Glycemic Gap as a Predictor of Adverse Outcomes in Patients with Type 2 Diabetes Diagnosed with COVID-19 in a Tertiary Hospital in Metro Manila: A Retrospective Cohort Study

Mariel C. Enverga, MD[1], Maria Jocelyn C. Isidro, MD[1], Carolyn N. Montano, MD[1]

Abstract

Background: Although elevated glucose levels are associated with adverse outcomes in the critically ill, HbA1c-based adjusted glycemic variables have not been extensively utilized as a tool to evaluate patients in the acute critical condition.[1,2]

Objective: This study aims to determine whether glycemic gap can predict adverse outcomes in patients with type 2 diabetes diagnosed with COVID-19.

Methodology: A single center and retrospective study of adult patients with type 2 diabetes diagnosed with COVID-19. Glycemic gap was calculated as the difference between the admission blood glucose and A1c-derived average glucose. Logistic regression was used to determine association of glycemic gap and several adverse clinical outcomes. A decision curve analysis was used to determine the clinical utility of a clinical decision model based on this cut-off.

Results: A total of 150 diabetic patients with COVID-19 were analyzed. Median baseline HbA1c was 7.5% (range 4.79–18.42), while median admitting blood glucose was 196 (range 71–506) mg/dL. From these, computed glycemic gaps ranged from -180.5 to 312.8 mg/dL, with a median of 13.75 mg/dL.

On univariate analysis, for every unit increase in glycemic gap, odds of developing ARDS increased five times (cOR 4.798, 95% CI 2.08 to 11.09); odds of developing shock increased four times (cOR 4.48, 95% CI 1.48 to 13.44). No single cut-off value for glycemic gap was able to discriminate patients with favorable outcome from those with adverse outcome. The decision curve analysis graphically shows that glycemic gap has a positive net benefit for threshold risk of 50% or higher.

Conclusion: Higher glycemic gaps were significantly associated with increased risk for poor outcomes in diabetic patients with COVID-19. Glycemic gap should be correlated with clinical status and other laboratory parameters to make it a more powerful discriminant among COVID-19 infected patients.

Keywords: Glycemic gap, type 2 diabetes, adverse outcome, COVID-19

Introduction

The novel coronavirus disease 2019 (COVID-19) has spread rapidly and has caused not only significant disease burden but also economic impact to millions of people globally. Severe cases of COVID-19 have been observed to be predominantly affecting the elderly population and individuals with underlying comorbidities, which include heart diseases, chronic renal and respiratory diseases, immunocompromised states, and diabetes, among others.[3,4,5] According to one meta-analysis, 12 to 22% of the COVID-19 patients had diabetes as a risk factor.[3,4]

As a global pandemic, the incidence of diabetes has been increasing over the years. As of 2019, International Diabetes Federation (IDF) data showed that 3,993,300 of the total 63,265,700 Filipino adult population have diabetes, with a 6.3% prevalence of diabetes in the adults.[6] The existence of the two global pandemics, diabetes and COVID-19 has been associated with worse prognosis, with a 2-fold increased risk of a more severe infection requiring treatment in the critical care unit.[3,4] The treatment plan

[1] Section of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, Makati Medical Center, Makati City, Philippines
Corresponding author: Mariel C. Enverga, MD
E-mail address: mariel.enverga@gmail.com

for these patients must include careful attention to the management of the comorbidities.

Blood glucose levels at the time of admission at the hospital is proven to be a strong predictor in the development of complications and unfavorable outcome.[1] In patients with any severe infection and critical illness, stress-induced hyperglycemia commonly occurs secondary to excessive cytokine release and increased levels of counter regulatory hormones (glucagon, cortisol, catecholamine and growth hormone), thereby increasing gluconeogenesis, decreasing glycogenolysis and augmenting insulin resistance.[1] If diabetic patients have any concurrent critical illness, the admission blood glucose may be affected by poor glycemic control and worsened by the acute stress. With uncontrolled hyperglycemia, the host response to the control of viremia and regulation of cytokine release may be affected.

A number of clinical scoring systems and markers have been utilized to evaluate patients in the acute critical condition; however, the admission glucose level, glycemic gap and glycemic variability have not been extensively studied and utilized as a prognostication tool.[7-9] The glycemic gap is calculated as a difference between the A1c-derived average glucose (ADAG) and the admission blood glucose, which may be a better indicator of disease outcome.[1,2,7]

Recent investigations have shown that HbA1c-based adjusted glycemic variables such as glycemic gap and stress hyperglycemia ratio, were linked to severity of the disease, unfavorable prognosis and poor outcome in diabetic patients with critical illness, acute heart failure, community acquired pneumonia, liver abscess, acute respiratory failure, and even cardiogenic shock.[7-10]

The objective of this study is to determine whether glycemic gap can predict adverse outcomes (ARDS, acute respiratory failure, septic shock, upper gastrointestinal bleeding, and acute kidney injury) in patients with type 2 diabetes diagnosed with COVID-19.

Methodology

This study was approved by the Institutional Review Board of the Makati Medical Center. The authors adhered to the ethical considerations set out in relevant guidelines, which included the Declaration of Helsinki, National Ethics Guidelines for Health Research and Data Privacy Act of 2012.

This is a single-center study conducted in a private, tertiary hospital in Metro Manila. In addition, this utilized a retrospective cohort analysis, which included adult patients with diabetes mellitus type 2 who were laboratory-confirmed (RT-PCR) to have COVID-19. Medical records of the study population from March 1, 2020, to August 31, 2020, were reviewed using the electronic medical record system.

For each patient, the following data was analyzed: age (years), sex, body mass index (kg/m^2), comorbidities, blood glucose level (mg/dL) at the time of admission at the emergency department, HbA1c level (%) on admission, other laboratory parameters, and outcome data.

The following adverse outcomes were likewise evaluated: presence of multiorgan dysfunction, ARDS, acute respiratory failure that needed ventilator support, septic shock (persistent hypotension despite adequate fluid resuscitation or use of vasopressors), upper gastrointestinal bleeding (presence of melena or massive hematochezia), acute myocardial infarction during hospitalization, and acute kidney injury (increase in serum creatinine by 50% from baseline serum creatinine or increase in serum creatinine by 0.3 mg/dL in 48 hours).

In this study, patients were classified as diabetic if they had at least one of the following criteria: (1) known case of diabetes mellitus type 2 on previous records or previous admission; (2) use of anti-diabetic medications, whether oral or insulin treatment; (3) previous laboratory results which included at least one of the following criteria: fasting blood sugar (FBS) ≥ 126 mg/dL, random blood sugar (RBS) ≥ 200 mg/dL with signs of polyuria, polydipsia or weight loss, 2-hour oral glucose tolerance test (OGTT) ≥ 200 mg/dL or HbA1c ≥ 6.5% (American Diabetes Association).

The exclusion criteria included the following: (1) age less than 18 years old; (2) initial blood glucose of less than 70 mg/dL at the emergency department; (3) admitting diagnosis of hyperglycemic emergency, diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar state (HHS); (4) any use of corticosteroid, whether oral, parenteral or topical, within 3 months prior to admission; (5) mortality within 24 hours of admission; (6) patients with any acute or chronic blood loss, hemolytic anemia and known hemoglobin variants.

Measurement of Blood Glucose and Glycemic Gap. The result of the HbA1c was converted to the A1c-derived average glucose (ADAG) using the following equation: ADAG in mg/dL = (28.7 × HbA1c) - 46.7. The glycemic gap was calculated as the difference between the admission blood glucose and ADAG (i.e., glycemic gap = admission blood glucose - ADAG).

Sample Size. The sample size was computed using an online software, *OpenEpi,* Version 3. Based on the study conducted in the United States, the percentage of severe cases among COVID-19 patients with diabetes mellitus was 32%.[11] The margin of error used is 8%. At 95% confidence level and considering 10% attrition rate, the final sample size was 146.

Data Analysis Plan. Descriptive statistics was used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for categorical variables. Shapiro-Wilk test was used to determine the normality distribution of continuous variables. Continuous quantitative data that met the normality assumption were summarized using mean and standard deviation (SD), while those that did not were described using median and range. Logistic regression was used to determine association of glycemic gap and several adverse clinical outcomes. Adjusted analyses controlled for age, sex and presence of any comorbidity.

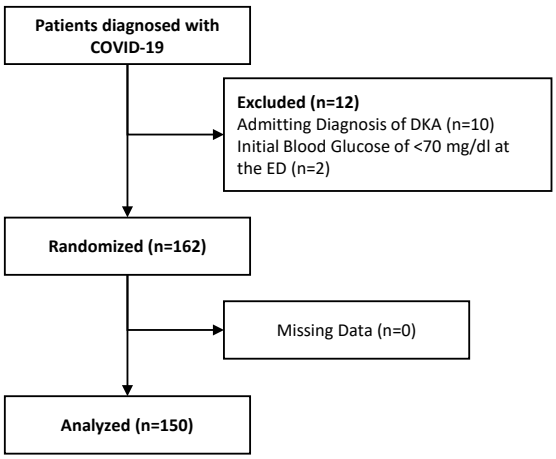

Figure 1. Flow diagram of patients included in the study

Receiver operating characteristic (ROC) curve was constructed to determine the optimal cut-off value of glycemic gap in predicting poor outcomes. Youden's J index was defined for all points along the ROC curve, and the maximum value of the index was used as a criterion for selecting the best cut point.

A decision curve analysis was used to determine the clinical utility of the glycemic gap-based strategy as compared to treat all and treat none strategies. Net benefit is the difference between the number of true-positive results and the number of false-positive results, the latter weighted by a factor that reflects the cost of a false-positive relative to a true positive result. The decision curve can help a user determine graphically which among several clinical models would be of greatest benefit for any chosen threshold of the weighting factor.

All valid data was included in the analysis. There was no missing data in this study. Null hypothesis was rejected at 0.05 α-level of significance. STATA 15.0 was used for data analysis.

Results

We analyzed a total of 162 patients with diabetes (28%) out of 580 COVID confirmed cases. This study excluded 10 patients who had diabetic ketoacidosis and 2 patients with hypoglycemia as admitting diagnosis (*Figure 1*). We had 150 COVID-19 patients with type 2 diabetes included for final data analysis (*Table I*). These had a mean (±SD) age of 59 ± 13 years and a median BMI of 27.24 (range 18.14–52.22) kg/m^2. Males accounted for 64%. Three-fourths concomitantly had hypertension, 15% had chronic kidney disease, while 7% were affected with cerebrovascular disease. A third received a critical COVID-19 classification, 27% were categorized as severe COVID-19 cases, a third was classified as moderate COVID-19 cases, while 6% were considered mild cases.

Diabetic ketosis was noted in 15% upon admission. The median baseline HbA1c was 7.5% (range 4.79–18.42%), while the median admitting CBG was 196 (range 71–506) mg/dL. From these, computed glycemic gaps ranged from -180.5 to 312.8 mg/dL, with a median of 13.75 mg/dL. No missing data was included in this study.

Table I. Baseline characteristics of patients (n=150).

	Mean ± SD; Frequency (%); Median (Range)
Age	59.45 ± 13.23
Sex	
Male	96 (64)
Female	54 (36)
BMI (kg/m2) [n=113]	27.24 (18.14–52.22)
Comorbidities	
Hypertension	112 (74.67)
CKD	23 (15.33)
CVD	11 (7.33)
Cancer	5 (3.33)
Others	16 (10.67)
Duration of diabetes (years) [n=129]	5 (0–30)
Diabetic complication	
Diabetic ketosis	22 (14.67)
Hypoglycemia	1 (0.67)
Medications	
Oral hypoglycemic agent (OHA)	99 (66)
Injectables	21 (14)
Initial CBG (mg/dL)	196 (71–506)
HbA1c (%)	7.5 (4.79–18.42)
ADAG (mg/dL)	168.55 (90.77–481.95)
Glycemic gap (mg/dL)	13.75 (-180.5–312.8)
COVID-19 Severity	
Mild	9 (6)
Moderate	50 (33.33)
Severe	41 (27.33)
Critical	50 (33.33)
Outcomes	
Intubated or HFNC	68 (45.33)
HFNC only	26 (17.33)
Pneumonia	137 (91.33)
ARDS	38 (25.33)
RF or AKI	71 (47.33)
AKI only	37 (24.67)
Heart failure or myocarditis	1 (0.67)
Gastrointestinal bleeding	2 (1.33)
Shock	15 (10)
Mortality	21 (14)
Composite poor outcome	137* (91.33) 81† (54)

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; HFNC, high flow nasal cannula; RF, renal failure.
*With any of the following: intubated or HFNC, pneumonia, ARDS, renal failure, AKI, heart failure, myocarditis, gastrointestinal bleed, shock, mortality
†With any of the following: ARDS, renal failure, AKI, gastrointestinal bleed, mortality.

The prevalence rates of adverse outcomes were as follows: pneumonia - 91%; ARDS – 25%, renal failure or acute kidney injury (AKI) - 47%; and AKI only - 25%. Twenty-one patients died, resulting in a mortality rate of 14% (95% CI 8.88–20.60%).

Crude associations showed that for every unit increase in glycemic gap, the odds of developing ARDS increased by approximately five times (cOR 4.798, 95% CI 2.08 to 11.09), or the odds of developing shock increased by four times (cOR 4.48, 95% CI 1.48 to 13.44) (*Table II*). Even after adjusting for age, sex, and

Table II. Association between glycemic gap and adverse outcomes (n=150).

Adverse Outcome	Crude Odds Ratio (95% CI)	*p Value*	Adjusted Odds Ratio* (95% CI)	*p Value*
ARDS	4.798 (2.08–11.09)	<0.001	4.919 (2.10–11.53)	<.001
RF or AKI	1.916 (0.90–4.07)	.091	1.833 (0.84–4.01)	.129
AKI only	1.416 (0.62–3.25)	.412	1.304 (0.56–3.05)	.541
Shock	4.456 (1.48–13.44)	.008	5.014 (1.56–16.10)	.007
Mortality	2.3 (0.87–6.07)	.093	2.418 (0.89–6.54)	.082
Composite Poor outcome	3.586 (0.95-13.60)*	.060	3.612 (0.93-14.04)	.064
	2.121 (0.97-4.63)†	.059	2.083 (0.94-4.64)	.073

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; RF, renal failure.
*****Controlled for age and sex and any comorbidity.
† Refers to any kind of treatment

any comorbidity, the association between glycemic gap and these outcomes remained (*p<0.05*).

Referring to discriminative ability, the areas under the ROC curve were 0.5899 for mortality; 0.5783 for any poor outcome (as listed in *Table II*); and 0.5762 for the composite outcome of ARDS, renal failure, AKI, gastrointestinal bleeding, and mortality (*Figure 2*).

Decision curve analysis showed that a strategy based on our glycemic gap cut-off would result in net benefit higher than both *treat all* and *treat none* strategies over the range of 49% (almost 1:1 odds) to 75% (3:1 odds) probability thresholds (*Figure 3*). Over this range, the net reduction in interventions would range from about none in the lower threshold to almost 30% in the upper threshold probability, as compared to a treat all strategy (*Figure 4*).

Discussion

Stress-induced hyperglycemia has been associated with increased mortality in hospitalized patients[1,2]. Diabetic patients with poor glucose control are susceptible to infectious diseases because of suppressed immunity, increased release of inflammatory mediators, and chronic diabetes-related complications. Hyperglycemia in acute illness relatively reflects the activation of stress response system, which becomes active in response to conditions such as severe trauma, sepsis, respiratory failure, and shock of any cause.

This study showed that an increasing glycemic gap is associated with the development of adverse outcomes (ARDS and shock) in diabetic patients with COVID-19.

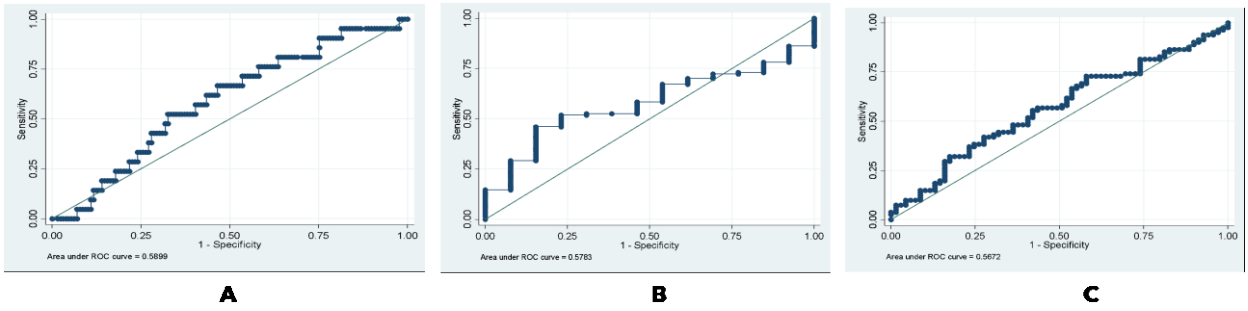

Figure 2. ROC curves of glycemic gap for discriminating adverse outcomes. (A) Mortality; (B) Composite outcome of intubation, HFNC use, pneumonia, ARDS, renal failure, AKI, heart failure, myocarditis, gastrointestinal bleeding, shock, and mortality; (C) Composite outcome of ARDS, renal failure, AKI, gastrointestinal bleeding, and mortality.

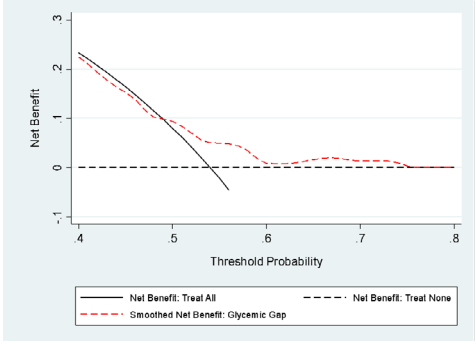

Figure 3. Decision curve analysis of the glycemic gap in predicting poor outcome

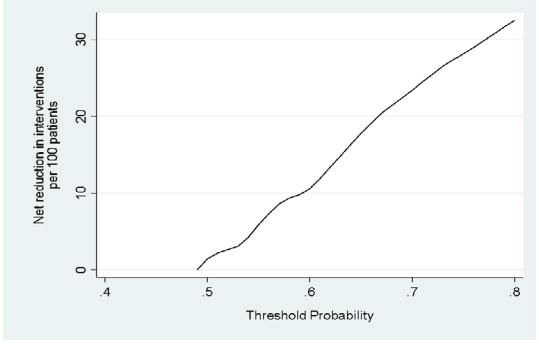

Figure 4. Net reduction in interventions

For every unit increase in glycemic gap, the odds of developing ARDS are increased by approximately five times (cOR 4.798, 95% CI 2.08 to 11.09) and the odds of developing shock is increased by four times (cOR 4.48, 95% CI 1.48 to 13.44).

In the study of Donagaon et. al., glycemic gap was considered a good predictor of increased multiorgan dysfunction syndrome ($p<0.01$), ARDS ($p=0.026$), shock ($p= 0.043$), gastrointestinal bleeding ($p=0.013$), and acute kidney injury ($p=0.01$), renal failure ($p<0.01$) and increased mortality in diabetic patients at the critical care unit.[2] In the study of Cheng et. al., patients with elevated glycemic gap had an odds ratio of 3.84 for the increased incidence of several adverse outcomes with some findings like our study.[8] Another study concluded that elevated glycemic gap was associated with poor outcome in critically ill patients, where the non-survivors had higher APACHE-II scores, admission glucose levels, average glucose levels within 24 hours and glycemic gaps ($p<0.001$).[1]

In the study of Cheng et. al., they found out that a glycemic gap at 40 mg/dl had comparable discriminative performance for distinguishing the development of pneumonia-related adverse outcomes in diabetic patients.[8] On the other hand, in the study of Kataja et. al., a glycemic gap more than 80mg/dL was linked to increased need for renal replacement therapy and incidence of shock.[10]

With the use of glycemic gap, the net benefit ranges from 49 to 75% (*Figure 3*), this may imply that the use of glycemic gap may help us make better clinical decision in the identification of possible adverse outcome in patients with COVID-19. Since the specificity of glycemic gap is not 100%, some patients without the disease may be subjected to unnecessary interventions. Glycemic gap should be correlated with the clinical status and other laboratory parameters to make it a more powerful discriminant among the COVID-19 infected patients.

However, in this study, no single glycemic gap cut-off value was able to determine either a favorable or an adverse outcome among the COVID-19 patients. The sample size may also have been small as well, hence not much variation was identified between the glycemic gap and adverse outcomes. The adequacy of glycemic control during the hospitalization may have also influenced the outcomes. Glycemic gap can be used with appropriate patients as part of shared decision-making.

Implications to clinical practice and public health. A study showed that knowing the glycemic gap may not only eliminate the influence of chronic hyperglycemia on the assessment of disease severity but may also be used as a better indicator of outcomes in patients with critical illness.[1,2,7]

In a study by Cheng et. al., they believed that the glycemic gap could explain the "diabetes paradox" and issues about the association between acute hyperglycemia, long-term glucose control and poor clinical outcomes.[8] This study also suggests that glycemic gap could be incorporated into other clinical scoring systems to improve its discriminative performance.

Limitation and recommendations of the study. This study was primarily a retrospective investigation conducted in a single center, which may introduce a selection bias. Greater sample size or a multi-center study may be able to identify a glycemic gap cut-off value since this may yield more variation between the glycemic gap and adverse outcome in the study population. The investigators recommend a prospective study using glycemic gap in patients with and without diabetes as another area of investigation.

Another future research endeavor is that this study may still be validated to confirm its use in clinical practice and in other settings, which may include primary care facilities and the government hospitals.

To the best of our knowledge, this is the first study conducted in the Philippine setting that determined whether glycemic gap could predict the adverse outcomes in patients with type 2 diabetes diagnosed with COVID-19.

Conclusion

This study showed that higher glycemic gaps on hospital admission in this institution were associated with increased risk for poor outcomes in patients with diabetes diagnosed with COVID-19. Glycemic gap can be used as an adjunctive tool to determine the severity of illness and clinical outcome of certain acute illnesses in patients with Type 2 diabetes.

Conflict of Interest

The authors declare that they have no conflict of interest relevant to this article.

Acknowledgements

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