaved as a protective factor (OR: 0.39, 95% CI 0.16-0.97, p=0.042). In relation to age and sex, the probability of death increases with the presence of SH, being highest in those >65 years old; as it happened in the diabetes group, patients with SH between 18-49 years had higher chances of death than those between 50-64 years (OR: 59, 95% CI 11.26-309.10; p<0.001; OR: 28.55, 95% CI 5.97-136.59, p<0.001, respectively).

Our analysis on mortality revealed that diabetes is an independent risk factor for increased mortality (OR: 2.55, 95% CI 1.60-4.08, p<0.001). Moreover, it increased when adjusted to concomitant heart disease if both conditions were present (OR: 8.41, 95% CI 4.17-16.97, p<0.001). The trend remains when adjusting for CKD (OR: 7.54, 95% CI 3.79-14.99, p<0.001) and HTN (OR: 4.03, 95% CI 2.33-6.94; p<0.001). With SH the same findings were obtained, having a higher probability of dying in patients with SH than those without it, worsening if two pathologies were present (heart disease OR: 17.07, 95% CI 5.80-50.27, p<0.001; CKD OR: 8.98, 95% CI 2.97-27.16, p<0.001; HTN OR: 9.73, 95% CI 5.05-18.78, p<0.001).

Glycemic control

The HbA1c value was obtained before inpatient admission in 149 patients. Median HbA1c for patients with DM was 7.3% (IQR: 6.7%-8.7) with 11.5% (13/113) of patients with a value <6.5%.

In-hospital glycemic control was studied in 374 patients, from which 86.6%

were out of treatment goals. In these patients, there was a higher frequency of ARDS, IMV, vasopressor support requirement, inpatient hospitalization time, ICU transfer need (table 4).

Diabetes vs stress hyperglycemia

We found that patients with diabetes presented a higher frequency of HTN (63.9%, p=0.001) and angiotensin II receptor blockers (ARB) use (47.8%, p=0,006) compared with SH group. There were no differences regarding age, heart disease and CKD or angiotensin-converting enzyme inhibitors (ACEI) use.

With respect to inflammatory markers, NLR, D-dimer and ultra-high sensitivity troponin-I values were higher in patients with SH.

Inpatient global stay was significantly higher in those with SH (p<0.001) and there was no difference in ICU stay time. Patients with SH had higher chances of requiring IMV (OR: 2.85, 95% CI 1.23-6.61, p=0.001); likewise, the risk of dying was higher in this group (OR 2.15, 95% CI 1.20-3.84, p=0.009)(figure 3). When adjusting for BMI, normal-weight or overweight in SH group, compared with patients with diabetes in the same BMI category had higher probability of dying. Obese patients with SH did not have higher statistically significant chances of dying.

Related to age, having over 65 years of age was associated with higher risk of death in both groups, being significantly higher in those older than 65 with SH (OR: 8.80, 95% CI 2.40-32.29, p=0.001); in the 18-49 year old group, this probability was 3 times higher (OR: 4.89; CI 1.09-21.95, p=0.001) for those who had SH; and it was not significant in the 50-64 year old group (OR: 2.37,

95% CI 0.58-9.60, p=0.228). SH increases the risk of death independent of sex.

Discussion

To our knowledge, this is the first study that compares the clinical outcomes of COVID-19 patients that present with diabetes or SH, with those in absence of these conditions in Latin America and the Caribbean.

The proportion of diabetes in the study was 27%. Previous studies have shown the prevalence of diabetes in patients hospitalized due to COVID-19 ranges between 5 and 20%, being higher as the severity of the disease increases (21). The need for ICU transfer in our population was 42%, a high number when compared to what has been published for COVID-19 in general (22,23). Nonetheless, it can be explained due to the fact that our institution is a regional reference center for high complexity pathologies.

Diabetes and SH have been associated with a higher mortality. The finding of a higher mortality in the diabetes group (adjOR: 3.16, 95% CI 2.08-4.81) and SH group (adjOR: 8.12, 95% CI 5.12-12.88) that develop COVID-19 is consistent with what has been reported in literature in other population groups. A meta-analysis that included 83 studies performed in China, USA, France, Italy, Australia and the United Kingdom with 78,874 patients admitted to inpatient treatment due to COVID-19 found that preexisting diabetes was related to approximately twice the risk of having severe or critical COVID-19 (n=22 studies; random effects OR: 2.10, 95% CI 1.71-2.57, I^2=41.5%) and with threefold the risk of inpatient mortality (n=15 studies; random effects OR: 2.68, 95% CI 2.09-3.44, I^2=46.7%) (24). Another meta-analysis that included 33

studies, conducted mainly in China, showed that diabetes in patients with COVID-19 was associated with an increase in twice the mortality and severity of COVID-19, compared to the -without diabetes group (combined OR: 1.90, 95% CI 1.37–2.64, p<0.01) (25).

The impact of diabetes over mortality increased if patients, on top of it, suffered from cardiovascular disease, CKD or HTN. Another meta-analysis that comprised 35 studies conducted in China, France, Italy, Greece and USA discovered that cardiovascular disease was strongly associated with both severity and mortality in COVID-19 patients (random effects OR: 4.02, 95% CI 2.76–5.86, I^2=53.08; and random effects OR: 6.34, 95% CI 3.71–10.84, I^2=50.14), meanwhile diabetes and HTN were moderately associated with severity and mortality, respectively (diabetes random effects OR: 2.35, 95% CI 1.80–3.06, I^2=34,78 and random effects OR: 2.50, 95% CI 1.74–3.59; HTN random effects OR: 2.98, 95% CI 2.37-3.75, I^2=49.89 and random effects OR: 2.88, 95% CI 2.22-3.74, I^2=35.57) (26). Regarding CKD, a meta-analysis of observational studies that included 13 studies adding up to a total of 18,822 patients found that the presence of diabetes in patients with CKD with COVID-19 was correlated with a greater risk of mortality (RR: 1.41, 95% CI 1.15-1.72, I^2=70%) (27).

In our population, BMI was not determinant for mortality, being SH and diabetes independent risk factors for death. These results could be an information bias derived from the study design, the lack of standardization in the protocol to measure height and weight of patients during the pandemic's peak and the small sample size in the group of patients with BMI recorded in

charts. The result found in patients with obesity, without alterations in glucose, is not previously reported and could be explained by the small sample size.

When analyzing the impact of age on mortality, we found that the risk of dying was higher among older patients (above 65 years old) and that it increased considerably if on top of that the patient had a glucose alteration (diabetes or SH). The impact of age on mortality in patients with COVID-19 was assessed in a meta-analysis that included 27 studies driven in 34 different geographical sites. This study reported an exponential relation between age and COVID-19 mortality, being very low in children and young adults younger than 25 years old (0.002% up to 10 years old and 0.01% until 25 years old), but rises progressively to 0.4% for those who are 55 years old, 1.4% up to 6 years old, 4.6% for 75 years old and 15% for those who are 85 years old (28).

We found a higher risk of death in patients with ages between 18 and 49.9 years old compared to those aged 50-64. The forementioned could be owing to the younger patients consulting later to health services (vs those older than 50), which could have impacted in this group. Moreover, this could be explained by our sample's size.

The presence of diabetes and SH was associated with a higher need for ICU management and worse clinical outcomes (ARDS, IMV, vasopressor and inotrope support, *de novo* RRT). A study done in Colombia that evaluated the factors associated with admission and mortality in ICU in COVID-19 patients found among the factors related to ICU admission: severe pneumonia (OR: 9.86, 95% CI 5.99–16.23), each point increase in the NEWS-2 score (OR: 1.09, 95% CI 1.00–1.19), history of heart disease of ischemic origin (OR: 3.24,

95% CI 1.16–9.00) and COPD (OR 2.07, 95% CI 1.09–3.90); while for mortality, age younger than 65 years (OR: 3.08, 95% CI 1.66-5.71), acute kidney injury (OR: 6.96, 95% CI 4.41-11.78), ICU admission (OR: 6.31, 95% CI 3.63-10.95) and for every point increase in the Charlson comorbidity index (OR 1.16, 95% CI 1.00-1.35), but only 20.5% of cases had a history of diabetes (29). A meta-analysis that included 78 studies of critically-ill patients, with 21,510 patients treated in ICU, showed that the mortality rate in patients with mechanical ventilation was as high as 47.9% (95% CI 41.6%-54.2%, $I^2 = 96.9\%$) and RRT was 58.7% (95% CI 50.0%-67.2%; $I^2=83.1\%$) (30). Another study performed in New Jersey showed that 79.5% of intubated patients had diabetes (31).

When comparing the outcomes between those with hyperglycemia (diabetes vs SH), we found that the presence of SH is linked to a higher risk of complications and death, when compared to the presence of diabetes (figure 2). A probable explanation could be because hyperglycemia is a stress and inflammatory marker that potentially contributes to adverse metabolic responses to infection (32), and it would be consistent with an observational study performed in New York with 133 patients, that described that patients with SH have adjusted hazard ratio (HR) higher for 14 day mortality (HR: 7.51, 95% CI 1.70-33.24) and 60 days (HR: 6.97, 95% CI 1.86-26.13), when compared to the group without diabetes. Similarly, there were higher levels of CRP, procalcitonin and lactate (33).

A study conducted in France showed that at least a quarter of COVID-19 hospitalized patients had diabetes, additionally it was associated with a higher

risk of ICU admission but not with mortality (34). Our study found that most cases corresponded to SH instead of diabetes, and that this populational group required ICU management on a greater deal. Furthermore, there was a higher mortality in the diabetes group. This association was described in England's National Cohort study (adjHR: 1.23, 95% CI 1.14-1.32) since 26.4% of deceased patients had diabetes (35).

Patients with SH and diabetes received steroids more frequently than those without diabetes, which could have influenced the results; however, the type and dose of these are unknown, and a specific analysis of their effects on adverse outcomes cannot be made taking into account that there are studies that suggest lower mortality with its use (36,37).

The mechanism by which the population with glucose abnormalities have worse outcomes is poorly understood. Nevertheless, historically it has been shown that hyperglycemia alters the immune system response to infection (compromises chemotaxis, phagocytosis, innate cellular immunity), increases the release of pro-inflammatory chemokines, generates abnormalities in the coagulation system, increases oxidative stress and at a pulmonary level, induces a prolonged inflammatory response, bronchial hyperreactivity and the development of fibrosis in the airway (38), all of which potentially explains the unfavorable outcomes seen in patients with diabetes and viral infections in previous pandemics (i.e., MERS or AH1N1) (10,24,39-41).

SH presents with a higher prevalence of rise in acute phase reactants, suggesting that this phenomenon is derived from immune system dysregulation. These observations are related at a molecular level with various

mechanisms including reduction in neutrophil degranulation, expression of cytokines, phagocytosis and cellular toxicity (40).

Likewise, it worsens the patient's inflammatory state and oxidative stress which generates an increased hyperglycemia that augments cellular glucotoxicity. Simultaneously, insulin resistance induces an increase in circulating free fatty acids inducing lipotoxicity which constitutes, together with inflammation and glucotoxicity, the most important characteristics of acute illness-related hyperglycemia; Additionally, insulin resistance and secondary hyperinsulinemia can promote endothelial dysfunction and alterations in the fibrinolytic system (42), meaning all of the previous elements add up for worse clinical outcomes.

In our population, those patients with diabetes and SH had significantly higher levels of NLR, serum concentrations of CRP, D-dimer and ultra-high sensitivity troponin-I, compared to the group without diabetes. Which suggests a greater inflammatory response that was apparently higher in SH patients since inflammatory response markers where higher when compared to the patients with diabetes.

Our study has certain limitations, and our descriptions must be interpreted in the context of its design. First, our institution is a reference center for the management from the Colombian southwest, reason for which there could be a selection bias within our population. Second, clinical data from every patient was obtained directly from clinical records and secondary databases (clinical and microbiology laboratories). Ergo, there can be an information bias from missing relevant patient data (as it happened with BMI and HbA1c, which was strikingly lower than what was reported in other local studies, not knowing if

this could have had an impact on the outcomes evaluated) and their present comorbidities; due to this, neither is there a clear specification with respect to the type of diabetes from the included patients, though most of them probably correspond to type 2 diabetes considering local prevalence when compared to type 1 diabetes in the country (43). Third, the only clinical tests considered for the study were those taken at hospital admission, and those laboratory parameters were not followed-up during inpatient stay.

The main limitation of this study is that when designing the methodology, including the variables and planning the statistical analysis, the conditions that were considered relevant at the time of design were taken into account, in the midst of global ignorance of the disease course of SARS-CoV-2 infection, and confounding factors of the individual or their pathology that could influence the outcomes in a positive or negative way may be left out of the analysis.

One of the strengths from the study was the adjustment for common confounding factors in the population, some of which have been suggested as risk factors for adverse outcomes in COVID-19, such as HTN, cardiovascular disease and CKD. Data adjustment to age also results in a strong point from the study given the known relation and reports of greater age and worse outcomes in COVID-19. Even though the retrospective aspect of the study impedes us from excluding every potential confounding factor, the strength of association found between diabetes and SH and adverse outcomes that prevail after adjusting for co-variables, supports the hypothesis that alterations in glucose metabolism within the hospital such as diabetes and specially SH constitute risk factors for the development of severe COVID-19 and unwanted

clinical outcomes. The number of patients included counts as a strength as there is no data reported in Latin-American populations of this kind.

Another limitation of the study was that the coexistence of infections and their possible impact on outcomes was not analyzed; With respect to other drugs received by patients, an analysis of the effect of receiving ACEIs or ARBs was carried out (because the initial literature during the pandemic reported some data that suggested worse outcomes in patients who received them) without finding significant differences between those. Who received it and those who did not. The previous use of other drugs such as immunosuppressants was an exclusion criterion to avoid these as confounding factors.

Despite our limitations, our study constitutes a contribution for the knowledge of the behavior from COVID-19 patients that have diabetes and those that develop SH in Colombia and Latin America, aiming to establish public health strategies and strategies at a clinical level that favor preferable clinical outcomes in this population.

Diabetes and SH are associated with unfavorable clinical outcomes and higher mortality in patients with COVID-19; among the alterations, the presence of SH grants a significantly higher risk. This group of patients must be considered as high risk in the moment of diagnosing COVID-19 to initiate early therapeutical measures that allow to mitigate adverse outcomes.

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Competing of interest

No declared.

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Table 1. Demographic and clinical characteristics of patients included in the study (n=945).

Characteristics	Total, n=945	Without diabetes, n=563	Diabetes, n=255	Stress hyperglycemia, n=127	p-value
Demographic					
Age (years), median (IQR)	**61 (50 - 72)**	**57 (45 - 68)**	**66 (57 - 73)**	**67 (56 - 76)**	**<0,001**
Male sex, n (%)	596 (63,1)	347 (61.6)	166 (65.1)	83 (65.4)	0.540
Clinical					
BMI (kg/m^2), median (IQR)	27.1 (24.4-30.5)	27.1 (24.2-30.1)	27.4 (24.8-31.3)	26.8 (24.2-30.1)	0.184
Comorbidities, n (%)					
Hypertension	**427 (45.2)**	**205 (36.4)**	**163 (63.9)**	**59 (46.5)**	**<0.001**
Chronic kidney disease	**99 (10.5)**	**41 (7.3)**	**44 (17.3)**	**14 (11.0)**	**<0.001**
Neoplasms	97 (10.3)	57 (10.1)	25 (9.8)	15 (11.8)	0.819
Heart disease	**96 (10.2)**	**41 (7.3)**	**40 (15.7)**	**15 (11.8)**	**0.001**
Coronary artery disease	56 (58.3)	20 (48.8)	28 (70.0)	8 (53.5)	0.140
Cerebrovascular disease	34 (3.6)	20 (3.6)	11 (4.3)	3 (2.4)	0.614
Chronic obstructive lung disease	32 (3.4)	17 (3.0)	10 (3.9)	5 (3.9)	0.863
Chronic heart failure	26 (27.1)	10 (24.4)	11 (27.5)	5 (33.3)	0.705
Arrhythmias	25 (2.6)	8 (1.4)	12 (4.7)	5 (3.9)	0.372
Pulmonary hypertension	6 (0.6)	5 (0.8)	1 (0.4)	-	0.158
Smoking, n (%)	71 (7.5)	38 (6.7)	21 (8.2)	12 (9.5)	0.508
Drugs, n (%)					
ACEI	38 (4)	19 (3.4)	14 (5.5)	5 (3.9)	0.361
ARB	**300 (31.7)**	**136 (24.2)**	**122 (47.8)**	**42 (33.1)**	**<0.001**
Laboratory					
Glycated hemoglobin (%), median (IQR)	**7.2 (6.5-8.4)**	**NA**	**7.3 (6.7-8.7)**	**6.2 (5.7-6.3)**	**<0.001**
Thrombocytopenia (<150.000/uL), n (%)	**41 (4.3)**	**27 (4.8)**	**4 (1.6)**	**10 (7.9)**	**0.012**
Neutrophil/lymphocyte rate, median (IQR)	**6.3 (3.4 – 11.0)**	**5.5 (3.0 – 10.4)**	**6.7 (3.9 – 11.1)**	**8.9 (5.1 – 14.7)**	**<0.001**
C-reactive protein (mg/dL), median (IQR)	**11.1 (5.4 – 21.2)**	**8.9 (3.9 – 18.8)**	**14.1 (6.9 – 23.8)**	**15.6 (9.5 – 25.7)**	**<0.001**
Erythrocyte sedimentation rate (mg/dL), median (IQR)	28 (13 - 40)	22 (13 - 46)	37 (30 - 43)	24.5 (12 - 30)	0.238
Interleukin 6, median (IQR)	31.1 (9.9 – 92.9)	28.3 (6.6 – 91.8)	32.4 (10.2 - 101)	31.1 (13.4 – 86.8)	0.830
D-dimer (ug/mL), median (IQR)	**1 (0.6 – 1.8)**	**0.9 (0.5 – 1.5)**	**1.1 (0.6 – 2.0)**	**1.4 (0.9 – 5.5)**	**<0.001**
Ultra-high sensitivity troponin-I (ng/L), median (IQR)	**7.7 (3.4 – 25.9)**	**5.35 (2.6 – 16.9)**	**10.6 (4.4 – 44.6)**	**17.9 (7.9 – 85.4)**	**<0.001**

ARB: Angiotensin II receptor blocker; ACEI: angiotensin converting enzyme inhibitor; BMI: body mass index; IQR: interquartile range.

Table 2. Level of healthcare attention and stay-in times of the included patients.

Characteristics	Total, n=945	Without diabetes, n=536	Diabetes, n=255	Stress hyperglycemia, n=127	p-value
Inpatient hospital stay (days), median (IQR)	**8 (4-18)**	**6 (3-12)**	**11 (5-23)**	**17 (10-29)**	**<0.001**
Transfer to general hospitalization rooms, n (%)	**422 (44.7)**	**325 (57.7)**	**84 (32.9)**	**13 (10.2)**	**<0.001**
Stay-in time in general hospitalization rooms (days), median (IQR)	4 (2-7)	4 (2-7)	4 (2-7)	7 (4-11)	0.171
ICU transfer, n (%)	523 (55.3)	238 (42.3)	171 (67.1)	114 (89.8)	-
ICU stay-in time (days), median (IQR)	**8 (4-16)**	**6 (3-11)**	**11 (5-18)**	**12 (7-22)**	**<0.001**
Steroid use, n (%)	**757 (80.1)**	**415 (73.7)**	**221 (86.7)**	**121 (95.3)**	**<0.001**

IQR: interquartile range. ICU: intensive care unit.

Table 3. Clinical outcomes of patients with glucose alterations (diabetes and stress hyperglycemia) compared to normoglycemic patients during inpatient hospital stay.

Clinical outcomes	**Diabetes OR (95% CI)**	**Stress hyperglycemia OR (95% CI)**
Logistic regression model		
ARDS	3.35 (2.44-4.60)	7.93 (4.74-13.29)
Invasive mechanical ventilation	4.20 (3.02-5.84)	16.23 (10.16-25.94)
Vasopressor requirement	4.53 (3.17-6.46)	10.98 (7.10-16.98)
Inotrope requirement	5.14 (2.86-9.22)	8.96 (4.79-16.76)
De novo renal replacement therapy requirement	5.38 (3.42-8.46)	4.44 (2.56-7.68)
ICU requirement	2.78 (2.04-3.79)	11.97 (6.59-21.77)
Mortality	3.16 (2.08-4.81)	8.12 (5.12-12.88)
	Diabetes β-coefficient (95% CI)	**Stress hyperglycemia β-coefficient (95% CI)**
Linear regression model		
SOFA score	1.63 (1.10-2.17)	2.30 (1.67-2.93)
Inpatient stay in general hospitalization rooms	6.62 (3.86-9.37)	13.48 (9.90-17.06)
ICU stay-in time	5.78 (3.11-8.45)	8.16 (5.17-11.16)

ARDS: acute respiratory distress syndrome; ICU: intensive care unit

Table 4. Clinical outcomes according to glycemic control.

Characteristics	Glycemic control during hospitalization		p-value
	Out of goals, n=324	Within goals‡, n=50	
SOFA score, median (IQR)*	4 (3-7)	4 (2-5)	0.081
ARDS, n (%)	**260 (80.2)**	**27 (54.0)**	**<0.001**
IMV requirement, n (%)	**196 (60.5)**	**21 (42.0)**	**0.014**
Vasopressor requirement, n (%)	**-**	**17 (34.0)**	**0.047**
Inotrope requirement, n (%)	57 (17.6)	9 (18.0)	0.944
De novo renal replacement therapy, n (%)	81 (25.0)	11 (23.4)	0.761
Diabetic ketoacidosis, n (%)	15 (4.6)	1 (2.0)	0.399
Inpatient stay in general hospitalization rooms, median (IQR)†	**14 (7-27)**	**8 (3-21)**	**0.004**
Intensive care unit transfer requirement, n (%)			
General hospitalization rooms	**66 (20.4)**	**23 (46.0)**	**<0.001**
ICU	258 (79.6)	27 (54.0)	
ICU inpatient stay, median (IQR)*	12 (7-21)	12 (5-19)	0.673
Mortality, n (%)	**102 (31.5)**	**8 (16.0)**	**0.025**

*n=196/324 and n=29/50 respectively
†n=317/324 and n=50/50 respectively
‡Glycemic levels between 140-180 mg/dL
ARDS: acute respiratory distress syndrome; IVM: invasive mechanical ventilation; ICU: intensive care unit

Figure 1. Patient selection flow chart

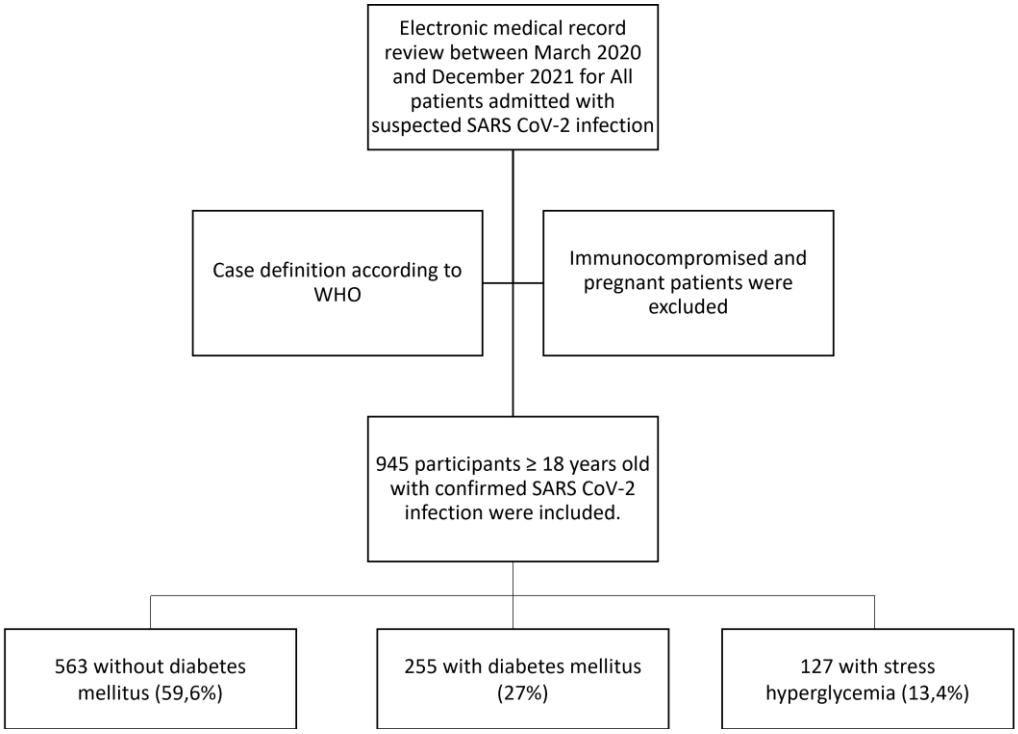
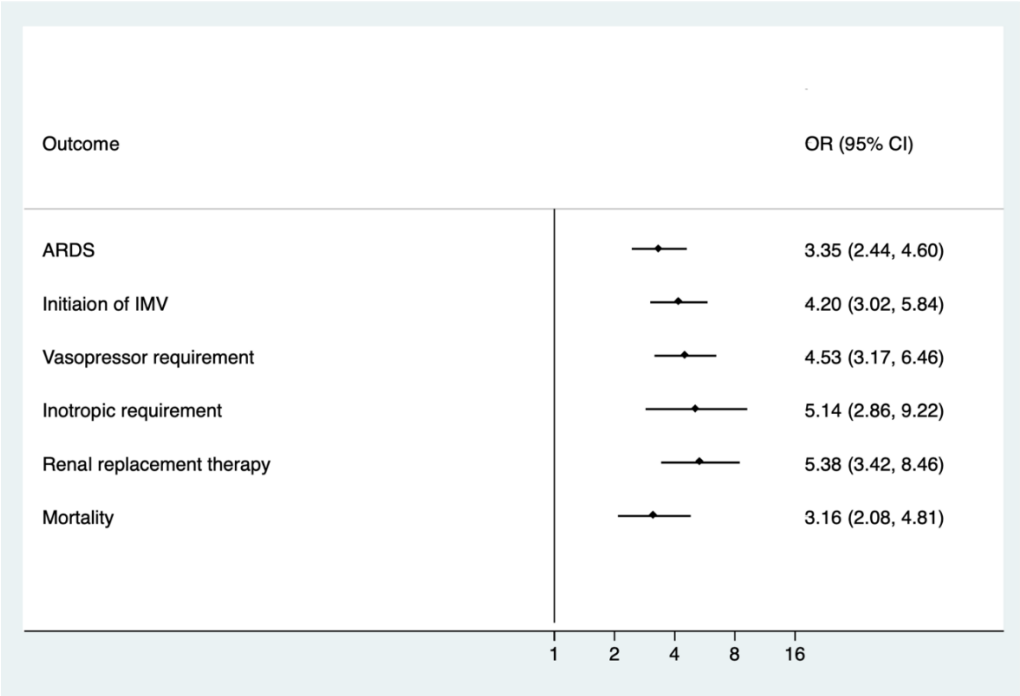
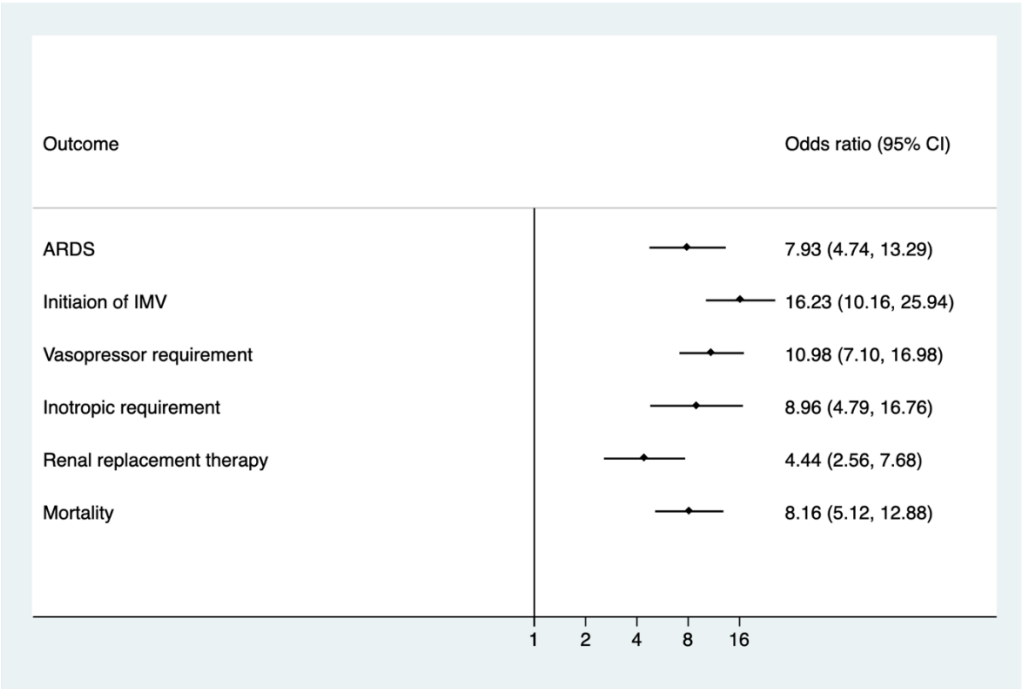


Figure 2. Clinical outcomes of patients treated in ICU (n=523).

a) Patients with DM

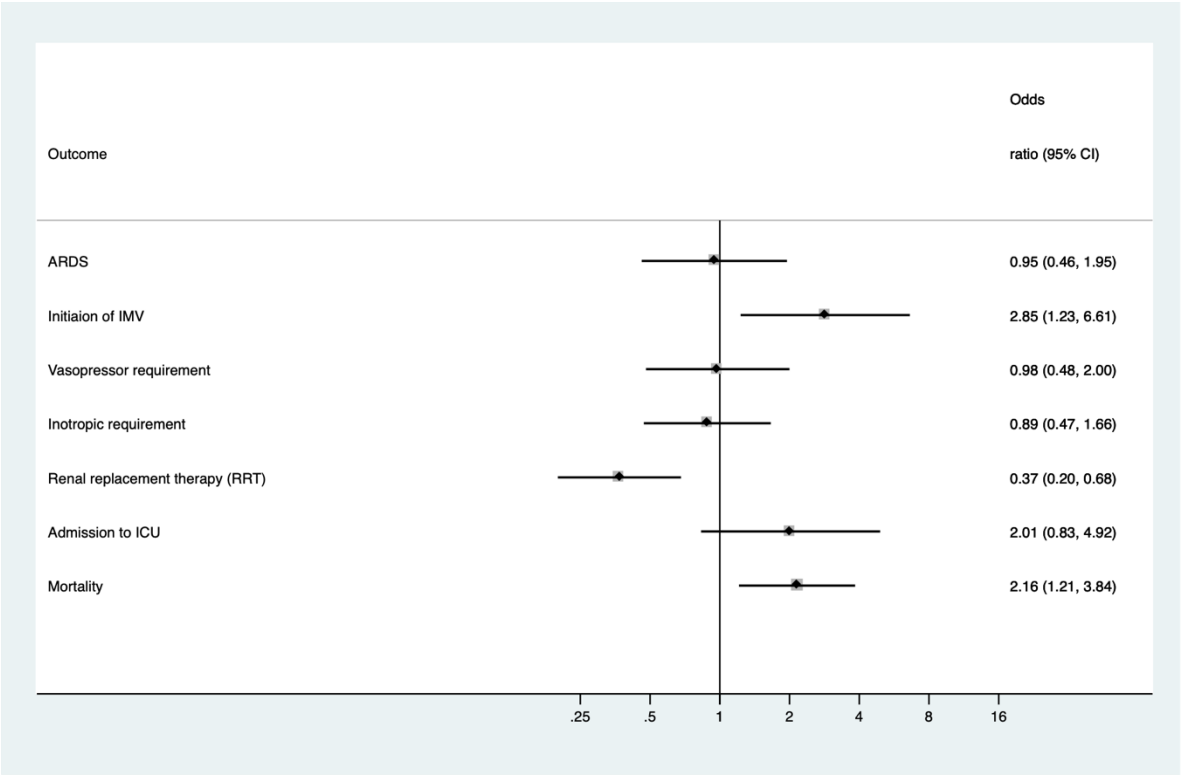


b) Patients with HE



ARDS: acute respiratory distress syndrome; IMV: invasive mechanical ventilation

Figure 3. Logistic regression model between diabetes and stress hyperglycemia for clinical outcomes.



ICU: intensive care unit; IMV: invasive mechanical ventilation
Note: SOFA score and inpatient stay in ICU variables were not included.