

Effect of Baseline HbA1c and Inpatient Glycemic Control on Mortality and Organ Dysfunction among Patients with Diabetes Mellitus Hospitalized for COVID-19: A Multicenter Retrospective Cohort Study

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Abstract

Background. Individuals with diabetes mellitus (DM) show increased susceptibility to COVID-19 infection with higher risk for severe disease and mortality.

Objectives. We investigated whether glycemic-related factors may affect the outcomes of patients with DM hospitalized due to COVID-19.

Methodology. This is a multicenter retrospective cohort study under the initiative of the Philippine College of Endocrinology, Diabetes, and Metabolism involving eight training hospitals in the Philippines from January 2021 to January 2022. Patients with DM hospitalized due to COVID-19 were included. Univariable and multivariable analyses were done to determine whether baseline glycemic control based on glycosylated hemoglobin (HbA1c) and inpatient glycemic control based on capillary blood glucose are associated with composite poor clinical outcome of mortality and end-organ dysfunction.

Results. Among 1,093 patients, 54% had HbA1c >7%. Critical COVID-19 disease was greater in patients with poor baseline glycemic control (28.43% vs 19.72%, $p = 0.001$) and poor inpatient glycemic control (25.7% vs 12.64%, $p < 0.001$). Both poor baseline glycemic (AOR 1.41, $p = 0.017$) and poor inpatient glycemic control (AOR 2.6, $p < 0.001$) were associated with composite poor clinical outcome of mortality and end-organ dysfunction after adjusting for each other, but lost significance after adjusting for age, COVID-19 severity, and presence of comorbidities. COVID-19 severity had the greatest association with composite poor clinical outcome after adjusting for all other variables. HbA1c >7% increased the odds of poor inpatient control (OR = 3.10, 95% CI: 2.32–4.17, $p < 0.001$), even after adjusting for steroid use.

Conclusion. COVID-19 severity had the greatest impact and is the only variable with a statistically significant association with composite poor clinical outcomes after adjusting for all other variables. Poor glycemic control on admission and during hospitalization were associated with more severe COVID-19, although they did not directly impact clinical outcomes. Measures to optimize glycemic control both in the long term and during hospitalization should be considered to prevent severe COVID-19, hence improving clinical outcomes and survival.

Key words: COVID-19, diabetes mellitus, glycemic control, mortality

INTRODUCTION

Diabetes mellitus (DM) is prevalent among Coronavirus disease 2019 (COVID-19) patients who develop Acute Respiratory Distress Syndrome (ARDS) and disease progression.¹ Patients with DM were found to have a two-fold increased risk of mortality and three-fold increased risk of severe disease due to COVID-19.² A retrospective observational study in the United States of America (USA) revealed that patients with DM or uncontrolled hyperglycemia >180 mg/dL have a four-fold higher mortality and longer hospital stay.³ In contrast, the CORONADO study showed that glycosylated hemoglobin (HbA1c), presence of DM complications, age, and use of glucose-lowering medications were not associated with poor outcomes.⁴

The first cases of COVID-19 in the Philippines were reported in January 2020, involving Chinese nationals who traveled from Wuhan.⁵ Local community transmission was confirmed in March 2020, leading to the implementation of Enhanced Community Quarantine in Luzon and eventually nationwide.⁶ By January 2022, the Philippines reported 3,242,374 cases with 52,929 deaths (1.6% mortality).⁷

The Inter-Agency Task Force for the Management of Emerging Infectious Diseases (IATF-EID) and the National Task Force against COVID-19 devised the National Action Plan Against COVID-19.⁸ Case detection and management were guided by the Unified COVID-19 Algorithms that were regularly released by the Healthcare Professionals Alliance Against COVID-19.⁹ Roll-out of COVID-19 vaccination started in March 2021, with a total of 55,093,313 doses administered as of January 2022, representing 64.9% of the eligible population.⁷

Recent reports describe the relationship between DM and COVID-19 to be syndemic, wherein two or more co-occurring diseases amplify each other synergistically.¹⁰ This study aimed to investigate whether glycemic-related factors affect the prognosis of patients with DM hospitalized for COVID-19. The relationship of baseline glycemic control and inpatient glycemic control with severe disease, death from any cause, and occurrence of new or worsened organ dysfunction were investigated. Identification of risk factors contributing to life-threatening COVID-19 infection will allow us to formulate strategies to alleviate morbidity and mortality in this vulnerable population and guide us in the management of patients with DM during the pandemic and beyond.

METHODOLOGY

Study design and setting

This is a multicenter retrospective cohort study under the initiative of the Philippine College of Endocrinology, Diabetes and Metabolism (PCEDM) involving eight training hospitals in the Philippines. This study was carried

out in accordance with the Declaration of Helsinki, Good Clinical Practice, and the National Ethical Guidelines for Health and Health-Related Research 2017. The study was approved by the research ethics committee of the different institutions: University of Santo Tomas Hospital Research Ethics Committee (Manila City, Metro Manila; REC-2021-04-061-OO-CR), Makati Medical Center Institutional Review Board (Makati City, Metro Manila; MMCIRB 2021-048), St. Luke's Medical Center Quezon City Institutional Review Board (Quezon City, Metro Manila; SL-21132), The Medical City Institutional Review Board (Pasig City, Metro Manila; GCS MED 2021-059), Chinese General Hospital and Medical Center Research Ethics Review Board (Manila City, Metro Manila; RERB 2021-F-18), Chong Hua Hospital Institutional Review Board (Cebu City, Cebu; 3921-04), East Avenue Medical Center Institutional Ethics Review Board (Manila City, Metro Manila; EAMC IERB 2021-58), and St. Luke's Medical Center Global City Institutional Review Board (Taguig City, Metro Manila; SL-21187). All institutions involved are located in urban areas, with seven hospitals in the National Capitol Region and one hospital in the Central Visayas Region. Management of COVID-19 in these hospitals were guided by the latest Unified COVID-19 Algorithms.⁹

Study participants

Individuals aged 18 years or older diagnosed with either DM type 1 or DM type 2 who were hospitalized due to COVID-19 in the eight participating hospitals from January 1, 2021 to January 31, 2022 were included. Diagnosis of COVID-19 was confirmed through reverse transcriptase polymerase chain reaction (rt-PCR) test for SARS-COV2. Diagnosis of DM was defined by the presence of at least one criterion: 1) fasting blood sugar of ≥ 126 mg/dL, a 2-hour postprandial blood glucose of ≥ 200 mg/dL during a 75 g oral glucose tolerance test, or a random blood sugar ≥ 200 mg/dL with classic symptoms of hyperglycemia or hyperglycemic crisis¹¹ at any time prior to admission, 2) an HbA1c $\geq 6.5\%$ ¹¹ at any point prior to or during admission, 3) personal history of DM, and 4) history of intake of glucose-lowering medications. Patients fulfilling any of the following were excluded: 1) pregnant women with gestational or overt DM, 2) patients deemed eligible for discharge less than 24 hours from arrival but stayed in the hospital for an extended period for other reasons, 3) patients who died less than 24 hours from arrival at the hospital, and 4) individuals with unknown outcomes (including those that were still admitted or were transferred to another hospital) at the conclusion of the study. These patients were excluded to ensure that complete data on inpatient glycemic control and outcomes will be available.

Sample size

This study required a minimum sample of $n = 956$ to detect a small effect size (OR=1.25) with 80% power and a significance level of 0.05 (two-tailed), assuming a baseline outcome probability of 0.3 and an R^2 of 0.2. The chosen OR

corresponds to a small effect size, consistent with guidelines indicating odds ratios less than 1.5 require larger samples for detection.¹² A conservative baseline probability was selected to ensure generalizability across multiple outcomes. R^2 was set to reflect minimal variance from covariates other than glycemic control, recognizing differences in interpreting R^2 in logistic regression compared to linear regression.^{13,14}

Study procedure

Study site investigators were invited to participate to facilitate data collection in eight training hospitals. Medical records were reviewed and data were extracted from hospital charts using standardized data collection forms (DCF). Data management was supervised by a biostatistician.

Definition of study variables

Baseline glycemic control was defined using the HbA1c level recorded at admission or within three months prior to admission. In accordance with the American Diabetes Association guidelines, good baseline glycemic control was defined as HbA1c $\leq 7\%$, while any HbA1c $> 7\%$ was classified as poor baseline glycemic control.¹⁵ At least three point-of-care capillary blood glucose (CBG) measurements per day were collected to calculate the following: (a) the proportion of patient-days with severe hyperglycemia (CBG ≥ 300 mg/dL), (b) the proportion of patient-days with hypoglycemia (CBG ≤ 70 mg/dL), and (c) the proportion of patient-days with mean CBG within the target range 140 to 180 mg/dL. Good inpatient glycemic control was defined as $\geq 85\%$ of patient-days with mean CBG levels between 140 to 180 mg/dL, while poor inpatient glycemic control was defined as $> 15\%$ of patient-days outside the target range.^{15,16}

BMI was categorized according to the World Health Organization (WHO) Asia-Pacific classification.¹⁷ Smoking history was defined as having smoked at least 100 cigarettes in their entire life. Initial vital signs, laboratory examinations, quick sequential organ failure assessment (qSOFA),¹⁸ and all interventions administered in the hospital were collected. Potential confounders such as age, gender, pre-existing comorbidities, duration of DM, and medication intake were collected. The use of systemic corticosteroids and insulin were also analyzed to decrease confounding bias. Possible effect modifiers such as BMI and severity of COVID-19 were also considered. Severity of COVID-19 was classified according to WHO guidelines.¹⁹

Study outcomes

Primary outcome measure is composite poor clinical outcome, defined as the composite of death from any cause and new/worsened organ dysfunction characterized by at least one of the following: respiratory decompensation requiring non-invasive or invasive ventilation; congestive heart failure; requirement for vasopressors, inotropes, or

mechanical circulatory support; ventricular tachycardia or fibrillation lasting at least 30 seconds associated with hemodynamic instability or pulseless electrical activity; resuscitated cardiac arrest; or initiation of renal replacement therapy (RRT).

Secondary outcome measures included overall and in-hospital mortality, requirement for invasive mechanical ventilation, and requirement for intensive care unit (ICU) admission.

Statistical analysis

Descriptive statistics was used to summarize demographic and clinical characteristics cohort. Frequency and proportion were used for categorical variables, while median with interquartile range (IQR) were used for non-normally distributed continuous variables. Mann-Whitney U test and Fisher's Exact/Chi-square test were applied to determine the difference of rank and frequency, respectively, between patients with poor versus good baseline glycemic control and between patients with poor versus good inpatient glycemic control.

To determine the association of baseline glycemic control and inpatient glycemic control with patient outcomes, OR and the corresponding 95% confidence interval (CI) were calculated in a univariable model using unadjusted glycemic control variables, a glycemic control model where baseline glycemic control and inpatient glycemic control variables were adjusted for each other, and a multivariable model where glycemic control variables were adjusted for each other, age, COVID-19 severity, and comorbidities. Age was considered a confounder since older patients are generally at higher risk for severe outcomes from COVID-19 and may have complex health issues affecting their glucose control. Severity of COVID-19 was also considered a confounder since it can directly impact patient outcomes such as mortality and need for intensive care. The number of comorbidities was also considered, since patients with multiple comorbidities may experience more complications and worse prognosis regardless of glycemic control.

Chi-square test was used to analyze the independence of baseline and inpatient glycemic control. All statistical tests were two-tailed tests. Shapiro-Wilk test was used to test the normality of continuous variables. Missing values were neither replaced nor estimated. Null hypotheses were rejected at 0.05 α -level of significance. STATA 13.1 (College Station, TX, USA) and R 4.2.2 (The R Foundation) were used for data analysis.

RESULTS

A total of 1,093 patients with DM hospitalized for confirmed COVID-19 were included in the study. Sixty-three patients were excluded: 4 patients due to pregnancy, 18 patients due to unknown outcome, and 41 patients due to incomplete data.

Table 1 shows the clinical characteristics of the study population. Upon admission, 54% (n = 591) had poor baseline glycemic control (HbA1c >7%). Mean age was 60.83 years (SD ± 14.6), with 53.89% being males. There were no significant differences in BMI (median 25.59 kg/m², IQR: 23.3 kg/m² to 28.7 kg/m²) between the subgroups. However, in terms of BMI categories, there were more patients with BMI <18.5 kg/m² and BMI ≥30 kg/m² in the good baseline glycemic control group (p = 0.003) and good inpatient glycemic control group (p = 0.001) than the poor control group.

Presence of hypertension (75.1% vs 65.48%, p = 0.001), chronic kidney disease (CKD) (12.5% vs 7.78%, p = 0.011), active malignancy (4.18% vs 1.35%, p = 0.004), diabetic retinopathy (1.79% vs 0%, p = 0.001), and cerebrovascular disease (CVD) (9.96% vs 7.11%, p = 0.09) was significantly higher among patients with good baseline glycemic control. Presence of 3 or more comorbidities were more common in the good baseline glycemic control group (p <0.001) and good inpatient glycemic control group (p = 0.009) than the poorly controlled groups.

In terms of COVID-19 severity, majority presented with moderate disease (39.98%), followed by severe (29.92%) and critical (24.43%) disease. Critical disease was greater in patients with poor baseline glycemic control (28.43% vs 19.72%, p = 0.001) and poor inpatient glycemic control (25.7% vs 12.64%, p <0.001). Likewise, the incidence of ARDS, septic shock, and ICU admission were significantly higher in those with poor baseline and poor inpatient glycemic control. qSOFA scores of 2 or higher were more common in patients with poor baseline glycemic control (7.82% vs 4.9, p <0.001) and poor inpatient glycemic control (7.06% vs 1.88%, p <0.001).

Highest FiO₂ requirements were significantly greater in those poor baseline glycemic control (median 44, IQR 28-100 vs 49, IQR 21-90, p <0.001) and poor inpatient glycemic control (median 44, IQR 28 to 100 vs 28, IQR 21 to 52, p <0.001). Initial PF ratio was significantly lower in patients with poor baseline glycemic control (median 262.43, IQR 147-366 vs 323, IQR 207- 400, p <0.001) and poor inpatient glycemic control (275, IQR 160-364 vs 357, IQR 262-414, p <0.001). Lowest PF ratio throughout admission was also significantly lower in patients with poor baseline glycemic control (median 213, IQR 100-334 vs 293, IQR 147-370, p <0.001) and poor inpatient glycemic control (median 216, IQR 100-329 vs 300, IQR 200-400, p <0.001).

Table 2 presents the interventions and medications that were administered to patients. Intravenous corticosteroid use was significantly higher in patients with poor baseline glycemic control (95.17% vs 93.94%, p <0.001) and poor inpatient glycemic control (94.36% vs 93.72%, p <0.001). Consequently, these groups also had greater episodes of steroid-induced hyperglycemia and required significantly higher levels of insulin. In addition, a higher proportion of patients with poor baseline and inpatient glycemic control

were given three or more antibiotics, anticoagulants, bronchodilators, inotropes, Tocilizumab, oxygen support, and hemoperfusion as part of their COVID-19 management. There were no significant differences in the requirement for RRT, prone positioning, and convalescent plasma therapy between the subgroups.

Patient outcomes are summarized in Table 3. Composite poor clinical outcome was more common in patients with poor baseline glycemic control (39.26% vs 25.1%, p <0.001) and poor inpatient glycemic control (35.07% vs 15.99%, p <0.001). Requirement for mechanical ventilation and ICU admission were also increased in patients with poor baseline glycemic control and poor inpatient glycemic control. Overall mortality was higher in patients with poor baseline glycemic control (19.8% vs 11.55%, p <0.001) and poor inpatient glycemic control (15.66% vs 7.06%, p <0.001). A similar trend was seen for in-hospital mortality, being higher in patients with poor baseline glycemic control (16.75% vs 11.55%, p = 0.015) and poor inpatient glycemic control (14.73% vs 6.69%, p = 0.001).

Tables 4 shows the relationship between glycemic control and adverse clinical outcomes in univariable and multivariable models. Poor baseline glycemic control confers increased risk (Crude OR (COR) 1.93, 95% CI 1.49-2.51, p <0.001) for composite poor clinical outcome, remaining significant after adjusting for glycemic control (AOR 1.41, 95% CI 1.07-1.87, p = 0.017), but lost significance after adjusting for age, COVID-19 severity, and number of comorbidities (AOR 1.02, 95% CI 0.66-1.58, p = 0.934). ICU admission, mechanical ventilation, and ICU admission were significantly increased in patients with poor baseline glycemic control in the univariable model but these trends were not significant in the glycemic control model and multivariable model.

Poor inpatient glycemic control was significantly associated with increased composite poor clinical outcome (COR 2.84, 95% CI 2.00-4.11, p <0.001), overall mortality (COR 2.44, 95% CI 1.51-4.17, p <0.001), in-hospital mortality (COR 2.41, 95% CI 1.47-4.17, p <0.001), mechanical ventilation (COR 2.76, 95% CI 1.85-4.24, p <0.001), and ICU admission (COR 3.02, 95% CI 1.90-5.08, p <0.001), remaining significant after adjusting for glycemic control. All these trends became non-significant after adjusting for age, COVID-19 severity, and number of comorbidities.

The association between baseline glycemic control and in-patient glycemic control was significant ($\chi^2 = 58.278$, p <0.001) (Supplementary Table 1). Logistic regression showed that poor baseline control increased the odds of poor inpatient control (OR = 3.10, 95% CI: 2.32–4.17, p <0.001), which remained significant after adjusting for steroid use (OR = 3.00, 95% CI: 2.23–4.06, p <0.001) (Table 5).

Supplementary Table 2 summarizes presenting symptoms and glucose-controlling medications administered. Comparison of time to reach composite poor clinical outcome

Table 1. Clinical characteristics of patients with DM hospitalized due to COVID-19

Characteristics	Total (n = 1093)	Baseline glycemic control		P-value	Inpatient glycemic control		P-value
		HbA1c >7% (n = 591, 54%)	HbA1c ≤7% (n = 502, 46%)		Poor control (n = 747, 74%)	Good control (n = 269, 27%)	
		Frequency (%); Mean ± SD; Median (IQR)			Frequency (%); Mean ± SD; Median (IQR)		
Age, years	60.82 ± 14.6	60.85 ± 14.91	60.77 ± 14.09	0.941	61.18 ± 14.16	58.83 ± 15.31	0.084
Sex				0.429			0.943
Male	589 (53.89)	325 (54.99)	264 (52.59)		402 (53.82)	144 (53.53)	
Female	504 (46.11)	266 (45.01)	238 (47.41)		345 (46.18)	125 (46.47)	
Height, cm	162 (157 to 168)	162 (157 to 168)	162 (157 to 168)	0.762	162 (157 to 168)	162 (156 to 168)	0.450
Weight, kg	68 (60 to 77)	69 (60 to 76)	68 (59 to 79)	0.954	68 (60 to 77)	68 (59 to 79)	0.882
Body Mass Index, kg/m²	25.59 (23.3 to 28.7)	25.59 (23.4 to 28.3)	25.62 (22.9 to 29.1)	0.815	25.71 (23.4 to 28.4)	25.59 (22.9 to 29.6)	0.841
BMI category				0.003			0.001
Underweight (<18.5)	14 (1.46)	3 (0.56)	11 (2.61)		6 (0.93)	7 (2.72)	
Normal (18.5 to 24.9)	414 (43.08)	235 (43.6)	179 (42.42)		277 (43.15)	106 (41.25)	
Overweight (25 to 29.9)	366 (167)	221 (41)	145 (34.36)		262 (40.81)	83 (32.3)	
Obese (≥30)	167 (17.38)	80 (14.84)	87 (20.62)		97 (15.11)	61 (23.74)	
Smoking status				0.455			0.036
Never smoker	927 (84.81)	508 (85.86)	419 (83.47)		644 (86.21)	217 (80.67)	
Previous smoker	119 (10.89)	61 (10.32)	58 (11.55)		71 (9.5)	41 (15.24)	
Current smoker	47 (4.3)	22 (3.72)	25 (4.98)		43 (4.28)	11 (4.09)	
Number of pack years	1 (1 to 2)	1 (0.5 to 2)	1 (1 to 3)	0.112	3 (1 to 20)	1 (1 to 5)	0.008
Duration of smoking, years	20 (10 to 36)	20 (10 to 30)	21 (15 to 40)	0.195	20 (10 to 22)	20 (10 to 36)	0.625
Co-morbid condition							
Hypertension	764 (69.9)	287 (65.48)	377 (75.1)	0.001	519 (69.48)	195 (72.49)	0.354
Ischemic Heart Disease	118 (10.80)	61 (10.32)	57 (11.35)	0.625	85 (11.38)	28 (10.41)	0.735
Chronic Kidney Disease	109 (9.97)	46 (7.78)	63 (12.5)	0.011	69 (9.24)	34 (12.64)	0.126
Cerebrovascular Disease	93 (9.51)	43 (7.28)	50 (9.96)	0.128	66 (8.84)	20 (7.43)	0.525
Chronic Respiratory Disease	68 (6.22)	23 (5.75)	34 (6.77)	0.531	39 (5.22)	25 (9.29)	0.027
Heart Failure	40 (3.66)	25 (4.23)	15 (2.99)	0.333	28 (3.75)	7 (2.6)	0.441
Active Malignancy	29 (2.65)	8 (1.35)	21 (4.18)	0.004	14 (1.87)	11 (4.09)	0.063
COVID vaccination	18 (1.65)	11 (1.86)	7 (1.39)	0.637	13 (1.74)	4 (1.49)	1.000
Chronic Liver Disease	15 (1.37)	6 (1.02)	9 (1.79)	0.305	12 (1.61)	1 (0.37)	0.203
Immunodeficient State	9 (0.82)	3 (0.51)	6 (1.2)	0.315	7 (0.94)	1 (0.37)	0.689
Others ¹	148 (13.54)	70 (11.84)	78 (15.54)	0.077	82 (10.98)	58 (21.56)	<0.001
Number of co-morbid conditions				<0.001			0.009
None	249 (22.78)	159 (26.9)	90 (17.93)		175 (23.43)	51 (18.96)	
1 to 2	714 (65.32)	380 (64.3)	334 (66.53)		495 (66.27)	172 (63.94)	
3 or more	130 (11.89)	52 (8.8)	78 (15.54)		77 (10.31)	46 (17.1)	
Duration of diabetes, years	10 (5 to 15)	9 (5 to 14)	10 (4 to 15)	0.457	8 (4 to 12)	7 (3 to 13)	0.002
Type of Diabetes				0.667			0.612
Type 1 Diabetes mellitus	5 (0.46)	2 (0.34)	3 (0.60)		3 (0.4)	2 (0.75)	
Type 2 Diabetes mellitus	1085 (99.54)	587 (99.66)	498 (99.4)		744 (99.6)	265 (99.25)	
Microvascular complications of diabetes							
Diabetic nephropathy	170 (15.55)	76 (12.86)	94 (18.73)	0.009	120 (16.06)	37 (13.75)	0.431
Diabetic neuropathy	59 (5.4)	31 (5.25)	28 (5.58)	0.893	46 (6.16)	11 (4.09)	0.279
Diabetic retinopathy	9 (0.82)	0	9 (1.79)	0.001	8 (1.07)	1 (0.37)	0.459
Macrovascular complications of diabetes							
Ischemic heart disease	121 (11.07)	62 (10.49)	59 (11.75)	0.507	89 (11.91)	26 (9.67)	0.318
Cerebrovascular disease	92 (8.42)	42 (7.11)	50 (9.96)	0.090	66 (8.84)	21 (7.81)	0.605
Peripheral arterial disease	23 (2.1)	15 (2.54)	8 (1.59)	0.278	17 (2.28)	6 (2.23)	0.966
Severity of COVID-19				0.001			<0.001
Mild disease	73 (6.68)	28 (4.74)	45 (8.96)		35 (4.69)	38 (14.13)	
Moderate disease	426 (38.98)	226 (39.24)	200 (39.84)		278 (37.22)	133 (49.44)	
Severe disease	327 (29.92)	169 (28.6)	158 (31.47)		242 (32.4)	64 (23.79)	
Critical disease	267 (24.43)	168 (28.43)	99 (19.72)		192 (25.7)	34 (12.64)	
Incidence of hyperglycemic crisis	32 (3.11)	24 (4.06)	10 (1.99)	0.055	23 (3.08)	1 (0.37)	0.009
DKA	16 (66.67)	11 (64.71)	5 (71.43)	1.000	11 (64.71)	1 (100)	1.000
HHS	8 (33.33)	6 (35.29)	2 (28.57)		6 (35.29)	0	
ARDS	287 (26.26)	181 (30.63)	106 (21.12)	<0.001	193 (25.84)	48 (17.84)	0.003
Mild ARDS	33 (11.5)	14 (7.73)	19 (17.92)	0.025	15 (7.77)	17 (35.42)	<0.001
Moderate ARDS	84 (29.27)	58 (32.04)	26 (24.53)		61 (31.61)	10 (20.83)	
Severe ARDS	170 (59.23)	109 (60.22)	61 (57.55)		117 (60.62)	21 (43.75)	
Sepsis	254 (23.24)	140 (23.69)	114 (22.71)	0.702	193 (25.84)	41 (15.24)	<0.001
Septic Shock	163 (14.91)	112 (18.95)	51 (10.16)	<0.001	113 (15.13)	18 (6.69)	<0.001
ICU Admission	194 (17.75)	129 (21.83)	65 (12.95)	<0.001	146 (19.54)	20 (7.43)	<0.001
Vital signs on admission							
Temperature	36.8 (36.5 to 37.5)	36.8 (36.5 to 37.6)	36.8 (36.5 to 37.3)	0.001	36.8 (36.5 to 37.6)	36.9 (36.5 to 37.5)	0.828
O₂ saturation	96 (94 to 98)	96 (93 to 98)	96 (94 to 98)	<0.001	96 (94 to 98)	97 (95 to 98)	<0.001
Systolic blood pressure, mmHg	120 (110 to 136)	120 (110 to 137)	122.5 (110 to 133)	0.525	120 (110 to 140)	120 (110 to 130)	0.997
Diastolic blood pressure, mmHg	80 (70 to 80)	70 (70 to 80)	80 (70 to 80)	0.042	73 (70 to 80)	80 (70 to 80)	0.016

Table 1. Clinical characteristics of patients with DM hospitalized due to COVID-19 (continued)

Characteristics	Total (n = 1093)	Baseline glycemic control		P-value	Inpatient glycemic control		P-value
		HbA1c >7% (n = 591, 54%)	HbA1c ≤7% (n = 502, 46%)		Poor control (n = 747, 74%)	Good control (n = 269, 27%)	
		Frequency (%); Mean ± SD; Median (IQR)			Frequency (%); Mean ± SD; Median (IQR)		
qSOFA				<0.001			<0.001
0	495 (45.92)	215 (36.56)	280 (57.14)		297 (40.3)	178 (66.92)	
1	513 (47.59)	327 (55.61)	186 (37.96)		388 (52.65)	83 (31.2)	
2	64 (5.94)	43 (7.31)	21 (4.29)		47 (6.38)	5 (1.88)	
3	6 (0.56)	3 (0.51)	3 (0.61)		5 (0.68)	0	
Heart rate, beats/minute				<0.001			0.022
<60	88 (78 to 100)	90 (80 to 105)	85 (77 to 98)		88 (79 to 102)	87 (76 to 98)	
60 to 100	25 (2.3)	10 (1.7)	15 (3)	<0.001	14 (1.88)	10 (3.76)	0.013
>100	796 (73.16)	405 (68.88)	391 (78.2)		537 (72.08)	207 (77.82)	
	267 (24.54)	173 (29.42)	94 (18.8)		194 (26.04)	49 (18.42)	
Respiratory rate, breaths/minute				<0.001			<0.001
≤30	22 (20 to 25)	23 (20 to 26)	21 (20 to 24)		22 (20 to 26)	20 (20 to 22)	
>30	1015 (93.12)	533 (90.19)	482 (96.59)	<0.001	687 (92.34)	258 (95.91)	0.047
	75 (6.88)	58 (9.81)	17 (3.41)		57 (7.66)	11 (4.09)	
Admission CBG Result	165 (121 to 230)	188 (139 to 259)	140 (111 to 189)	<0.001	174 (127 to 243)	139 (113 to 188)	<0.001
HbA1c	7.4 (6.5 to 9.5)	8.5 (7.4 to 10.7)	6.5 (5.98 to 6.89)	<0.001	7.6 (6.8 to 10)	6.7 (6.1 to 7.5)	<0.001
eGFR (ml/min)	77 (52 to 99)	78 (54 to 101)	77 (49 to 97)	0.142	77 (51 to 99)	82 (56 to 99)	0.414
eGFR category				0.025			0.137
<15	59 (5.72)	22 (3.85)	37 (8.04)		35 (5.05)	21 (7.98)	
15-29	52 (5.04)	26 (4.55)	26 (5.65)		37 (5.34)	11 (4.18)	
30-59	210 (20.37)	127 (22.24)	83 (18.04)		150 (21.65)	42 (15.97)	
60-89	320 (31.04)	174 (30.47)	146 (31.74)		213 (30.74)	82 (31.18)	
>90	390 (37.83)	222 (38.88)	168 (36.52)		258 (37.23)	107 (40.68)	
Hemoglobin (g/L)	13.2 (12.1 to 14.4)	13.4 (12.4 to 14.6)	13.1 (11.7 to 14.3)	<0.001	13.2 (12.1 to 14.4)	13 (12 to 14.7)	0.625
Initial troponin (n = 378)	0.025 (0.006 to 1.12)	0.031 (0.006 to 10.2)	0.024 (0.007 to 0.34)	0.113	0.03 (0.008 to 2.9)	0.011 (0.004 to 0.26)	<0.001
Repeat troponin (n = 21)	66.9 (15.2 to 471.3)	66.9 (21.7 to 471.3)	44.4 (0.03 to 202)	0.392	73.05 (24.35 to 336)	0.016 (0.004 to 353)	0.089
Ejection fraction (n = 134)	61 (51 to 66)	60.4 (49 to 66)	61 (55 to 66)	0.258	60 (48.5 to 66)	61.2 (56 to 66)	0.285
PaO₂/FiO₂ ratio (n = 881)	296 (170 to 385)	262.43 (147 to 366)	323 (207 to 400)	<0.001	275 (160 to 364)	357 (262 to 414)	<0.001
Highest FiO₂ requirement	40 (24 to 100)	44 (28 to 100)	49 (21 to 90)	<0.001	44 (28 to 100)	28 (21 to 52)	<0.001
Lowest PF ratio (n = 776)	270 (113 to 353)	213 (100 to 334)	293 (147 to 370)	<0.001	216 (100 to 329)	300 (200 to 400)	<0.001

Table 2. Interventions given to patients with DM hospitalized due to COVID-19

Characteristics	Total (n = 1093)	Baseline glycemic control		P-value	Inpatient glycemic control		P-value
		HbA1c >7% (n = 591, 54%)	HbA1c >7% (n = 502, 46%)		Poor control (n = 747, 74%)	Good control (n = 269, 27%)	
		Frequency (%); Median (IQR)			Frequency (%); Median (IQR)		
Steroid induced hyperglycemia	832 (91.13)	491 (94.79)	341 (86.33)	<0.001	614 (93.6)	154 (81.05)	<0.001
Highest total daily insulin dose (units/kg/day) (n=782)	0.8 (0.47 to 1.2)	0.95 (0.63 to 1.3)	0.56 (0.32 to 0.89)	<0.001	1.11 (0.8 to 1.34)	0.4 (0.2 to 0.63)	<0.001
Antibiotics	935 (85.54)	543 (91.88)	392 (78.09)	<0.001	668 (89.42)	199 (73.98)	<0.001
Anticoagulants	905 (82.8)	506 (85.62)	399 (79.48)	0.007	637 (85.27)	201 (74.72)	<0.001
Antiviral	877 (80.24)	499 (84.43)	378 (75.3)	<0.001	592 (79.25)	220 (81.78)	0.374
Systematic corticosteroids	874 (79.96)	499 (84.43)	375 (74.7)	<0.001	640 (85.68)	169 (62.83)	<0.001
Inhaled bronchodilators	361 (33.03)	233 (39.42)	128 (25.5)	<0.001	265 (35.48)	58 (21.56)	<0.001
Tocilizumab	227 (20.77)	143 (24.2)	84 (16.73)	0.002	154 (20.62)	52 (19.33)	0.653
Vasopressors/Inotropes	144 (13.17)	105 (17.77)	39 (7.77)	<0.001	98 (13.12)	17 (6.32)	0.003
Anti-fungal	124 (11.34)	84 (14.21)	40 (7.97)	0.001	94 (12.58)	9 (3.35)	<0.001
Chloroquine	39 (3.57)	19 (3.21)	20 (3.98)	0.495	26 (3.48)	10 (3.72)	0.857
IV immunoglobulin	9 (0.82)	6 (1.02)	3 (0.6)	0.446	8 (1.07)	0	0.088
Oxygen support				<0.001			<0.001
None	264 (24.15)	111 (18.78)	153 (30.48)		136 (18.21)	114 (42.38)	
Nasal cannula	323 (29.55)	161 (27.24)	162 (32.27)		231 (30.92)	82 (30.48)	
Face mask	90 (8.23)	47 (7.95)	43 (8.57)		61 (8.17)	25 (9.29)	
High flow nasal cannula	236 (21.59)	151 (25.55)	85 (16.93)		190 (25.44)	31 (11.52)	
Non-invasive ventilation	9 (0.82)	6 (1.02)	3 (0.6)		8 (1.07)	1 (0.37)	
Mechanical ventilation	171 (15.65)	115 (19.46)	56 (11.16)		121 (16.2)	16 (5.95)	
Prone positioning	832 (76.12)	457 (77.33)	375 (74.7)	0.310	575 (76.97)	199 (73.98)	0.322
Renal replacement therapy	110 (10.06)	57 (9.64)	53 (10.56)	0.617	82 (10.98)	19 (7.06)	0.066
Hemoperfusion	156 (14.27)	97 (16.41)	59 (11.75)	0.028	117 (15.66)	13 (4.83)	<0.001
Blood Transfusion	92 (8.42)	44 (7.45)	48 (9.56)	0.209	71 (9.5)	14 (5.2)	0.029
Convalescent plasma therapy	41 (3.75)	24 (4.06)	17 (3.39)	0.559	24 (3.21)	11 (4.09)	0.499

Table 3. Outcome of patients with DM hospitalized due to COVID-19

	Total (n = 1093)	Baseline glycaemic control		P-value	Inpatient glycaemic control		P-value
		HbA1c >7% (n = 591, 54%)	HbA1c ≤7% (n = 502, 46%)		Poor control (n = 747, 74%)	Good control (n = 269, 27%)	
	Frequency (%); Median (IQR)				Frequency (%); Median (IQR)		
Poor clinical outcome	358 (32.75)	232 (39.26)	125 (25.1)	<0.001	262 (35.07)	43 (15.99)	<0.001
Overall mortality	175 (16.01)	117 (19.8)	58 (11.55)	<0.001	117 (15.66)	19 (7.06)	<0.001
In-hospital mortality	157 (14.36)	99 (16.75)	58 (11.55)	0.015	110 (14.73)	18 (6.69)	0.001
Mechanical ventilation	260 (23.79)	164 (27.75)	96 (19.12)	0.001	192 (25.7)	30 (11.15)	<0.001
ICU admission	176 (16.1)	111 (18.78)	65 (12.95)	0.009	140 (18.74)	22 (8.18)	<0.001
Length of ICU stay, days	9 (5 to 17.5)	9 (5 to 15)	10 (5 to 19.5)	0.329	10 (6 to 18)	7 (4 to 13)	0.139
Length of hospital stay, days	10 (7 to 15)	11 (8 to 15)	10 (7 to 14)	0.002	11 (8 to 16)	8 (6 to 12)	<0.001

Table 4. Association of glycaemic control with patient outcomes in univariable and multivariable models

	Univariable Model ¹		Glycaemic control Model ²		Multivariable model ³	
	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Baseline glycaemic control						
Poor clinical outcome	1.93 (1.49, 2.51)	<0.001	1.41 (1.07, 1.87)	0.017	1.02 (0.66, 1.58)	0.934
Overall mortality	1.89 (1.35, 2.67)	<0.001	1.34 (0.92, 1.97)	0.130	0.94 (0.56, 1.58)	0.816
In-hospital mortality	1.54 (1.09, 2.19)	0.015	1.19 (0.81, 1.76)	0.400	0.79 (0.47, 1.33)	0.382
Mechanical ventilation	1.62 (1.22, 2.17)	<0.001	1.21 (0.89, 1.66)	0.200	0.8 (0.51, 1.26)	0.342
ICU admission	1.88 (1.36, 2.61)	<0.001	1.38 (0.98, 1.97)	0.069	0.77 (0.46, 1.3)	0.333
Inpatient glycaemic control						
Poor clinical outcome	2.84 (2.00, 4.11)	<0.001	2.60 (1.82, 3.78)	<0.001	1.36 (0.75, 2.5)	0.308
Overall mortality	2.44 (1.51, 4.17)	<0.001	2.26 (1.38, 3.89)	0.002	1.17 (0.56, 2.48)	0.680
In-hospital mortality	2.41 (1.47, 4.17)	<0.001	2.30 (1.38, 4.02)	0.002	1.23 (0.59, 2.62)	0.588
Mechanical ventilation	2.76 (1.85, 4.24)	<0.001	2.62 (1.74, 4.06)	<0.001	1.3 (0.7, 2.45)	0.417
ICU admission	3.02 (1.90, 5.08)	<0.001	2.77 (1.72, 4.69)	<0.001	1.44 (0.69, 3.02)	0.333

¹ The univariable models consider only unadjusted baseline and inpatient glycaemic

² The glycaemic control models consider only baseline and inpatient glycaemic control adjusted for each other

³ The multivariable models consider the glycaemic control variables adjusted for each other and age, COVID-19 severity and comorbidities

Table 5. Logistic regression using baseline glycaemic control to predict inpatient glycaemic control

	Unadjusted Model 1		Steroid Use Adjusted Model 2	
	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Poor baseline glycaemic control	3.10 (2.32, 4.17)	<0.001	3.00 (2.23, 4.06)	<0.001

Model 1 predicts inpatient glycaemic control using baseline glycaemic control.
Model 2 predicts inpatient glycaemic control using baseline glycaemic control adjusted for steroid use.

or discharge is summarized in Supplementary Table 3. Supplementary Table 4 presents the results of the multivariable-adjusted model predicting patient outcomes, where COVID-19 severity had the greatest association with composite poor clinical outcome (AOR 9.25, 95% CI 6.91-12.71, 95% CI), overall mortality (AOR 11.85, 95% CI 7.85-18.81, $p < 0.001$), in-hospital mortality (AOR 11.13, 95% CI 7.36-17.75, $p < 0.001$), mechanical ventilation (AOR 8.29, 95% CI 6.17-11.4, $p < 0.001$), and ICU admission (AOR 15.33, 95% CI 10.33-23.68, $p < 0.001$) after adjusting for all other variables. Presence of three or more comorbidities was significantly associated with composite poor clinical outcome (AOR 1.5, 95% CI 1.02-2.19, $p = 0.038$) and mechanical ventilation (AOR 1.62, 95% CI 1.1-2.41, $p < 0.015$) after adjusting for all other variables.

DISCUSSION

Baseline HbA1c, BMI, and comorbidities

There was greater occurrence of BMI $< 18.5 \text{ kg/m}^2$ and BMI $\geq 30 \text{ kg/m}^2$ in patients with good baseline glycaemic control in this cohort. Data from the National Health and Nutrition Examination Survey 2017–2018 showed that each 1 kg/m^2 increase in BMI resulted in 0.015% increase in HbA1c (95% CI 0.011-0.018; $p < 0.001$) in patients without DM, but was non-significantly associated with a 0.01% decrease in HbA1c in patients with DM (95% CI -0.04 -0.03; $p = 0.68$).²⁰ The loss of significance of BMI as a predictor of glycaemic control in patients with known DM may be due to the type of glucose-lowering medication administered and the complex mechanisms involved in DM.

Surprisingly, pre-existing hypertension, CKD, and CVD were more common in patients with HbA1c $< 7\%$. A possible explanation may be better health-seeking behavior in patients who were able to achieve good baseline glycaemic control, leading to more frequent physician visits and earlier diagnosis of co-morbidities.^{21,22} Recent studies suggest that HbA1c variability may be a more powerful predictor of microvascular and macrovascular complications in patients with DM. Greater HbA1c variability based on HbA1c-standard deviation, HbA1c-coefficient of variance, and HbA1c variability score were associated with increased

risks of all-cause mortality, cardiovascular events, progression to chronic kidney disease, amputation, and peripheral neuropathy.²³ A longitudinal review of HbA1c and glycemic control over the past two to three years prior to admission may provide more information on these unexpected findings.

HbA1c is an accurate and reliable measure of long-term glycemic control, but it may be affected by hemoglobinopathies and conditions that modify erythrocyte turnover.²⁴ In this study, hemoglobin levels were significantly lower in patients with HbA1c <7% (13.1 g/L vs 13.4 g/L $p < 0.001$). Patients with CKD with eGFR <30 ml/min per 1.73 m² may have lower HbA1c due to shortened erythrocyte survival from anemia, blood transfusions, erythropoiesis-stimulating agents, or iron-replacement therapies.²⁵ Other possible causes of lower hemoglobin levels in patients with HbA1c <7% were not documented in this study.

Glycemic control and COVID-19 severity

Poor baseline glycemic control is significantly associated with more severe COVID-19. In the present study, patients with DM with HbA1c >7% exhibited higher rates of critical illness, ICU admission, and invasive mechanical ventilation. This dose-dependent relationship between HbA1c and risk of severe COVID-19 was also seen in a study in Indonesia, where HbA1c level $\geq 8\%$ was associated with a 3.55-fold increased risk of severe illness (95% CI 1.68–7.52; $p = 0.001$).²⁶ Similarly, analysis of the Kaiser-Permanente database in the USA showed a linear relationship between HbA1c levels and COVID-19 severity, with OR of 2.32 (95% CI 1.90–2.84) for HbA1c 7–8.9% and 2.61 (95% CI 1.94–3.52) for HbA1c $\geq 9\%$.²⁷ Poor inpatient glycemic control was significantly associated with more severe COVID-19. This is consistent with a report that hyperglycemia even in patients without DM was associated with a lower likelihood of non-severe COVID-19 ($p < 0.02$).²⁸

Patients with poor baseline and inpatient glycemic control required more aggressive management involving corticosteroids, antibiotics, bronchodilators, anticoagulants, and inotropes. This finding is consistent with previous studies where patients with poor glycemic control are more likely to need invasive interventions.^{29–33} One study found that every 1% increase in longitudinal HbA1c over the two to three years prior to COVID-19 infection was associated with a 12% increased risk of ICU admission.³⁴

The widespread use of corticosteroids, a standard treatment in severe COVID-19 cases, further complicates glycemic control. Hyperglycemia induced by corticosteroids can lead to higher insulin dose requirement and increased risk of hyperglycemic crises. In this study, there was a significant association between poor inpatient glycemic control and hyperglycemic crisis. This concurs with another study where patients with uncontrolled DM developed DKA more often (18.18% vs 3.45%, $p = 0.0257$).³⁵ SARS-CoV-2-

mediated hyperglycemic emergencies may be due to binding of the virus to ACE2 receptors on pancreatic islets, leading to immune-mediated destruction of beta cells or beta cell death induced by inflammatory cytokines like TNF- α and IFN γ .³⁶

Risk of mortality and composite poor clinical outcome

Mortality was higher in patients with poor baseline and inpatient glycemic control in the univariable and glycemic control models. Lombardi et al., reported that patients with uncontrolled DM had a 54% higher risk of dying during COVID-19 hospitalization compared to those with normoglycemia.³⁷ In a center in Colorado, USA, odds of death and/or intubation within 7 days of admission increased by 19% for every 1 unit increase in HbA1c (OR 1.19, 95% CI 1.01 to 1.43; $p = 0.04$).³² HbA1c has been included as a variable in a predictive model for COVID-19 that had an area under the curve of 0.889 for predicting hospitalization and 0.967 for predicting mortality.³⁸

Uncontrolled hyperglycemia contributes to systemic inflammation and increases the risk of multi-organ failure. Hyperglycemia in critically ill patients, regardless of pre-existing DM, is linked to increased mortality, prolonged ICU stay, and higher resource utilization. Patients with secondary hyperglycemia and COVID-19 had a significantly higher risk of death, ICU admission, and mechanical ventilation (OR 5.47, 95% CI 1.51–19.82, $p = 0.010$).³⁹

Good inpatient glycemic control lowers the risk for composite poor clinical outcome. In a matched propensity analysis, good inpatient glycemic control had adjusted HR of 0.47 (95% CI, 0.27–0.83, $p = 0.009$) for ARDS, adjusted HR of 0.24 (95% CI, 0.08–0.71, $p = 0.010$) for acute heart injury, adjusted HR of 0.12 (95% CI, 0.01–0.96, $p = 0.046$) for acute kidney injury, and adjusted HR of 0.14 (95% CI, 0.03 - 0.60, $p = 0.008$) for 28-day mortality compared with poor inpatient glycemic control.²⁹ A study in Brazil used glycemic variability as a measure for glycemic control and found that overall mortality is increased at standard deviation ≥ 44.7 mg/dL (3.7% vs 12.6%, $p < 0.001$) and coefficient of variation $\geq 27.5\%$ (29.7% vs 12.3%, $p < 0.001$).⁴⁰

Inpatient glycemic control demonstrated a stronger association with adverse outcomes control in the univariable and glycemic control models. The syndemic relationship between DM and COVID-19 may explain why poor inpatient glycemic control has greater effect on mortality and composite primary outcome than poor baseline glycemic control. Hyperglycemia activates inflammatory pathways and increases oxidative damage, leading to increased susceptibility to COVID-19 infection with an exaggerated cytokine response, eventually leading to organ failure wherever ACE2 receptors are located.⁴¹ In turn, COVID-19 can directly decrease beta-cell insulin secretion and induce beta-cell apoptosis⁴² while corticosteroids given as part of COVID-19 treatment worsen insulin resistance, thereby further worsening hyperglycemia.

After adjusting for age, COVID-19 severity, and number of comorbidities, neither baseline glycemic control nor inpatient glycemic control were significantly associated with any patient outcome. COVID-19 severity appears to have a central role in patient prognosis, with number of comorbidities having a less significant effect. This is similar to the findings of the CORONADO study, where multivariable analysis showed that the presence of microvascular (OR 2.14, 95% CI 1.16–3.94) and macrovascular (OR 2.54, 95% CI 1.44–4.50) complications were associated with seven-day mortality, while HbA1c was not significantly associated with any outcome.⁴ This suggests that baseline glycemic control and inpatient glycemic control do not directly influence patient outcomes, but contribute indirectly via their significant effect on COVID-19 severity and comorbidities.

The strong relationship between poor baseline glycemic control and poor inpatient glycemic control, even after adjusting for corticosteroid use, suggests that adequate long-term control of DM will mitigate glycemic excursions during admission for COVID-19, hence reducing COVID severity, occurrence of end-organ dysfunction, and mortality.

Since only patients hospitalized for at least 24 hours were included, this study may be affected by selection bias. Mild COVID-19 cases may have been managed as outpatients, while the most critical cases may have expired less than 24 hours after admission. HbA1c should always be interpreted with caution since it may not be reflective of glycemic control in certain populations, such as those with CKD, anemia, and hemoglobinopathies. Longitudinal HbA1c may be a more reliable measure of long-term baseline glycemic control.

During the data collection period of this study (January 1, 2021 to January 31, 2022), the Philippines faced successive surges in COVID-19 cases linked to the emergence of COVID-19 variants. The Alpha variant (B.1.1.7) was initially detected in January 2021.⁴³ The more aggressive Delta variant (B.1.617.2) drove a major wave of moderate to severe infections from July to August 2021.⁴⁴ By late December 2021, Omicron subvariants (BA.1 and BA.2) triggered another spike in infections, with daily cases peaking in early January 2022.⁴⁵ The differences in transmissibility and disease severity of these variants may have affected the findings in our study, but were not included in our data collection since results of genome sequencing were not routinely done on all samples. Similarly, data on vaccination status were not available for some patients.

Management of COVID-19 across eight institutions were guided by the Unified COVID-19 Algorithms, which was developed by the Healthcare Professionals Alliance Against COVID-19. These algorithms were revised throughout the duration of data collection to reflect most recent evidence and policy updates: Version 1 was released on November 7, 2020,⁴⁶ Version 2 was released on June 21, 2021, and

Version 4 was released on February 21, 2022.⁹ New antiviral medications and other strategies introduced in later versions of the algorithms may have affected clinical outcomes, but this cannot be avoided due to continuous developments in COVID-19 management.

Results of this study may be applicable primarily to adult patients of Asian descent with DM with confirmed COVID-19. Differences in age, ethnicity, and underlying health conditions in other populations may limit generalizability. Variability in treatment protocols, healthcare resources, and glucose control measurement practices across regions could further impact the applicability of the results. Lastly, the temporal context of the study, reflecting a specific wave of the pandemic, raises questions about the relevance of the findings as the virus evolves, COVID-19 vaccination becomes routine, and treatment strategies change. Thus, while our findings offer valuable insights, caution is warranted in generalizing these results to diverse populations or future contexts.

CONCLUSION

COVID-19 severity had the greatest impact and is the only variable with a statistically significant association with composite poor clinical outcomes after adjusting for all other variables. Similar to other studies, poor glycemic control on admission and during hospitalization were associated with more severe COVID-19, although they did not directly impact clinical outcomes. Inpatient glycemic control had a stronger influence on clinical course, while HbA1c >7% was predictive of poor inpatient glycemic control. Strategies to optimize glycemic control both in the long term and during hospitalization should be considered to prevent severe COVID-19, hence improving clinical outcomes and survival.

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Statement of Authorship

All authors claim fulfillment of ICMJE authorship criteria.

CRedit Author Statement

MDSJ, JLN, JPMB, MS: Conceptualization, Investigation, Data curation, Resources, Writing – original draft, Writing – reviewing and editing, Visualization; **JC, RC, DE, MKAT:** Conceptualization, Investigation, Data curation, Resources, Writing – original draft; **EPP:** Conceptualization, Methodology, Writing – reviewing and editing, Visualization; **SMP:** Conceptualization, Methodology, Validation; **CC, CDP, KF, MPK, EM, CCT:** Supervision.

Data Availability Statement

Datasets are not publicly available because participants in the study did not give written consent for their data to be shared.

Author Disclosure

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SUPPLEMENTARY TABLES

Supplementary Table 1. Baseline vs inpatient glycemic control contingency table

Baseline glycemic control	Inpatient glycemic control		Total
	Good	Poor	
<i>Good</i>	182	301	483
<i>Poor</i>	87	446	533
<i>Total</i>	269	747	1016

Chi-square test: 58.278 (1 degree of freedom), p-value <0.001

Supplementary Table 2. Other Clinical Characteristics of the Cohort

	Total (n = 1093)	Baseline glycemic control		P-value	Inpatient glycemic control		P-value
		HbA1c >7% (n = 591, 54%)	HbA1c ≤7% (n = 502, 46%)		Poor control (n = 747, 74%)	Good control (n = 269, 27%)	
		Frequency (%); Median (IQR)			Frequency (%); Median (IQR)		
Presenting Symptoms							
Cough	809 (74.02)	442 (74.79)	367 (73.11)	0.534	554 (74.16)	191 (71)	0.335
Fever at home	647 (59.19)	348 (58.88)	299 (59.56)	0.853	438 (58.63)	166 (61.71)	0.386
Shortness of breath	571 (52.24)	341 (57.7)	230 (45.82)	<0.001	402 (53.82)	113 (42.01)	0.001
Fatigue	407 (37.24)	249 (42.13)	158 (31.47)	<0.001	304 (40.7)	72 (26.77)	<0.001
Sputum production	217 (19.85)	103 (17.43)	114 (22.71)	0.033	152 (20.35)	52 (19.33)	0.790
Difficulty breathing	205 (18.76)	138 (23.35)	67 (13.35)	<0.001	156 (20.88)	26 (9.67)	<0.001
Anosmia	133 (12.17)	100 (16.92)	33 (6.57)	<0.001	108 (14.46)	5 (1.86)	<0.001
Myalgia or arthralgia	125 (11.44)	76 (12.86)	49 (9.76)	0.127	76 (10.17)	41 (15.24)	0.034
Sore throat	123 (11.25)	70 (11.84)	53 (10.56)	0.565	76 (10.17)	33 (12.27)	0.358
Diarrhea	117 (10.7)	65 (11)	52 (10.36)	0.769	93 (12.45)	19 (7.06)	0.017
Nasal congestion or colds	112 (10.25)	58 (9.81)	54 (10.76)	0.618	79 (10.58)	27 (10.04)	0.907
Anorexia	84 (7.69)	59 (9.98)	25 (4.98)	0.002	71 (9.5)	9 (3.35)	0.001
Chills	64 (5.86)	46 (7.78)	18 (3.59)	0.004	59 (7.9)	0	<0.001
Headache	53 (4.85)	34 (5.75)	19 (3.78)	0.158	38 (5.09)	14 (5.2)	1.000
Nausea and vomiting	32 (2.93)	16 (2.71)	16 (3.19)	0.720	24 (3.21)	8 (2.97)	1.000
Desaturation	27 (2.47)	18 (3.05)	9 (1.79)	0.241	18 (2.41)	9 (3.35)	0.386
Dysgeusia	24 (2.2)	17 (2.88)	7 (1.39)	0.102	19 (2.54)	3 (1.12)	0.224
Others	159 (14.55)	78 (13.2)	81 (16.14)	0.170	100 (13.39)	49 (18.22)	0.055
Glucose-controlling Medications during Admission							
DPP4 Inhibitors	747 (68.34)	444 (75.13)	303 (60.36)	<0.001	543 (72.69)	157 (58.36)	<0.001
Basal Bolus	690 (63.13)	429 (72.59)	261 (51.99)	<0.001	547 (73.23)	97 (36.06)	<0.001
Metformin	303 (27.72)	170 (28.76)	133 (26.49)	0.416	194 (25.97)	95 (35.32)	0.004
PRN short/ rapid acting insulin	186 (17.02)	76 (12.86)	110 (21.91)	<0.001	107 (14.32)	67 (24.91)	<0.001
Sulfonylurea	77 (7.04)	39 (6.6)	38 (7.57)	0.555	53 (7.1)	23 (8.55)	0.421
IV Insulin drip	71 (6.5)	55 (9.31)	16 (3.19)	<0.001	58 (7.76)	2 (0.74)	<0.001
Basal only	60 (5.49)	37 (6.26)	23 (4.58)	0.234	35 (4.69)	23 (8.55)	0.031
Premixed	60 (5.49)	48 (8.12)	12 (2.39)	<0.001	54 (7.23)	0	<0.001
SGLT2 Inhibitors	38 (3.48)	17 (2.88)	21 (4.18)	0.251	21 (2.81)	12 (4.46)	0.227
Basal plus	16 (1.46)	10 (1.69)	6 (1.2)	0.616	8 (1.07)	8 (2.97)	0.043
Thiazolidinediones	13 (1.19)	3 (0.51)	10 (1.99)	0.027	8 (1.07)	5 (1.86)	0.346
GLP 1 RA	8 (0.73)	4 (0.68)	4 (0.8)	1.000	5 (0.67)	3 (1.12)	0.443
Others	11 (1.01)	5 (0.85)	6 (1.2)	0.763	9 (1.2)	2 (0.74)	0.737

Supplementary Table 3. Comparison of time to reach primary composite outcome, death, or discharge between patients with poor and good glycemic control

	Baseline glycemic control		P-value	Inpatient glycemic control		P-value
	HbA1c >7%	HbA1c ≤7%		Poor control	Good control	
Time to first occurrence of either death from any cause or new/worsened organ dysfunction, days, median (IQR)	14 (9)	13 (14)	0.407	15 (12)	11 (9)	0.019
Time to discharge, days, median (IQR)	11 (7)	10 (7)	0.002	11 (7)	8 (6)	<0.001

Supplementary Table 4. Multivariable-adjusted model predicting patient outcomes

Characteristic	Poor clinical outcome		Overall mortality		In-hospital mortality		Mechanical ventilation		ICU admission	
	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Baseline glycemic control	1.02 (0.66, 1.58)	0.934	0.94 (0.56, 1.58)	0.816	0.79 (0.47, 1.33)	0.382	0.8 (0.51, 1.26)	0.342	0.77 (0.46, 1.3)	0.333
Inpatient glycemic control	1.36 (0.75, 2.5)	0.308	1.17 (0.56, 2.48)	0.680	1.23 (0.59, 2.62)	0.588	1.3 (0.7, 2.45)	0.417	1.44 (0.69, 3.02)	0.333
Age	0.99 (0.98, 1.01)	0.424	1.02 (1, 1.04)	0.063	1.02 (1, 1.04)	0.077	1 (0.98, 1.02)	0.909	1 (0.98, 1.02)	0.782
COVID-19 severity	9.25 (6.91, 12.71)	<0.001	11.85 (7.85, 18.81)	<0.001	11.13 (7.36, 17.75)	<0.001	8.29 (6.17, 11.4)	<0.001	15.33 (10.33, 23.68)	<0.001
Comorbidities	1.5 (1.02, 2.19)	0.038	1 (0.65, 1.55)	0.988	1.03 (0.67, 1.59)	0.897	1.62 (1.1, 2.41)	<0.015	0.92 (0.59, 1.42)	0.696

P-values computed using likelihood ratio test