ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Predictors of Poor Glycemic Control and Increased Glucose Variability Among Admitted Moderate to Critical COVID-19 Patients with Type 2 Diabetes Mellitus: A Single Center Cross-sectional Study*

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Abstract

Objectives. COVID-19 exacerbates the long-standing, low-grade chronic inflammation observed in diabetes leading to heightened insulin resistance and hyperglycemia. Mortality increases with hyperglycemia and poor glycemic variability, hence, this study aims to identify the predictors associated with poor glycemic control and increased glucose variability among patients with COVID-19 and Type 2 Diabetes Mellitus (T2DM).

Methodology. A retrospective chart review of 109 patients with moderate to severe COVID-19 and T2DM admitted from March 2020 to June 2021 was done. Logistic regression was done to determine predictors for hyperglycemia and poor variability.

Results. Of the 109 patients, 78% had hyperglycemia and poor variability and 22% had no poor outcomes. Chronic kidney disease (eOR 2.83, CI [1.07-7.46], p = 0.035) was associated with increased glycemic variability. In contrast, increasing eGFR level (eOR 0.97, CI [0.96-0.99], p = 0.004) was associated with less likelihood of increased variability. Hs-CRP (eOR 1.01, CI [1.00-1.01], p = 0.011), HbA1c (eOR 1.86, CI [1.23-2.82], p = 0.003), severe COVID-19 (eOR 8.91, CI [1.77-44.94], p = 0.008) and critical COVID-19 (eOR 4.42, CI [1.65-11.75], p = 0.003) were associated with hyperglycemia. Steroid use (eOR 71.17, CI [8.53-593.54], p<0.001) showed the strongest association with hyperglycemia.

Conclusion. Potential clinical, laboratory and inflammatory profiles were identified as predictors for poor glycemic control and variability outcomes. HbA1c, hs-CRP, and COVID-19 severity are predictors of hyperglycemia. Likewise, chronic kidney disease is a predictor of increased glycemic variability.

Key words: COVID-19, type 2 diabetes, hyperglycemia, risk factors

INTRODUCTION

The Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has had a significant impact on medicine. Among COVID-19 patients with Type 2 Diabetes Mellitus (T2DM), disease severity is increased with associated higher mortality risk.[1,2] In the TurCoviDia study, 30-day mortality was increased among COVID-19 patients with T2DM. Furthermore, older age, male gender, obesity, insulin treatment, lymphopenia and pulmonary involvement on admission were independently associated with mortality.[3] In the Coronavirus SARS-CoV-2 and Diabetes Outcomes study (CORONADO), diabetes-related phenotypes were investigated to determine their association with admitted patients with COVID-19. In the same study, body mass index (BMI), not the long-term glucose control, was independently associated with the severity of COVID-19.[4] Although the exact mechanism remains unclear, the dysregulated immune and inflammatory response of the host with COVID-19 and T2DM has been implicated.[5] Among hospitalized COVID-19 patients with T2DM, COVID-19 increases the risk of poor glycemic control.

In COVID-19, inflammatory markers such as interleukin-6 (IL-6), ferritin, D-dimer, procalcitonin, high-sensitivity C-reactive peptide (hs-CRP) and lactate dehydrogenase (LDH) are used to assess disease prognosis. However, the correlation of these inflammatory markers with poor glycemic control indices – hyperglycemia, hypoglycemia

eISSN 2308-118x (Online)
Printed in the Philippines

Received: October 31, 2022. Accepted: January 25, 2023.
Published online first: June 21, 2023.
https://doi.org/10.15605/jafes.038.02.07

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* *This paper has been presented in the following conventions: 2022 ICE/AOCE/AFES – Abstract poster presentation, August 25-25, 2022, Singapore (Virtual) and 2022 SICEM – Abstract poster presentation, October 27-29, 2022, Gwangju, Korea (Virtual).*

and glycemic variability in patients with COVID-19 and T2DM are yet to be established. Optimal glycemic variability (blood glucose within 70 to 180 mg/dL) was associated with lower mortality than poorly controlled blood glucose.[6] Since poor glycemic variability is associated with increased mortality, early intensification of treatment might be needed, hence necessitating the identification of the predictors for poor glucose control and increased glucose variability. This study aimed to identify the predictors for poor glycemic control indices and increased glucose variability among patients with moderate to critical COVID-19 infection and T2DM admitted to a tertiary hospital in Manila, Philippines. In addition, this study hypothesized that the inflammatory markers including procalcitonin, hs-CRP, LDH, D-Dimer, ferritin and IL-6 are associated with poor glycemic control and increased glucose variability.

METHODOLOGY

This is a retrospective cross-sectional study involving patients admitted at the University of Santo Tomas Hospital with a diagnosis of moderate to critical COVID-19 and T2DM from March 2020 to June 2021. Medical records of all patients who were admitted were systematically reviewed. A total of 109 patients were included in the study. A minimum of 88 patients are required for this study based on a 65.18% prevalence of patients with poorly controlled blood glucose.[6] The sample was also based on an assumed 2.5 odds ratio of any significant covariates of the outcome, poor glycemic control and increased glycemic variability. This computation also accounts for a 5% level of significance and 10% desired half-width of confidence interval.[7]

Patients who met the following criteria were included in the study: 1) ≥18 years old with moderate to critical COVID-19 infection confirmed through Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) via nasopharyngeal and/or oropharyngeal swab with T2DM admitted at the University of Santo Tomas Hospital; 2) capillary blood glucose (CBG) monitoring with at least 4-point monitoring in patients feeding per orem, 6-point monitoring timed before feeding in patients on enteral nasogastric tube feeding, 6-point monitoring timed every 4 hours in patients on parenteral nutrition or continuous nasogastric tube feeding, and 6-point monitoring timed every 4 hours in patients on nothing per orem, during 72 hours of hospital stay; and 3) availability of the following laboratory tests and inflammatory markers: complete blood count (CBC) with emphasis on absolute lymphocyte count and platelet count, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum creatinine, glycosylated hemoglobin (HbA1c), high-sensitivity C-reactive protein (hs-CRP), procalcitonin, lactate dehydrogenase (LDH), serum ferritin, interleukin-6 (IL-6) and D-dimer.

Patients who met the following criteria were excluded from the study: 1) expired before the 72nd hour of hospital stay; and 2) other types of diabetes mellitus aside from T2DM including type 1 diabetes mellitus (T1DM), gestational diabetes mellitus, monogenic diabetes syndromes and disease of the exocrine pancreas.

A total of 396 charts with a diagnosis of COVID-19 were retrieved and screened for eligibility in the study. After screening, 109 patient records passed the eligibility criteria. Data were collected and reviewed retrospectively from the medical records section of the University of Santo Tomas Hospital. Medical data were recorded using a data collection form, and each patient was assigned a numerical code. Computations for glycemic control indices and glycemic variability were derived from CBG monitoring of admitted patients during their 72 hours of hospital stay. Data analysis was handled by a biostatistician. The following were the independent variables observed in the study: 1) laboratory profile including absolute lymphocyte count, platelet count, SGOT, SGPT, serum creatinine; and HbA1c; 2) inflammatory markers including hs-CRP, LDH, IL-6, serum ferritin, procalcitonin and D-dimer. Co-variates observed were as follows: 1) demographics including age, sex, weight and body mass index using the Asia-Pacific classification; 2) comorbidities including hypertension, ischemic heart disease, cerebrovascular disease, immunodeficient state, chronic kidney disease, chronic respiratory disease, chronic liver disease, chronic heart failure, active tuberculosis, active malignancy and hematologic disease; 3) steroid-induced hyperglycemia – defined as new-onset inpatient hyperglycemia above 180 mg/dL or worsening of current glycemic control above 180 mg/dL, 24 hours after initiation of corticosteroids in patient with T2DM, 4) COVID-19 disease severity including moderate, severe and critical COVID-19 and 5) hyperglycemia inpatient therapy including the use of metformin, sulfonylurea, thiazolidinediones, sodium-glucose cotransporter-2 inhibitor (SGLT2i), dipeptidyl peptidase 4 inhibitor (DPP4i), glucagon-like peptide-1 receptor agonist (GLP1 RA), multidose basal bolus insulin therapy including the total daily dose expressed in units/kg/day, basal insulin only, bolus insulin only, premixed insulin and insulin drip.

COVID-19 disease severity was defined as 1) moderate, if the patient had signs of non-severe pneumonia (e.g., fever, cough, dyspnea, or difficulty of breathing), respiratory rate 21-30 breaths/min, SpO_2 >92% on room air is present; 2) severe, if the patient had severe pneumonia or severe acute respiratory infection (fever, cough, dyspnea, respiratory rate >30 breaths/minute, severe respiratory distress or SpO_2 ≤92% on room air); and 3) critical, if the patient presented with COVID-Acute Respiratory Distress Syndrome, sepsis or septic shock.[8]

The following are the observed dependent variables: 1) glycemic control indices[9,10] including a) glucose mean defined as the average of daily glucose value computed within 72 hours of hospital stay; b) glucose maximum, minimum and 50th percentile (median) values as derived

from the daily CBG monitoring within 72 hours of hospital stay; c) the percentage of glucose values in the target range, below and above a target value wherein a range of 70 mg/dL to 180 mg/dL was set for this study;[6] d) hypoglycemia index[9,10] which represents the average of hypoglycemic values per day (lower limit of 70 mg/dL); e) hyperglycemia index[9,10] which represents the average of hyperglycemic values (upper limit of 180 mg/dL) and 2) glycemic variability[9,10] which includes standard deviation (SD) defined as the measure of dispersion of glucose values from the mean derived from CBG values within 72 hours of hospital stay and coefficient of variation (CV) with a set threshold of 36%.

Outcome measures used in this study were the glycemic control indices and glycemic variability. Poor glycemic control indices were defined as a percentage above the target range (>180 mg/dL) of ≥25%, a percentage below the target range (<70 mg/dL) of ≥4%, or both. Cut-off values were based on the International Consensus on Time in Range.[11] A study done utilizing the data from self-monitoring blood glucose showed that "points in range" was comparable to the time in range evaluated by continuous glucose monitoring.[12] A blood glucose range of 70 – 180 mg/dL was associated with markedly lower mortality compared to individuals with poorly controlled blood glucose.[6] Increased glycemic variability was defined as a CV of ≥36%. The set threshold of 36% was used to define between stable and unstable glycemia. Lower CV was associated with lower rates of hypoglycemia.[13]

Ethical consideration

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. This study (REC-2021-07-090-TF) was approved by the UST Hospital Research Ethics Committee.

Statistical analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables, median and interquartile range for non-normally distributed continuous variables and mean and SD for normally distributed continuous variables. Independent Sample T-test, Mann-Whitney U test and Fisher's Exact/ Chi-square test were used to determine the difference of mean, rank and frequency respectively, between patients with and without poor glycemic control and increased glucose variability. Estimated odds ratio and corresponding 95% confidence intervals from binary logistic regression were computed to determine significant predictors for poor glycemic control indices and increased glycemic variability. All statistical tests were two-tailed tests. Shapiro-Wilk test was used to test the normality of the 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) was used for data analysis.

RESULTS

A total of 109 patients were admitted with the diagnosis of moderate to critical COVID-19 with T2DM as a comorbidity. Among these patients, 78% developed poor glycemic control and/or increased glucose variability, while 22% had no poor outcomes. Mean age was 59 (range 47-64) years and sex distribution (male n = 62, 56.8% vs female n = 47, 43.1%) between the groups was not statistically significant. Obese body mass index (mean 28.0, range 22-34) was observed between both sexes with hypertension (n = 82, 75.2%) as the leading comorbidity. In terms of severity, 28% were classified as moderate, 19% were classified as severe and 52% were classified as critical. Steroid use was frequently observed in the poor outcome group (n = 61, 82.43%). Patients with severe and critical COVID-19 were frequently found to have poor glycemic outcomes compared to those with moderate COVID-19 (19 [22.35%], 48 [56.47%] vs 2 [8.33%], 9 [37.5%] $p = 0.009$).

In the laboratory profile of COVID-19 patients, the poor outcome group had statistically significant higher HbA1c levels (7.82 [6.96-10.28], $p = 0.002$). For the inflammatory markers, there was an increased trend in median hs-CRP in the poor outcome group compared to the other group, however, it did not reach statistical significance (116.29 [36.52-210] vs 50.38 [22.1-136.5] $p = 0.059$). The use of DPP4i and multiple basal-bolus insulin injections were more frequent in the poor outcome group. Moreover, the total daily insulin dose is higher in the poor outcome group (1 [0.6-1.3] vs 0.4 [0.1-1.1] $p = 0.034$). The clinical, demographic, laboratory, inflammatory marker and inpatient hyperglycemic therapy profiles are listed in Table 1.

In the poor outcome group, patients had higher glucose mean, glucose maximum, glucose minimum and glucose median values. Likewise, the hyperglycemia index (1.5 [0.9-2.87] vs 0.14 [0.03-0.34] $p<0.001$) and percentage above range (55 [44-73] vs 11 [10-20] $p<0.001$) was higher in the poor outcome group. Hypoglycemia was only observed in the poor outcome group, as seen in the percentage below range and hypoglycemia index. As expected, patients in the good outcome group had higher target-in-range percentages compared to the poor outcome group (100 [89.5-100] vs 46 [31-56] $p<0.001$). The glycemic control indices profile is listed in Table 2.

Hyperglycemia is frequently observed in the study population. Nonetheless, acceptable glycemic variability is observed. The patient outcomes are listed in Table 3.

COVID-19 patients on DPP4i alone were 69.71% less likely to have poor glycemic control indices. However, patients on basal-bolus insulin therapy were 10.5 times more likely to have poor glycemic control indices. For every u/kg/day increase in the patient's total daily insulin dose, the odds

Table 1. Clinical, demographic, laboratory, inflammatory markers, and inpatient hyperglycemic therapy profile among study participants (n = 109)

	Poor glycemic control and/or increased glucose variability			
	Total (n = 109)	**Yes (n = 85, 78%)**	**No (n = 24, 22%)**	***p***
	Frequency (%); Mean ± SD; Median (IQR)			
Clinical and demographic profile				
Age	59.83 ± 12.29	59.83 ± 12.15	59.79 ± 13.04	0.988
Sex				0.105
Male	62 (56.88)	52 (61.18)	10 (41.67)	
Female	47 (43.12)	33 (38.82)	14 (58.33)	
Weight, kg	75.59 ± 18.46	76.29 ± 18.19	73.26 ± 19.58	0.493
BMI, kg/m^2	28.04 ± 6.06	28.28 ± 6.03	27.21 ± 6.23	0.467
Comorbidities				
Hypertension	82 (75.23)	63 (74.12)	19 (79.17)	0.790
Chronic kidney disease	25 (22.94)	19 (22.35)	6 (25)	0.788
Ischemic heart disease	10 (9.17)	9 (10.59)	1 (4.17)	0.454
Cerebrovascular disease	10 (9.17)	7 (8.24)	3 (12.5)	0.688
Chronic respiratory disease	6 (5.5)	5 (5.88)	1 (4.17)	1.000
Chronic liver disease	3 (2.75)	3 (3.53)	0	1.000
Chronic heart failure	2 (1.83)	1 (1.18)	1 (4.17)	0.393
Immunodeficient	2 (1.83)	2 (2.35)	0	1.000
Active TB	1 (0.92)	0	1 (4.17)	0.220
Steroid use	62 (70.45)	61 (82.43)	1 (7.14)	**<0.001**
Severity of COVID-19				**0.009**
Moderate	31 (28.44)	18 (21.18)	13 (54.17)	
Severe	21 (19.27)	19 (22.35)	2 (8.33)	
Critical	57 (52.29)	48 (56.47)	9 (37.5)	
Laboratory and inflammatory markers profile				
Absolute lymphocyte Ct, cell/mm^3	1470 (1071, 1925)	1470 (1071, 1840)	1477.5 (1052, 2107)	0.611
Platelet count, 10^3/mm^3	241 (219, 291)	245 (224, 291)	226.5 (209.5, 292)	0.141
HbA1c, %	7.40 (6.79, 9.3)	7.82 (6.96, 10.28)	6.92 (6.32, 7.57)	**0.002**
SGPT, U/L	41 (28.7, 64.8)	42.1 (28.4, 65.7)	39.6 (29.1, 61.5)	0.886
SGOT, U/L	46.3 (33.2, 65.4)	46.75 (35.4, 66.2)	37.2 (26.9, 60.3)	0.255
Creatinine, mg/dL	0.94 (0.7, 1.23)	0.97 (0.72, 1.26)	0.88 (0.62, 1.16)	0.256
eGFR, ml/min/1.73m^2	80.8 (56.25, 102)	79.8 (53.6, 100.8)	87.95 (63.5, 109.5)	0.395
Procalcitonin, ng/mL	0.14 (0.7, 0.42)	0.16 (0.08, 0.44)	0.1 (0.06, 0.21)	0.102
hs-CRP, mg/L	102.12 (32.8, 185.3)	116.29 (36.52, 210)	50.38 (22.1, 136.5)	0.059
LDH, U/L	321 (244, 443)	321 (244, 464)	312.5 (229, 370)	0.215
D-Dimer, mg/L FEU	0.9 (0.5, 1.5)	0.9 (0.5, 1.6)	1.05 (0.5, 1.5)	0.662
Ferritin, ng/mL	1025 (543, 1756)	1082 (581, 2197)	721.45 (498.6, 1323)	0.215
IL-6, pg/mL	51.15 (25.38, 86.9)	62.41 (26.75, 95.5)	40.57 (24.15, 58.33)	0.142
Hyperglycemic inpatient therapy profile				
Oral Hypoglycemia agents:				
DPP4i	88 (80.73)	73 (85.88)	15 (62.5)	**0.017**
Sulfonylurea	22 (20.18)	20 (23.53)	2 (8.33)	0.150
Metformin	18 (16.51)	12 (14.12)	6 (25)	0.221
SGLT2i	7 (6.42)	5 (5.88)	2 (8.33)	0.648
Thiazolidinediones	5 (4.59)	5 (5.88)	0	0.584
Insulin Therapy:				
Basal bolus insulin therapy	61 (55.96)	58 (58.24)	3 (12.5)	**<0.001**
Insulin drip	10 (9.17)	10 (11.76)	0	0.113
Basal insulin only	9 (8.26)	5 (5.88)	4 (16.67)	0.105
Premixed Insulin	8 (7.34)	8 (9.41)	0	0.196
Bolus Only	2 (1.83)	2 (2.35)	0	1.000
Total daily insulin dose, u/kg/day	0.9 (0.5 to 1.3)	1 (0.6 to 1.3)	0.4 (0.1 to 1.1)	**0.034**

Table 2. Glycemic control profile among study participants (n = 109)

	Poor glycemic control and/or increased glucose variability			
	Total (n = 109)	**Yes (n = 85, 78%)**	**No (n = 24, 22%)**	***p***
	Median (IQR)			
Glucose mean, mg/dL	188 (153, 213)	197 (177, 230)	135.5 (126, 149.5)	**<0.001**
Glucose maximum, mg/dL	266 (231, 340)	300 (255, 353)	178.5 (157, 198.5)	**<0.001**
Glucose minimum, mg/dL	110 (90, 132)	118 (95, 137)	97.5 (83.5, 105)	**<0.001**
Glucose median, mg/dL	177 (148, 212)	190 (171, 230)	139.5 (123, 147)	**<0.001**
Percentage target in range	54 (33, 75)	46 (31, 56)	100 (89.5, 100)	**<0.001**
Percentage below range	15.5 (13.5, 36)	15.5 (13.5, 36)	-	**-**
Percentage above range	50 (36, 69)	55 (44, 73)	11 (10, 20)	**<0.001**
Hypoglycemia index	2.61 (0.02, 3.66)	2.61 (0.02, 3.66)	-	**-**
Hyperglycemia index	1.34 (0.69, 2.79)	1.5 (0.9, 2.87)	0.14 (0.03, 0.34)	**<0.001**

Table 3. Glycemic control indices and variability outcomes among study participants (n = 109)

	Frequency (%); Median (IQR)
Glycemic control indices	
Hyperglycemia; ≥25% percentage above target range	79 (72.48)
Hypoglycemia; ≥4% percentage below target range	1 (0.92)
Both hyperglycemia and hypoglycemia	2 (1.83)
Good glycemic control; >70% percentage in target range	27 (24.77)
Glycemic variability	
SD, mg/dL	50 (36, 66)
CV, %	26 (19, 34)
Glycemic variability outcome	
Poor; CV ≥36%	26 (23.85)
Good; CV <36%	83 (76.15)

of having poor glycemic control indices also increase twelvefold. For every mg/L increase in the patient's hs-CRP, the odds of having poor glycemic control indices also increased by 0.74%, and for every percent increase in the patient's HbA1c, the odds of having poor glycemic indices also increased by 86.43%. Patients on steroids were 71.2 times more likely to have poor glycemic control indices. In terms of COVID-19 severity, patients with severe COVID-19 were 8.9 times more likely to have poor glycemic control indices compared to patients with moderate COVID-19. Patients with critical COVID-19 were 4.4 times more likely to have poor glycemic control indices compared to patients with moderate COVID-19. Factors associated with poor glycemic control indices are listed in Table 4.

COVID-19 patients with chronic kidney disease were 2.8 times more likely to have increased glycemic variability. In addition, the odds of increased glycemic variability decrease by 2.11% for every ml/min/1.73m^2 increase in eGFR. For every U/L increase in SGPT, the odds of having increased glycemic variability decrease by 3.85%. Patients on thiazolidinediones were 14.9 times more likely to have increased glycemic variability. For every mg/dL increase in the patient's glucose minimum, the odds of having increased glycemic variability decrease by 4.7%. Factors associated with increased glycemic variability are listed in Table 5. The researchers failed to create a multivariate model due to low number (0 to 1) of variables left after the stepwise method from the significant variables on the univariate result.

DISCUSSION

T2DM has been described as a state of chronic low-grade inflammation and it is known that CRP, IL-1β, IL-6 and other cytokines are elevated in T2DM.[14] Upon infection with SARS-CoV-2, this preexisting chronic inflammation is further augmented leading to a heightened inflammatory response. Comorbidities including hypertension, dyslipidemia, advancing age, cardiovascular disease and obesity contribute to the ongoing inflammation which leads to hyperimmune response and increased severity of COVID-19.[2,14] Poorly controlled T2DM has been reported in several studies as a poor prognostic factor for COVID-19.[1-4] Indeed, local and international guidelines were created to address hyperglycemia in COVID-19. This retrospective study was designed to: 1) Describe the demographic characteristics, clinical and laboratory profiles, including inflammatory markers of patients with moderate to critical COVID-19 infection and T2DM; and 2) Show the correlation of the identified predictors with glycemic control and variability. This study showed that baseline HbA1c and hs-CRP are potential risk factors for hyperglycemia and poor glycemic variability. Of interest, COVID-19 severity, including severe and critical COVID-19 are predictors of hyperglycemia as well. Chronic kidney disease is likewise a predictor of poor variability. To the researcher's knowledge, this is the first study to show the association

Table 4. Factors associated with poor glycemic control among study participants (n = 109)

Parameters	Univariate		
	Estimated odds ratio	95% CI	*p*
DPP4i only	0.3029	0.1209 to 0.7586	**0.011**
Basal bolus insulin therapy	10.509	3.3132 to 33.330	**<0.001**
Total daily insulin dose, u/kg/day	12.377	1.3799 to 111.02	**0.025**
hs-CRP, mg/L	1.0074	1.0017 to 1.0130	**0.011**
HbA1c, %	1.8643	1.2340 to 2.8166	**0.003**
Steroid use	71.167	8.5331 to 593.54	**<0.001**
Severity of COVID-19			
Moderate	(reference)	-	-
Severe	8.9062	1.7654 to 44.930	**0.008**
Critical	4.4063	1.6523 to 11.750	**0.003**

Table 5. Factors associated with increased glycemic variability among study participants (n = 109)

Parameters	Univariate		
	Estimated odds ratio	95% CI	*p*
Chronic kidney disease	2.8333	1.0763 to 7.4585	**0.035**
SGPT, U/L	0.9615	0.9362 to 0.9874	**0.004**
eGFR, ml/min/1.73m^2	0.9789	0.9648 to 0.9933	**0.004**
Thiazolidinediones	14.909	1.5852 to 140.22	**0.018**
Glucose minimum, mg/dL	0.9530	0.9302 to 0.9764	**<0.001**

of clinical, laboratory, and inflammatory marker profiles to glycemic control indices and variability for patients with T2DM and COVID-19.

Among hospitalized patients, the coexistence of T2DM and COVID-19 may lead to poor blood glucose control and variability. It was observed that during the first 72 hours of admission, there was frequent hyperglycemia, low occurrence of hypoglycemia and good glycemic variability among the study population. This glycemic pattern is similar to the study of Cheng where hyperglycemia on admission was associated with disease severity in COVID-19.[2] Critical COVID-19 was frequently observed in the present study.

Patients with T2DM are in a state of low-grade chronic inflammation, and concomitant COVID-19 infection can induce high levels of cytokines including IL-6, IL1β, TNFα, MCP-1 and inducible protein-10 that confers a high degree of insulin resistance leading to hyperglycemia.[15,16] In addition, high IL-6 level, an index of hypercytokinemia, correlated with hyperglycemia and difficulties with glycemic control.[17] However, this study, did not show an association between IL-6 and hyperglycemia and glycemic variability. IL-6 is shown to be elevated both in poor and good outcome groups. Further studies with a bigger sample size should be done to further explore an association between IL-6 and hyperglycemia in COVID-19 patients.

In contrast, in a study of COVID-19 patients with T2DM, a lower incidence of elevated serum CRP has been observed among patients with well-controlled blood glucose.[6] In the same study, elevated HbA1c was observed in the poor blood glucose control group. This study showed an association between the risk of hyperglycemia and increased hs-CRP and HbA1c on admission. It may be suggested that stringent glycemic control should be observed in COVID-19 patients with elevated baseline HbA1c and hs-CRP. Other inflammatory markers including procalcitonin, LDH and D-Dimer were observed to be elevated in COVID-19 patients with T2DM.[1,2] However, these inflammatory markers were not associated with poor glycemic control and increased glycemic variability in the present study. The inflammatory markers in previous studies were used as tools for prognostication of COVID-19 severity and not as predictors for poor glycemic control and increased variability.[18,19] Further studies are needed to show the direct correlation of procalcitonin, LDH and D-dimer to glycemic control in COVID-19 patients. Although these inflammatory markers did not show an association with the studied outcomes, COVID-19 severity showed a correlation with hyperglycemia.

Laboratory profiles including absolute lymphocyte count, platelet count and SGOT did not show an association with poor glycemic control indices and increased variability. In a study by Noordam et al., the researchers analyzed the association of elevated liver enzyme concentration with glycemic variability and hyperglycemia in individuals without diabetes mellitus. In the same study, hyperglycemia is associated with elevated ALT and GGT, with the latter showing the strongest correlation. The association of AST was weaker than GGT in terms of hyperglycemia.[20] Elevated ALT, AST and GGT were not correlated with higher glycemic variability.[20] Decreased glucose disposal was probably the mechanism of hyperglycemia in patients with elevated liver enzymes.[20] In this study, patients with elevated SGPT were less likely to have poor glycemic variability, compared to the Noordam study. However, elevated SGPT and SGOT did not show an association with hyperglycemia in the present study. Noordam found that GGT is probably related to glucose metabolism as compared with SGPT and SGOT.[20] This probably explains the poor correlation of SGPT and SGOT to hyperglycemia. Further investigation is needed to prove this association.

As expected, the presence of steroid hyperglycemia showed the strongest correlation with hyperglycemia. Among the comorbidities, chronic kidney disease was associated with poor glycemic variability probably due to impaired glucose metabolism in these patients.

Elevated body mass index did not show an association with poor glycemic control indices and increased glycemic variability in the present study.

In the study population, DPP4i and basal-bolus insulin therapy were the most frequently used anti-hyperglycemic agents for COVID-19. DPP4i use was associated with improved glycemic control, however, the true correlation regarding the association with glycemic control cannot be determined. Patients who were admitted presenting with mild hyperglycemia were started with DPP4i as compared with those patients presenting with severe hyperglycemia where additional hypoglycemic agents, including insulin, were added. The causal relationship cannot be ascertained, that is whether the improved glycemic control was brought about by DPP4i use or that the baseline characteristics of the patients started on DPP4i had only modest glucose elevations resulting in improved control. Other oral hypoglycemic agents such as metformin, SGLT2i and thiazolidinediones did not show any correlation with good glucose control, possibly due to low frequency of and much later use in the study population. Of note, thiazolidinediones, specifically pioglitazone, were associated with poor glycemic variability as TZDs are known to lower glucose levels in approximately 2 weeks.[21] Pioglitazone works by activation of nuclear peroxisome proliferator-activated γ receptor hence, its glycemic effects cannot be immediately seen. Basal-bolus insulin therapy was associated with hyperglycemia, however, patients who were started on this regimen may have had severe hyperglycemia at baseline. The full therapeutic property of basal-bolus insulin therapy may not have been observed immediately during the initial 72 hours resulting in hyperglycemia. In addition, steroid-induced hyperglycemia, a possible confounder, may have affected the results.

The present study has limitations. Blood glucose monitoring was tested using a capillary blood glucose meter. To minimize changes in glucose variability, patients should be on at least 4-point CBG monitoring (e.g., three times a day before meals and at bedtime), similar to the study done by Tura et al.[9] However, continuous glucose monitoring is still recommended as more data points are required to obtain more accurate glucometrics such as percentage of target glucose in range, percentage above target range, percentage below target range, SD and CV. However, a strength of this study is that it reflects the commonly used modality of blood glucose monitoring in inpatient settings. Another limitation is that because of the study's observational nature, no causality was ascertained. Also, the researchers failed to create a multivariate model due to the low number of variables left after the stepwise approach. Increasing the sample size may improve this limitation. The researchers recommend doing prospective studies using continuous glucose monitoring to reflect the complete inter- and intraday blood glucose variations.

CONCLUSION

This study was able to identify potential predictors of poor glycemic control and increased glucose variability. Clinical predictors include chronic kidney disease for increased glycemic variability and COVID-19 severity for poor glycemic control, mainly hyperglycemia. Laboratory parameters such as HbA1c and hs-CRP were associated with poor glycemic control, mainly hyperglycemia.

Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
JPMB: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration, Funding acquisition; **EM:** Conceptualization, Methodology, Validation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **BM:** Conceptualization, Methodology, Validation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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