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# 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*

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## 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 crisis[11] at any time prior to admission, 2) an HbA1c ≥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 ≤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 ≥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$\alpha$-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/m$^2$, IQR: 23.3 kg/m$^2$ to 28.7 kg/m$^2$) between the subgroups. However, in terms of BMI categories, there were more patients with BMI <18.5 kg/m$^2$ and BMI ≥30 kg/m$^2$ 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 $FiO_2$ 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 |
| ***$O_2$ 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*** | 88 (78 to 100) | 90 (80 to 105) | 85 (77 to 98) | **<0.001** | 88 (79 to 102) | 87 (76 to 98) | **0.022** |
| <60 | 25 (2.3) | 10 (1.7) | 15 (3) | **<0.001** | 14 (1.88) | 10 (3.76) | **0.013** |
| 60 to 100 | 796 (73.16) | 405 (68.88) | 391 (78.2) | | 537 (72.08) | 207 (77.82) | |
| >100 | 267 (24.54) | 173 (29.42) | 94 (18.8) | | 194 (26.04) | 49 (18.42) | |
| ***Respiratory rate, breaths/minute*** | 22 (20 to 25) | 23 (20 to 26) | 21 (20 to 24) | **<0.001** | 22 (20 to 26) | 20 (20 to 22) | **<0.001** |
| ≤30 | 1015 (93.12) | 533 (90.19) | 482 (96.59) | **<0.001** | 687 (92.34) | 258 (95.91) | **0.047** |
| >30 | 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) | 1.3 (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 |
| ***$PaO_2/FiO_2$ 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 $FiO_2$ 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

| | 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 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) | | |
| ***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 glycemic control with patient outcomes in univariable and multivariable models

| | Univariable Model[1] | | Glycemic 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 glycemic 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 glycemic 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 glycemic

[2] The glycemic control models consider only baseline and inpatient glycemic control adjusted for each other

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

**Table 5.** Logistic regression using baseline glycemic control to predict inpatient glycemic control

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

Model 1 predicts inpatient glycemic control using baseline glycemic control.

Model 2 predicts inpatient glycemic control using baseline glycemic 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 <18.5kg/m$^2$ and BMI ≥30 kg/m$^2$ in patients with good baseline glycemic control in this cohort. Data from the National Health and Nutrition Examination Survey 2017–2018 showed that each 1kg/m2 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 glycemic 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 glycemic 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 $m^2$ 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 ≥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 ≥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-$\alpha$ and IFN$\gamma$.[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 ≥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 apoptosis[42] 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 | |
| ***Good*** | 182 | 301 | 483 |
| ***Poor*** | 87 | 446 | 533 |
| ***Total*** | 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