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In-Hospital Hyperglycemia and Sliding Scale Insulin Regimen as Risk Factors for Critical Illness and Mortality in Patients with COVID-19 and Type 2 Diabetes

ABSTRACT

Objective: Diabetes mellitus (DM) and in-hospital hyperglycemia are independent risk factors for severe pneumonia and mortality in patients with coronavirus disease 2019 (COVID-19). We aimed to identify the prevalence of critical COVID-19 disease and mortality in hospitalized patients with DM and COVID-19 infection and associated risk factors before the introduction of COVID-19 vaccines.

Materials and methods: All hospitalized patients ≥ 18 years old with DM and COVID-19 during 2020 were included. We compared clinical findings and outcomes between survivors and non-survivors. The main risk factors associated with mortality and critical COVID-19 were determined.

Results: Among 248 patients, 59.3% were discharged and 40.7% died. Their mean age was 60 ± 12.9 years, and 58.1% were male. Critical COVID-19 was associated with age ≥ 60 years (OR 3.13, p = 0.003), hypoxemia on admission (OR 4.86, p ≤ 0.001), inpatient hyperglycemia (OR 6.15, p = 0.001), and sliding scale insulin (OR 2.70, p = 0.010). Increased mortality was associated with age ≥ 60 years (OR 2.29, p = 0.028), cancer (OR 7.77, p = 0.023), hypoxemia (OR 3.42, p = 0.004) hypotension on admission (OR 10.21, p = 0.044), leukocytosis (OR 2.42, p = 0.048), anemia (OR 3.07, p = 0.013), thrombocytopenia (OR 4.66, p = 0.006), inpatient hyperglycemia (OR 4.44, p = 0.007), and sliding scale insulin (OR 3.24, p = 0.003). The basal bolus

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regimen was protective mortality (OR 0.17, p = 0.003). Conclusions: COVID-19 was associated with a mortality of 40.7% in hospitalized patients with DM. Inpatient hyperglycemia and sliding scale insulin increased the risk of critical COVID-19 and mortality, while the implementation of a basal plus insulin regimen (basal insulin + sliding scale prandial insulin) protected against mortality. Defining strategies for in-hospital glucose control should be a priority. (Clin Diabetol 2025; 14, 1: 40–49)

Keywords: type 2 diabetes, COVID-19, mortality

Introduction

Since the outbreak of the coronavirus-19 (COVID-19) infection in December 2019, more than 350 million people worldwide have been infected and more than 5 million have died as of this writing. Before the application of vaccines against COVID-19 in Mexico, the median age of COVID-19 infection was 44 years [interquartile range (IQR) 33–56], affecting both men and women equally; approximately a quarter of patients required hospitalization, and overall reported mortality was about 10% [1]. The clinical presentation ranged from mild symptoms to severe pneumonia, sepsis, acute kidney injury, acute respiratory distress syndrome, respiratory failure, and multiple organ dysfunction. Mortality due to COVID-19 pneumonia has been related to male gender, older age (> 60 years), and comorbidities such as diabetes mellitus (DM), obesity, hypertension, respiratory disease, cancer, and cardiovascular disease [2–6].

Among patients with COVID-19 infection, DM is an independent risk factor for severe pneumonia, hospitalization, admission to an intensive care unit, and intubation [7–8]. Prior to vaccination, in patients with DM and COVID-19, the incidence rate of death was as high as 1153 cases per 100,000 person-days, compared to 292 cases per 100,000 persons-days in those without DM [1]. Older age, male gender, lower socioeconomic status, poorer glycemic control, previous cardiovascular disease, smoking status, and the presence of comorbidities are some of the factors that have been recognized as predictors of poor outcome [9]. The need to carry out studies to ascertain the relationship between patients with COVID-19 and diabetes was established. However, most of the studies have been carried out with a population that does not include patients of Hispanic origin; hence, little is known about the predictors of mortality and severe disease in this group of patients.

The present study was conducted with the aim of identifying the prevalence of hospital mortality in Hispanic patients with DM and COVID-19 pneumonia. The main factors associated with hospital mortality and critical disease were also identified.

Materials and methods

Hospital-based cohort study

An analytical, retrospective, cohort study was carried out in High Specialty Medical Unit (UMAE) No. 25 of the Mexican Institute of Social Security (IMSS) in Monterrey, Nuevo León, Mexico during the period from March to December 2020. Additionally, patients from 6 IMSS second-level hospitals and one third-level private hospital, all with similar low and medium socioeconomic and cultural status, were included. The study was carried out in accordance with the ethical standards established by the general health law and was approved by the local research and ethics committee in health research of the IMSS.

Study population

All patients aged 18 years and older with DM and a confirmed diagnosis of COVID-19-associated pneumonia who required hospitalization were included. Patients with viral pneumonia due to agents other than severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (respiratory syncytial virus, parainfluenza, influenza A, influenza B), glycated hemoglobin (HbA1c) < 6.5% at admission without a history of diabetes, and those with incomplete medical records were excluded. Regarding diabetes, age at diagnosis, disease duration, comorbidities, treatment, and presence of chronic complications were assessed. The clinical and biochemical outcome of hospital-acquired pneumonia was reviewed, including the presence and remission of symptoms, oxygen requirement, admission to the intensive care unit, biochemical parameters, treatment for diabetes, mechanical ventilation requirement, and reason for discharge.

DM was defined in patients who had a history documented medication usage or HbA1c at admission ≥ 6.5%. Diabetic kidney disease was defined in patients with a history of GFR ≤ 60 mL/min/1.73 m^2 during the 3 months prior to hospitalization. The diagnosis of diabetic neuropathy was defined according to what was documented in the medical file or use of treatment. History of acute myocardial infarction, unstable angina, cerebral vascular event, peripheral vascular disease, and amputations were defined as macrovascular complications.

The diagnosis of pneumonia due to SARS-CoV-2 was made by means of a pharyngeal exudate sample,

which was analyzed by reverse transcriptase polymerase chain reaction test. COVID-19 infection was categorized as mild, severe, or critical. Critically ill patients were defined as those with acute respiratory distress syndrome, septic shock, cardiac dysfunction, and/or exacerbation of cardiac, hepatic, renal, central nervous system, or thrombotic disease. Acute kidney injury was documented when there was an increase in serum creatinine concentration of ≥ 0.3 mg/dL during 48 h or an increase of ≥ 1.5 times in the last 7 days, or diuresis < 0.5 mL/kg/h for 6 hours.

The criteria considered for hospital discharge were absence of fever for at least 3 days, radiological improvement, and remission of respiratory symptoms [10].

Outcomes

Patients were classified into 2 groups according to the reason for discharge: group 1 (survivors) were patients who were discharged or transferred to another hospital, and group 2 (non survivors) included patients who died during hospitalization. The primary outcome was to determine the prevalence of in-hospital mortality and critical COVID disease. Demographic, clinical, and biochemical differences were considered as secondary outcomes.

Statistical analysis

Analysis was performed using SPSS version 22.0. Data were assessed for parametric and nonparametric distribution by the Kolmogorov-Smirnov test. Quantitative data with a normal distribution were presented as mean (SD) and those with a non-normal distribution were presented as median IQR. Qualitative variables are presented as frequency and percentage. Student's t-test or the Mann-Whitney U test was used for continuous variables. To evaluate differences in categorical variables we used the chi-square test or the Fisher´s exact test. Adjusted logistic regression analysis was performed to determine the main risk factors associated with mortality and critical illness. Odds ratios and 95% confidence intervals were calculated. A value of $p < 0.05$ was considered significant.

Results

A total of 248 patients were included, of whom 147 (59.3%) were discharged and 101 (40.7%) died. Table 1 shows the demographic characteristics and evolution of DM. The mean age was 60 (± 12.9) years, and 144 patients (58.1%) were male. Household managers/homemakers and retired patients comprised the majority of our study population (67/119 patients [56.3%]). 86.2% (n = 212/246) of patients were at home prior to admission and 13.8% (n = 34/246) were transferred from another hospital. Regarding the reason for admission, 102 patients (41.1%) were hospitalized with a confirmed diagnosis of COVID-19 pneumonia, 130 (52.4%) as a suspected case, and 16 (6.5%) were admitted for other reasons. The use of oral antidiabetics was the most common treatment modality (63.7%). Regarding complications associated with DM, macrovascular disease was identified in 16.1%, diabetic kidney disease in 15.7%, neuropathy in 6.5%, and retinopathy in 3.2%, with no differences between the 2 groups. More than half of the patients used antihypertensive treatment (56.9%), 12.9% statins, and 6.5% acetylsalicylic acid. Mortality increased with age, especially in those over 60 years of age, longer duration of DM, and use of antihypertensive treatment. Obesity was found in 40.0% and hypertension in 65.7%, without finding significant differences between the 2 groups. Chronic kidney disease and cancer were identified as more prevalent in patients with fatal outcomes, while dyslipidemia was more frequent in those who survived.

Table 2 shows the clinical and biochemical characteristics at hospital admission. In the non-survivor group, lower blood pressure and oxygen saturation were identified, as well as a higher proportion of patients with fever, dyspnea, and headache. Among the radiographic findings, bilateral infiltrate was the most prevalent, i.e., in 63.2% of the patients. Furthermore, differences in leukocytosis, lymphocytosis, neutrophilia, anemia, and thrombocytopenia were detected, in addition to a lower glomerular filtration rate and higher levels of C-reactive protein and D-dimer in non-survivors.

Regarding the clinical evolution during hospitalization (Tab. 3), 34.7% of the patients were classified as mild disease, 24.6% as moderate, and 40.7% in critical condition, with critical disease being most prevalent in non-survivors. The median hospital stay was 8 days (IQR 4–12): 8 days (IQR 5–13) in patients who survived and 7 days (IQR 3–10) in non-survivors ($p = 0.03$). 47.5% of the patients who were non-survivors were on invasive mechanical ventilation, compared to 4.5% of those who survived. The mean glucose during hospitalization was 10.1 mmol/L, IQR 7.66-14.49 mmol/L (182 mg/dl, IQR 138–261 mg/dL). A higher prevalence of hospital hyperglycemia was found in the group of non-survivors (67.7% vs 48.4%, $p=0.02$). A sliding scale insulin scheme was used in about half of the patients. Regarding the rest of the treatment, the use of basal insulin with special interest in basal plus insulin regimen (basal insulin + sliding scale prandial insulin) was more prevalent in survivors, while continuous insulin infusion was more common in non-survivors. 65.6% of patients required glucocorticoids

Table 1. Demographic Characteristics

	Total	Survivors	Non-survivors	P-value
N [%]	248	147 (59.3)	101 (40.7)	
Age [years], X [SD]	60.1 (12.9)	56.9 (12.5)	64.7 (12.1)	< 0.001
Age, n [%]				< 0.001
18–39 [years]	15 (6.0)	13 (8.8)	2 (2.0)	
40–79 [years]	217 (87.5)	130 (88.5)	87 (86.1)	
≥ 80 [years]	16 (6.5)	4 (2.7)	12 (11.9)	
Male gender, n [%]	144 (58.1)	91 (61.9)	53 (52.5)	0.14
Smoking, n [%]	23/192 (12.0)	14/118 (11.9)	9/74 (12.2)	0.95
Occupation, n [%]				0.04
Home/retired	67/119 (56.3)	30/65 (46.2)	37/54 (68.5)	
Employee	30/119 (25.2)	20/65 (30.8)	10/54 (18.5)	
Health	15/119 (12.6)	12/65 (18.5)	3/54 (5.6)	
Others	7/119 (5.8)	3/65 (4.6)	4/54 (7.4)	
Age at diagnosis of diabetes [years], X [SD]	49.6 (12.7)	47.9 (12.5)	52.4 (12.7)	0.06
Duration of diabetes [years], med [IQR]	10 (4–15)	8.5 (2–13)	10 (5–15)	0.02
Duration of diabetes, n [%]				0.18
< 5 [years]	40/139 (28.2)	30/86 (34.9)	10/53 (18.9)	
5–10 [years]	25/139 (17.3)	15/86 (17.4)	9/53 (17.0)	
> 10 [years]	75/139 (53.9)	41/86 (47.6)	34/53 (64.2)	
Home diabetes medication regimen				
Oral antidiabetics, n [%]	128 (63.7)	75 (65.2)	53 (61.6)	0.60
Insulin, n [%]	76 (37.8)	45 (39.1)	31 (36.0)	0.65
No treatment, n [%]	27 (13.4)	15 (13.0)	12 (14.0)	0.85
Diabetes associated complications				
Macrovascular, n [%]	40 (16.1)	20 (13.6)	20 (19.8)	0.19
Diabetic kidney disease, [%]	39 (15.7)	20 (19.8)	19 (12.9)	0.14
Neuropathy, n [%]	16 (6.5)	10 (6.8)	6 (5.9)	0.78
Retinopathy, n [%]	8 (3.2)	5 (3.4)	3 (3.0)	0.94
Other comorbidities				
Obesity, n [%]	66/165 (40.0)	36/101 (35.6)	30/64 (46.9)	0.15
Hypertension, n [%]	163 (65.7)	92 (62.6)	71 (70.3)	0.21
Dyslipidemia, n [%]	34 (13.7)	26 (17.7)	8 (7.9)	0.03
End stage renal disease, n [%]	29 (11.7)	12 (8.2)	17 (16.8)	0.03
Cancer, n [%]	14 (5.6)	3 (2.0)	11 (10.9)	**0.01**
Other treatments				
Any treatment for hypertension, n [%]	141 (56.9)	74 (50.3)	67 (66.3)	**0.01**
ACE inhibitors or MRAs [%]	119 (48.0)	65 (44.2)	54 (53.5)	0.15
Statins, n [%]	32 (12.9)	24 (16.3)	8 (7.9)	0.05
Acetylsalicylic acid, n [%]	16 (6.5)	8 (5.4)	8 (7.9)	0.43

In addition to these data, the following were evaluated: origin at the time of hospitalization and case definition at admission
ACE — angiotensin-converting enzyme; IQR — interquartile range; MRAs — mineralocorticoid receptor antagonists; SD — standard deviation

during hospitalization, and this requirement was more prevalent in the non-survivor group. The patients who died presented greater complications compared to the survivors in terms of admission to intensive care (23.8% vs. 11.6%, p = 0.01), acute respiratory distress syndrome (71.3% vs. 8.8%, p < 0.001), acute kidney injury (27.7% vs. 7.5%, p < 0.001), hemodynamic shock (19.8% vs. 1.4%, p < 0.001), sepsis (18.8% vs. 4.1%, p < 0.001), metabolic acidosis (11.9% vs. 2.0%, p = 0.01), disseminated intravascular coagulation (7.9% vs. 0.7%, p = 0.01), and multiple organ failure (15.8% vs. 0%, p < 0.001).

Table 2. Clinical and Biochemical Characteristics at Hospital Admission

	Total	Survivors	Non-survivors	P-value
N (%)	248	147 (59.3)	101 (40.7)	
Time from onset of symptoms to hospitalization (days)	7 (3–10)	7 (3–9)	7 (3–10)	0.76
Signs and anthropometry at admission				
Body mass index [kg/m2]	31.1 (7.2)	31.2 (7.2)	30.9 (7.5)	0.88
Respiratory rate [bpm]	22 (20–25)	22 (20–25)	22 (19–25)	0.87
Heart rate [bpm]	90 (80–103)	89 (80–100)	90 (80–105)	0.33
Temperature [°C]	36.8 (36.3–37.3)	36.7 (36.1–37.2)	36.8 (36.4–37.5)	0.45
Systolic pressure [mmHg]	126 (110–138)	130 (115–140)	120 (107–137)	0.02
Diastolic pressure [mmHg]	75 (67–81)	79 (70–82)	70 (36–80)	0.001
Oxygen saturation [%]	89 (83–94)	91 (86–95)	86 (76–92)	< 0.001
Symptoms, n [%]				
Dyspnea	190 (76.6)	105 (71.4)	85 (84.2)	0.02
Fever	162 (65.3)	87 (59.2)	75 (74.3)	0.01
Cough	152 (61.3)	88 (59.9)	64 (63.4)	0.58
Myalgias and arthralgias	108 (43.5)	67 (45.6)	41 (40.6)	0.44
Fatigue	88 (35.5)	53 (36.1)	35 (34.7)	0.82
Headache	82 (33.1)	56 (38.1)	26 (25.7)	0.04
Radiographic findings, n [%]				0.33
Bilateral infiltrate	115/182 (63.2)	72/112 (64.3)	43/70 (61.4)	
Ground glass opacities	49/182 (26.9)	29/112 (25.9)	20/70 (28.6)	
One-sided consolidation	13/182 (7.1)	6/112 (5.4)	7/70 (10.0)	
Biochemical findings				
Leukocyte count [K/uL]	9.8 (7.2–13.6)	9.0 (7.1–12.7)	10.9 (8.0–14.6)	0.03
Lymphocyte count [K/uL]	1.1 (0.7–1.6)	1.2 (0.8–1.7)	0.9 (0.7–0.9)	0.05
Neutrophils [K/uL]	8.3 (5.2–11.9)	7.1 (4.9–10.2)	9.6 (5.8–13.0)	0.01
Hemoglobin [g/dL]	13.2 (11.2–14.7)	13.7 (12.0–14.8)	12.1 (10.2–14.3)	0.001
Platelet count [K/uL]	238 (166–318)	255 (187–335)	195 (140–287)	0.001
Albumin [g/dL]	3.3 (2.8–3.6)	3.4 (2.9–3.7)	3.1 (2.7–3.6)	0.07
Glucose [mmol/L]	10.7 (7.3–15.9)	10.7 (7.7–15.7)	10.2 (7.0–16.8)	0.68
Creatinine [mg/dL]	0.83 (0.64–1.50)	0.80 (0.67–1.10)	0.90 (0.60–1.70)	0.13
Glomerular filtration rate [ml/min]	91 (45–107)	94 (54–110)	75 (32–102)	0.005
D-Dimer [ng/mL]	638 (395–1144)	601 (396–932)	950 (368–1766)	0.08
C-reactive protein [mg/L]	70 (15–127)	42 (11–87)	109 (41–191)	0.009

Continuous variables are expressed as median and interquartile range

Table 4 shows the main risk factors associated with mortality and critical illness. The results were adjusted by age, gender, and duration of DM. Among the general characteristics, age ≥ 60 years was significantly associated with critical illness and mortality while cancer was associated with higher mortality risk. Regarding the clinical presentation of COVID-19: hypoxemia, oxygen requirement at hospital admission and thrombocytopenia were all associated with severe illness and mortality. Hypotension, leukocytosis, and anemia were only associated with higher mortality risk. We found no association between the duration of DM, the presence of DM-related complications, or diabetes treatment prior admission with the risk of critical illness or fatal outcome. The persistence of hospital hyperglycemia significantly increased the risk of critical illness and mortality. In addition, sliding scale insulin during hospitalization increased both critical illness and mortality while the use of basal plus insulin scheme (basal insulin + sliding scale prandial insulin) reduced the risk of both critical illness and mortality.

Table 3. Clinical Course During Hospitalization

	Total	Survivors	Non-survivors	P-value
N [%]	248	147 (59.3)	101 (40.7)	
COVID-19 severity, n [%]				**< 0.001**
Mild	86 (34.7)	77 (52.4)	9 (8.9)	
Severe	61 (24.6)	52 (35.4)	9 (8.9)	
Critical	101 (40.7)	18 (12.2)	83 (82.2)	
Hospital stay, median [IQR] (days)	8 (4–12)	8 (5–13)	7 (3–10)	0.03
Maximum oxygen requirement, n (%)				<0.001
Noninvasive mechanical ventilation	5/231 (2.2)	2/132 (1.5)	3/99 (3.0)	
Invasive mechanical ventilation	53/231 (22.9)	6/132 (4.5)	47/99 (47.5)	
Average glucose during hospitalization [mg/dL], median [IQR]	182 (138–261)	176 (122–250)	202 (157–289)	0.02
Hospital hyperglycemia [> 180 mg/dL], n [%]	90/160 (56.3)	46/95 (48.4)	44/65 (67.7)	0.02
Treatment, n [%]				
Glucocorticoids	148/229 (64.6)	79/133 (59.4)	69/96 (71.9)	0.05
Statins	38/226 (16.8)	23/128 (18.0)	15/98 (15.3)	0.59
Plasmapheresis	14/248 (5.6)	7/147 (4.8)	7/101 (6.9)	0.47
Dialysis / hemodialysis	6/236 (2.5)	3/136 (2.2)	3/100 (3.0)	0.70
Treatment of hyperglycemia, n [%]				
Sliding scale insulin	119/239 (49.8)	64/140 (45.7)	55/99 (55.6)	0.09
Basal plus (Basal + sliding scale insulin)	46/239 (19.2)	37/140 (26.4)	9/99 (9.1)	0.01
Basal bolus (Basal + fixed prandial insulin)	37/239 (15.5)	21/140 (15.0)	16/99 (16.2)	0.73
Continuous insulin infusion	11/239 (4.6)	1/140 (0.7)	10/99 (10.1)	0.01
No treatment	26/239 (10.9)	17/140 (12.1)	9/99 (9.1)	0.50
Complications during hospitalization, n [%]				
Admission to intensive care	41/248 (16.5)	17/147 (11.6)	24/101 (23.8)	0.01
Acute respiratory distress syndrome	85/248 (34.3)	13/147 (8.8)	72/101 (71.3)	< 0.001
Acute kidney injury	39/248 (15.7)	11/147 (7.5)	28/101 (27.7)	< 0.001
Diabetic ketoacidosis	13/248 (5.2)	5/147 (3.4)	8/101 (7.9)	0.12
Hemodynamic shock	22/248 (8.9)	2/147 (1.4)	20/101 (19.8)	< 0.001
Sepsis	25/248 (10.1)	6/147 (4.1)	19/101 (18.8)	< 0.001
Metabolic acidosis	15/248 (6.0)	3/147 (2.0)	12/101 (11.9)	0.01
Disseminated intravascular coagulation	9/248 (3.6)	1/147 (0.7)	8/101 (7.9)	0.01
Multiple organ failure	16/248 (6.5)	–	16/101 (15.8)	< 0.001

COVID-19 — coronavirus-disease-2019; IQR — interquartile range

Discussion

We found a mortality rate of 40.7% in Hispanic patients with DM hospitalized with COVID-19 pneumonia in the period prior vaccination. Our main findings included the following: 1) Inpatient hyperglycemia was associated with a 4-fold increase of mortality and 6-fold increase of critical COVID-19 infection. 2) The use of sliding scale insulin further increased the risk of critical disease and death while the implementation of a basal plus insulin (basal insulin + sliding scale prandial insulin) regimen protected against fatal outcome. 3) The DM profile prior to hospitalization did not influence the outcome during hospitalization. 4) We did not find a higher prevalence of fatal outcome associated with hypertension, obesity, or cardiovascular disease.

Hyperglycemia at admission is an independent predictor of poor prognosis with a longer hospital stay and a 4-fold increase in mortality [7–11]. In patients with DM, an increased acute-to-chronic glycemic ratio [12] and poor glycemic control (blood glucose > 10 mmol/L or 180 mg/dL) have shown to be associated with increased risk of hospital mortality, intensive care unit admission, and mechanical ventilation. Conversely, patients with DM and optimal glycemic control (blood glucose 3.89–10 mmol/L or 70–180 mg/dL and HbA1c 6.6–8.2% prior to and during hospitalization)

Table 4. Risk Factors Associated with Critical COVID or Fatal Outcome (Logistic Regression Analysis)

Risk factor	Critical COVID			Risk factor	Fatal outcome		
	OR	IC 95%	P-value		OR	IC 95%	P-value
Age ≥ 60 [years]	3.13	1.49–6.58	0.003	Age ≥ 60 [years]	2.30	1.09–2.39	0.03
Oxygen requirement on admission	8.16	1.75–38.08	0.008	Cancer	7.77	1.34–45.19	0.02
Hypoxemia on admission [≤ 90%]	4.87	2.14–11.52	<0.001	Hypoxemia on admission [≤ 90%]	3.42	1.49–7.89	0.004
Thrombocytopenia [< 150 K/UL]	3.13	1.07–9.16	0.03	Hypotension on admission [≤ 90 mmHg]	10.22	1.070–97.598	0.04
Inpatient hyperglycemia (> 10 mmol/L)	6.15	2.07–18.24	0.001	Leukocytosis [≥ 10 K/UL]	2.42	1.01–5.80	0.05
Sliding scale insulin	2.70	1.27–5.72	0.01	Thrombocytopenia [< 150 K/UL]	4.66	1.56–13.99	0.006
				Anemia [< 12 g/dL]	3.07	1.262–7.482	0.01
				Inpatient hyperglycemia (> 10 mmol/L)	4.44	1.50–13.19	0.007
				Sliding scale insulin	3.24	1.49–7.02	0.003
				Basal + sliding scale insulin	0.17	0.05–0.55	0.003

The logistic regression analysis model was performed to evaluate the risk factors for mortality and critical COVID. Mortality adjusted to age ranges, gender and time of evolution of diabetes. In addition to these variables, the following were analyzed: Female gender, smoking, hypertension, obesity, cardiovascular disease, end stage renal disease, hypotension on admission [≤ 90 mmHg], anemia [< 12 g/dL], glomerular filtration rate [≤ 60 mL/min], diabetes duration, insulin treatment, oral antidiabetics, macrovascular complications, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, diabetic ketoacidosis on admission, ACE inhibitors or MRAs, acetylsalicylic acid, statins, glucose at admission ≥ 10 mmol/L, and continuous insulin infusion. These variables were not shown to be risk factors for mortality or severe disease

have significant reductions in inflammatory markers, severity of complications, and mortality risk compared to those with glucose levels >10 mmol/L (180 mg/dL) [8–13]. In our patients, persistent hyperglycemia during the hospital stay was more prevalent in those who died compared to those who survived (67.7% vs. 48.4%, p = 0.016), with a mean glucose level of 11.21 mmol/L, IQR 8.71–16.04 mmol/L (202 mg/dL, IQR 157–289 mg/dL) compared to 9.77 mmol/L, IQR 6.77–13.88 mmol/L (176 mg/dL, IQR 122–250 mg/dL) (p = 0.018). Furthermore, inpatient hyperglycemia increased the risk of both critical illness and mortality with an odds ratio (OR) of 6.15 (confidence interval [CI] 95% 2.07–18.24, p = 0.007) and 4.44 (CI 95% 1.50–13.19, p = 0.007), respectively.

The mechanisms that associate DM and adverse outcomes of COVID-19 include the following: 1) chronic inflammation, dysregulated immune function, and hypercoagulable state related to COVID-19 and DM [7]; 2) attenuation of the synthesis of pro-inflammatory cytokines and a drastic reduction in regulatory T-cell levels in the presence of hyperglycemia and insulinopenia [14–15]; 3) pulmonary dysfunction [8]; 4) possible increase of the viral replication rate and direct structural changes in the lung [16]; 5) secretion of hormones such as catecholamines and glucocorticoids, present in the state of acute infection [17]; and 6) increased levels and activity of angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase 4 (DPP-4) enzyme in patients with diabetes, which has also been identified as the cellular receptor that mediates the entry of SARS-COV2 into cells and subsequently leads to viral replication [7]. In our patients, some of these mechanisms were shown by the high prevalence of acute respiratory distress syndrome, acute kidney injury, hemodynamic shock, sepsis, metabolic acidosis, disseminated intravascular coagulation and multiple organ failure in non-survivors compared to survivors.

Patients with COVID-19 and DM have 40–50% increased risk of 28-day mortality compared to patients without DM [1–9]. According to McGurnaghan et al., longer duration of DM, more previous hospitalizations for hyperglycemia, diabetic ketoacidosis, lower estimated glomerular filtration rate, having retinopathy and the more diabetes drug subclasses were all associated with fatal or critical COVID-19 disease among patients with DM [9]. Holman conducted a large cross-sectional study and reported that previous cardiovascular disease is a risk factor for mortality [18]. Previous meta-analyses have also reported that older age, male sex [19–21],

current smoking [20] and obesity [22–23] confer highest COVID-19 in-hospital mortality. We found no association between mortality and the above-mentioned factors in our population.

Diabetes management during COVID-19 infection is crucial for the prevention of adverse outcomes. Among all the diabetes medications, metformin and DPP-4 inhibitors are the ones most studied that might contribute to mitigating the progression to severe COVID-19 complications. In experimental studies, metformin reduces the SARS-CoV-2 viral recognition by the ACE2 receptor [24]. Metformin has also been proven to reduce pro-inflammatory cytokines and contribute to a lower coagulation risk [7]. In patients with COVID-19 and DM, the use of metformin prior to and during the infection has been associated with reduced inflammation and reduced risk of early death [25–28]. The use of DPP-4 inhibitors has been related with a reduction of cytokine production, a decrease in platelet aggregation, and a reduction of the COVID-19 virus entry and replication within the respiratory tract [7]. A meta-analysis based on retrospective observational studies provided inconclusive results on the association between the use of DPP-4 inhibitors and outcomes of COVID-19 and concluded a neutral effect [29]. In a randomized clinical trial of hospitalized adult patients with DM and COVID-19, the use of linagliptin did not alter the clinical outcome compared with standard care [30]. Regarding the use of other diabetes medications, there are proven anti-inflammatory and anti-thrombotic benefits with the use of glucagon-like peptide-1 agonists (GLP-1a), sodium-glucose-linked transporter-2 inhibitors (SGLT2i), and thiazolidinediones [7]. The use of oral DM treatments was the most common treatment modality (63.7%) in our patients. Because this was a population that received care in a public hospital in Mexico, most of the patients who used oral treatments were on metformin or sulfonylureas, with very few patients using iDPP4, SGLT2i, or GLP-1a, so it was not possible to analyze whether there were differences in mortality or complications by evaluating each of the treatments individually.

The Standards of Medical Care in Diabetes recommend insulin as the preferred treatment for hospital hyperglycemia [31]. These recommendations are justified by the benefits of insulin beyond glycemic control: while it decreases plasma glucose with no adverse effects other than hypoglycemia, it also has crucial anabolic activity by stimulating protein synthesis, inhibiting intracellular triglyceride lipolysis, preventing diabetic ketoacidosis, limiting the lipotoxic effects of free fatty acids, and may also have a regulatory influence in the inflammatory response to infections [13–32]. Sardu et al. showed that insulin infusion-mediated optimal blood glucose control improves prognosis for hospitalized patients with COVID-19 and hyperglycemia [13]. Insulin can also be a marker for advanced DM and more severe disease. Riahi et al. showed that patients who were on insulin at home and were hospitalized with COVID-19 had increased rates of death, as well as peak in-hospital insulin requirements [33]. A meta-analysis that included observational studies that evaluated the use of insulin in patients with COVID-19 infection concluded that insulin treatment was associated with a more than twofold risk of mortality; however, there was substantial heterogeneity among studies, and they did not discriminate between prior use and inpatient use of insulin [32]. In our results, we found that prior insulin use was similar among both groups. On the other hand, the use of only sliding scale insulin without basal insulin during hospitalization was associated with both higher mortality (OR 2.70, CI 95% 1.27–5.72, $p = 0.01$) and critical COVID-19 infection (OR 3.24, CI 95% 1.49–7.02, $p = 0.003$) wile a basal plus insulin scheme (basal insulin + sliding scale prandial insulin) was related with an improved outcome.

Statins are frequently prescribed in patients with diabetes due to their cardioprotective effect. In patients with COVID-19, statin therapy is associated with a 35% decrease in the adjusted risk of COVID-19 related mortality. Some explanations of this benefit are their anti-oxidative, anti-inflammatory, anti-arrhythmic, anti-thrombotic properties as well as beneficial effects on endothelial dysfunction with a potential protective effect against fatal respiratory, cardiovascular, and thromboembolic complications in patients with COVID-19 [34]. In our patients, despite dyslipidemia being more prevalent in those who survived as well as the use of statins, we did not find a significant association with increased mortality or critical COVID.

As a retrospective study we must consider some limitations in the interpretation of our results: 1) It was not possible to collect the information regarding clinical history and DM profile in all our patients, including glycemic control prior to hospitalization, which could explain their lack of association with mortality and severe disease. 2) The inclusion of the patients was carried out consecutively, so it was not possible to match the patients; however, the estimation of risk factors was made adjusted to age, gender, and time of evolution of diabetes. 3) Our results reflect the rate of mortality and critical illness in patients with type 2 diabetes before the existence of vaccines for COVID-19, so they could differ from the population that is currently vaccinated. On the other hand, we confirmed that the persistence of hospital hyperglycemia and the insulin regimen

used during hospitalization are independent factors that influence mortality and critical illness, similarly to what happens with patients with diabetes who are hospitalized for other diseases.

Conclusions

In this study we observed a mortality rate of 40.7% in Hispanic patients with DM hospitalized with COVID-19 pneumonia prior to vaccination. Our baseline finding of advanced age as a mortality risk factor is in line with previous evidence in the literature. Our study also found that mortality increases in those with longer duration of DM and in those who use antihypertensive treatment. Patients with hypoxemia, oxygen requirement at hospital admission and thrombocytopenia were associated with severe illness and mortality.

Inpatient hyperglycemia significantly increased the risk of critical illness and mortality. The use of sliding scale insulin without basal insulin also increased the risk of critical illness and death, while the implementation of a basal plus insulin scheme (basal insulin + sliding scale prandial insulin) protected against fatal outcome. According to these results, defining strategies for in-hospital glucose control should be a priority for health.

Article information

Author contribution

D.L.Q.F. conceptualized the study, researched the data, wrote the manuscript, and reviewed/edited the manuscript. G.G.M. conceptualized the study and researched the data. I.A.M.D conceptualized the study and researched the data. D.S.G. researched the data. C.A.O.V researched the data. F.J.G.M. conceptualized the study and researched the data. R.O.M.C conceptualized the study and researched the data. J.J.C.D conceptualized the study and researched the data. R.F.G.B. conceptualized the study and researched the data. P.P.S. wrote the manuscript and reviewed/edited the manuscript. C.C.C. wrote the manuscript and reviewed/edited the manuscript. M.A.S.M. researched the data. S.G.C.H. researched the data. A.L.S.N. researched the data. E.S.C. researched the data.

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Conflict of interest

The authors declare no conflict interests.

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