Title

Glycemic Gap Predicts Mortality in a Large Multicenter Cohort Hospitalized With COVID-19.

Journal

Journal of Clinical Endocrinology and Metabolism (JCEM), 108(3)

Authors

McDonnell, Marie
Garg, Rajesh
Gopalakrishnan, Geetha
et al.

Publication Date

2023-02-15

DOI

10.1210/clinem/dgac587

Peer reviewed

Glycemic Gap Predicts Mortality in a Large Multicenter Cohort Hospitalized with COVID-19

Authors:

Marie E. McDonnell, MD [1, 2] (ORCID 0000-0002-2263-9783)

Rajesh Garg, MD[3] (ORCID 0000-0002-7779-1619)

Geetha Gopalakrishnan, MD [4, 5] (ORCID 0000-0002-1605-5781)

Joanna Mitri, MD, MS [2, 6, 7] (ORCID 0000-0002-3257-3618)

Ruth S. Weinstock, MD, PhD [8] (ORCID 0000-0001-5859-5666)

Margaret Greenfield, PTA, MS, CHES [8] (ORCID 0000-0001-5923-0685)

Sai Katta, MD [8] (ORCID 0000-0002-0716-840X)

Jasmin Lebastchi, MD [4, 5]

Nadine E. Palermo, DO [1, 2] (ORCID 0000-0002-7627-6957)

Ramya Radhakrishnan, MD [3]

Gregory P. Westcott, MD [2, 7] (ORCID 0000-0002-4321-3992)

Matthew Johnson, BA [1]

Donald C. Simonson, MD, MPH, ScD [1, 2] (ORCID 0000-0002-4670-6290)

Affiliations:

[1] Brigham and Women's Hospital, Boston, MA

[2] Harvard Medical School, Boston, MA

[3] University of Miami, Miller School of Medicine, Miami, FL

[4] Rhode Island Hospital, Providence, RI

[5] Warren Alpert Medical School of Brown University, Providence, RI

[6] Joslin Diabetes Center, Boston, MA

[7] Beth Israel-Deaconess Medical Center, Boston, MA

[8] State University of New York Upstate Medical University, Syracuse, NY

Short Title: Glycemic Gap and Mortality during Admission for COVID-19

Keywords: COVID-19, diabetes, glycemic gap, hospital mortality, stress hyperglycemia

Corresponding Author:

Marie E. McDonnell, M.D.

Division of Endocrinology, Diabetes and Hypertension

Brigham and Women's Hospital

221 Longwood Avenue

Boston, MA 02115

e-mail: mmcdonnell@bwh.harvard.edu

phone: 617-732-5693

Funding: This work was supported in part by the Brigham Education Institute- TechFoundation Data Science Internship Program. https://www.brighamtechfoundation.org/

Disclosures

NP receives research funding from Dexcom, Inc.; DCS – stockholder / shareholder of GI Windows; spouse owner of Phase V Technologies (each unrelated to current study); RW has received research funding from Dexcom, Inc. and Medtronic.

Footnote: To convert glucose in mmol/l to mg/dl, multiply by 18

ABSTRACT

Purpose: Diabetes or hyperglycemia at admission are established risk factors for adverse outcomes during hospitalization for COVID-19, but the impact of prior glycemic control is not clear.

Methods: We examined the relationship between clinical predictors including acute and chronic glycemia and clinical outcomes including ICU admission, mechanical ventilation (MV), and mortality among 1,786 individuals with diabetes or hyperglycemia (glucose > 10 mmol/l twice in 24 hrs.) admitted from March 2020 through February 2021 with COVID-19 infection at 5 university hospitals in the eastern U.S.

Results: The cohort was 51.3% male, 53.3% White, 18.8% Black, 29.0% Hispanic, with age = 65.6 ± 14.4 yrs., BMI = 31.5 ± 7.9 kg/m^2, glucose = 12.0 ± 7.5 mmol/l [216 ±135 mg/dl], and HbA_{1c} = 8.07 ± 2.25%. During hospitalization, 38.9% were admitted to the ICU, 22.9% received MV, and 10.6% died. Age ($p<0.001$) and admission glucose ($p=0.014$) but not HbA_{1c} were associated with increased risk of mortality. Glycemic gap, defined as admission glucose minus estimated average glucose based on HbA_{1c}, was a stronger predictor of mortality than either admission glucose or HbA_{1c} alone (OR = 1.040 [95% CI: 1.019, 1.061] per mmol/l, $p<0.001$). In an adjusted multivariable model, glycemic gap, age, BMI, and diabetic ketoacidosis on admission were associated with increased mortality, while higher eGFR and use of any diabetes medication were associated with lower mortality ($p<0.001$).

Conclusions: Relative hyperglycemia, as measured by the admission glycemic gap, is an important marker of mortality risk in COVID-19.

INTRODUCTION

During the current COVID-19 pandemic several investigations have illustrated that the presence of hyperglycemia during hospitalization increases the probability of poor outcomes and death, but this risk appears to vary across populations and settings [1-3]. While acute hyperglycemia with or without diabetes mellitus is well established to be associated with increased mortality and morbidity in hospitalized patients [4,5], the effect of chronic hyperglycemia as measured by HbA_{1c} is more controversial. Some studies suggest an association between HbA_{1c} and mortality in COVID-19 [6], yet others have shown no such association [7,8]. Previous studies in non-COVID related acutely ill patients have shown that the same level of hyperglycemia in patients without diabetes is associated with higher mortality than in those with diabetes [4,5]. Thus, people with diabetes or chronic hyperglycemia appear to have a higher glycemic threshold for increased mortality relative to those without diabetes and/or with baseline normoglycemia.

A measure that considers both acute and chronic hyperglycemia may be a useful index but has not been widely applied nor used in COVID-19 studies. The concept of "glycemic gap", defined as the difference between current plasma glucose and estimated average glucose (eAG) based on HbA_{1c}, as a predictor of severe illness has previously been validated in the acute setting [9,10]. In a preliminary report, we showed that a higher glycemic gap was associated with increased risk of in-hospital mortality, intensive care unit (ICU) admission and mechanical ventilation (MV) during admission for COVID-19 infection [11]. In another recent study, the acute-to-chronic (A/C) glycemic ratio was shown to have a similar association [12]. However, this study was conducted in a small homogenous population and included only those with pre-existing type 2 diabetes.

In the current study, we present data from a consortium of university hospitals on the association between glycemic gap and adverse clinical outcomes in patients hospitalized with COVID-19 infection. We hypothesized a higher-than-expected admission plasma glucose level defined by the glycemic gap would be a risk factor for mortality and other poor outcomes during hospitalization in

patients with COVID-19. We also examined other demographic, clinical and laboratory variables present at admission that may also be associated with poor clinical outcomes, including the need for MV or admission to the ICU.

METHODS

Overview and data acquisition

The COVIDEastDM consortium pooled data from 5 academic hospitals on the East Coast of the U.S. (Brigham and Women's Hospital, Boston, MA; Beth Israel-Deaconess Medical Center, Boston, MA; Rhode Island Hospitals and Lifespan Health System, Providence, RI; University of Miami, Miami, FL; and Upstate University Hospital, Syracuse, NY) to study the relationships between chronic and acute hyperglycemia and COVID-19 outcomes. Data were retrieved from electronic medical records using institution-specific methods and reviewed by at least two investigators per site according to consortium-defined rules for variable definitions and data acquisition. Data coordination was overseen by the Brigham and Women's Hospital site and entered into a REDCap web-based repository [13]. The study was reviewed and approved by the institutional review board at each participating hospital, and the requirement for obtaining written consent was waived.

Data were obtained retrospectively from electronic medical records of 8,219 adults with 10,225 hospitalizations between March 1, 2020, and February 28, 2021, with a COVID-19 related ICD-10 code *and* a positive COVID-19 PCR test *and* either established diabetes (DM) or hyperglycemia during hospitalization. The final study data set included individuals with a baseline HbA_{1c} who also met any one of the following criteria: 1) an ICD-10 code for diabetes (E08.00 – E13.9) at any time during the study period, 2) $HbA_{1c} \geq 6.5\%$ at any time between 3 months prior to admission through the day of admission for the first hospitalization, or 3) at least two glucose values (point of care or laboratory) ≥ 10 mmol/l within any 24-hour period during the admission. We identified 1,786 individuals who met the

inclusion criteria; the population was restricted mainly by the requirement for a baseline HbA_{1c} (see Figure 1). Among those who had more than one hospitalization, we included only the first hospitalization in this analysis.

The primary outcome of the analysis was death during hospitalization. Secondary outcomes were the need for MV or admission to the ICU. Additional exploratory outcomes included length of hospital stay, development of hyperglycemic crisis (diabetic ketoacidosis [DKA] or hyperglycemic hyperosmolar syndrome [HHS]) during the hospital admission, hypoglycemia (Level 1, defined as plasma glucose < 3.9 mmol/L [< 70 mg/dl], or Level 2, defined as plasma glucose < 3.0 mmol/L [< 54 mg/dL][14]) on admission, and treatment with glucocorticoids.

Predictor variables on admission included:

- Demographic characteristics (age, sex, race, and ethnicity),
- Anthropometric data (body mass index),
- Laboratory data related to diabetes and its management (admission plasma glucose, HbA_{1c}, estimated average glucose [eAG = 28.7 * HbA_{1c} – 46.7 mg/dl], glycemic gap [admission glucose – eAG], estimated glomerular filtration rate [eGFR], microalbuminuria, presence of diabetic ketoacidosis, and presence of hypoglycemia (< 3.9 mmol/l),
- Outpatient diabetes treatment (insulin, metformin, sulfonylureas, sodium-glucose co-transporter 2 (SGLT-2) inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1 agonists), dipeptidyl peptidase IV (DPP-4) inhibitors, or thiazolidinediones),
- Other medications that might affect the clinical course of acute COVID-19 infection (including angiotensin converting enzyme inhibitors [ACE-I], angiotensin receptor blockers [ARB], and statins), and

• Prior diagnoses of major comorbidities (hypertension, coronary artery disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, asthma, stroke, chronic liver disease, and cancer).

Statistical analysis:

A predictive model was developed to select the relevant predictor variables and to combine them statistically into a multivariable model following established guidelines [15]. We developed the model in two phases. The first phase included the following steps: 1) obtaining consensus from the clinical experts at each of the 5 study sites on the conceptual health model underlying the relationship between the primary and secondary outcomes and the variables available in the electronic medical record; 2) excluding any step 1 variables due to excessive missingness, poor quality, or lack of uniformity in data collection among sites; and 3) evaluating potential associations between the outcomes and predictors using exploratory and descriptive analyses to examine distributional properties (e.g. skewness) of the potential predictors, and examining the potential associations by comparing the mean, medians and proportions between the two levels of the dichotomous outcomes. For this third step, Student's t-test was used to compare continuous variables, and chi-square or Cochran–Mantel–Haenszel test were used to compare categorical variables, with a p-value < 0.10 as an initial threshold for assessing associations for inclusion.

The second phase of the model development consisted of building the multivariable logistic regression models to examine the relationship between predictor variables and the primary outcome (death during hospitalization), secondary outcomes (ICU admission or mechanical ventilation), or exploratory outcomes. Univariate logistic models with each outcome were initially performed. Statistically significant variables were subsequently selected using stepwise logistic regression ($p > 0.20$ to remove; $p < 0.10$ to retain). The linearity of the models was evaluated for

specification error using the linktest function, and appropriate transformations (if needed) were performed with Box-Tidwell analysis. As the multivariable model was used only for identifying epidemiologic associations and not for diagnostic or prognostic purposes, model validation was not undertaken.

Descriptive data are presented as means ± standard deviations for normally distributed continuous variables, median with interquartile range for non-normally distributed continuous variables, and as proportions (%) for categorical variables. Logistic regression results are expressed as odds ratios with 95% confidence intervals for the association between the predictor(s) and the respective outcome. Results are considered statistically significant at a type 1 error rate of $p < 0.05$. Graphical presentation of results in Figure 2 display multivariable logistic regression of the primary outcome (mortality in the hospital, expressed as a probability) as a function of significant independent model predictors. All analyses were performed using Stata version 15.1 (College Station, TX)

RESULTS

Cohort characteristics

Characteristics of the study population are shown in Table 1. The age of the sample was 65.6 ± 14.4 years, with nearly equal proportions of males and females, and a distribution of racial and ethnic backgrounds reflecting the diverse populations served by the 5 participating hospitals. BMI was 31.5 ± 7.9 kg/m^2, and individuals had evidence of both acute and chronic hyperglycemia (admission glucose = 12.0 ± 7.5 mmol/l; HbA_{1c} = 8.07 ± 2.25 %). The glycemic gap was 1.7 ± 6.2 mmol/l, indicating that individuals were more acutely hyperglycemic at admission than would have been predicted based on their HbA_{1c}. Approximately half were receiving medications for treatment of their diabetes, with insulin and metformin being most frequently prescribed. Diabetic ketoacidosis was present in 2.4% of the

cohort at admission, while hypoglycemia defined as plasma glucose <3.9 mmol/L (<70 mg/dl) was present in 1.8%.

Individuals had multiple additional comorbidities, with 62% having a diagnosis of hypertension. Common additional medical treatments included ACE-I or ARB in 31.4%, and statins in 37.6%.

Primary Outcome

Mortality during the hospitalization was 10.6%. In univariate analyses, the most significant demographic predictor associated with in-hospital morality was age (OR = 1.040 [95% CI: 1.028, 1.053] per year; p<0.001) (Table 2). Neither sex, race, nor ethnicity were independently associated with mortality.

Although admission glucose was significantly associated with in-hospital mortality (p = 0.014), HbA_{1c} did not show any significant relationship. In contrast, the glycemic gap, which incorporates both the admission glucose and HbA_{1c} in its calculation, was a more significant and consistent predictor in univariate analysis (OR = 1.040 [95% CI: 1.019, 1.061] per mmol/l, p< 0.001) and in subsequent multivariable models. The mortality rate was 7.4% for those with a negative glycemic gap, 12.7% for a glycemic gap of 0 to < 5.0 mmol/l, and 15.8% for a glycemic gap ≥ 5.0 mmol/l (p for trend < 0.001).

The other major factors associated with increased risk of mortality in univariate analysis were the presence of DKA at admission (OR = 3.45 [95% CI: 1.26, 9.48]; p = 0.016) and a diagnosis of chronic obstructive pulmonary disease (OR = 1.87 [95% CI: 1.30. 2.69], p = 0.001). Two factors significantly associated with *decreased* risk of mortality were higher estimated glomerular filtration rate (p < 0.001) and the use of any outpatient medication for treatment of diabetes (p = 0.05) (Table 2).

In an adjusted multivariable model, age, glycemic gap, and DKA on admission each remained significantly associated with in-hospital mortality, as was BMI (OR = 1.040 [95% CI: 1.004, 1.078] per kg/m^2; p = 0.030). Higher estimated GFR and use of any diabetes medication both remained significantly associated with decreased probability of death (Table 3 and Figure 2). There were no significant differences in the outcome among centers in the adjusted multivariable model. Neither Level

1 nor Level 2 hypoglycemia was associated with increased mortality as either a univariate predictor or in multivariable analysis; however, there were only seven individuals in the data set with Level 2 hypoglycemia on admission.

Secondary outcomes

Mechanical ventilation (MV) was required in 22.9% of the study population, and admission to the ICU occurred in 38.9% of individuals. In univariate analyses, older age was associated with a significantly lower odds of receiving MV, while Hispanic ethnicity was associated with increased risk for this outcome (Table 2). Glycemic gap was again highly significantly associated with intubation ($p = 0.001$). Other significant risk factors for mechanical ventilation included higher BMI and the presence of DKA on admission. The use of any diabetes medication, ACE-I, ARB, and statins were all associated with a lower risk of MV. In an adjusted multivariable model, the odds of receiving MV was significantly higher with increased glycemic gap, higher BMI, and DKA on admission, and was significantly lower with advancing age, among males, and in patients using an ACE-I or ARB (Table 3).

Risk factors for admission to the ICU again included glycemic gap, Hispanic ethnicity, and presence of DKA at the time of admission, while protective factors included outpatient use of any diabetes medications, ACE-I, or ARB. In a multivariable model, odds of ICU admission remained most strongly associated with glycemic gap and DKA on admission, while risk was significantly decreased in males and those using any diabetes medication.

Exploratory outcomes

Glucocorticoid treatment during hospitalization was associated with death in hospital (OR = 2.27 [95%CI 1.62, 3.18], $p < 0.001$), which persisted after adjusting for glycemic gap (adjusted OR = 2.41 [95%CI 1.71, 3.42], $p < 0.001$). A higher glycemic gap was not a significant predictor of hospital length of stay (LOS), although a longer LOS was strongly associated with inpatient mortality (OR = 1.020 [95%CI 1.012, 1.029] per day, $p < 0.001$). Significant predictors of the development of DKA during the

hospitalization included glycemic gap (OR = 1.077 [95%CI 1.052, 1.104] per mmol/l, p< 0.001) and use of insulin prior to admission (OR = 1.77 [95%CI 1.28, 2.46], p = 0.001). These relationships were maintained in an adjusted model.

DISCUSSION

The results of our study demonstrate that among adults with diabetes or hyperglycemia hospitalized for COVID-19, the glycemic gap is a stronger predictor of in-hospital mortality, need for mechanical ventilation, or ICU admission than either admission plasma glucose or HbA_{1c} alone, suggesting that relative hyperglycemia is an important marker of disease severity in COVID-19. Additional significant predictors of mortality include age, increased BMI, worse renal function, and the presence of DKA on admission, while mortality was lower among individuals who were receiving any diabetes treatment as an outpatient.

As noted, hyperglycemia on admission has been shown in both COVID and non-COVID illnesses to be related to morbidity and mortality [16-18]. A high glycemic gap has also been linked to worse outcomes in several clinical conditions [9,10,12,19-21] suggesting that an acute rise in blood glucose may reflect a more severe disease process in people hospitalized with COVID-19 when compared to individuals with chronic hyperglycemia presenting with similar admission glucose concentrations. Depending on the population and condition studied, the predictive capacity of glycemic gap varies with thresholds ranging from 30-80 mg/dL (1.7- 4.4 mmol/L) reported in the literature [19,22-24]. In addition, mean glycemic gap (average 7-day glucose minus estimated glucose based on HbA_{1c}) has also been reported to predict 28-day and 1 -year mortality risk in people with diabetes admitted to the ICU [19]. Furthermore, the discriminative performance of the Acute Physiology and Chronic Health Evaluation (APACHE) score typically used to assess mortality risk in the ICU increased when glycemic gap was incorporated into the assessment tool [19]. Importantly, our model only detected increased risk with a positive glycemic gap, and individuals with a strongly negative glycemic gap were relatively spared

compared to those with a glycemic gap closer to 0 or higher. This may be due a low prevalence of admission hypoglycemia, which is an independent risk factor for inpatient mortality [25] and also may be an important factor to produce the “u-shaped curve” finding reported by others [26].

It is well known that inflammation, the activation of stress response metabolic pathways, and the release of cytokines are associated with infections and also contribute to hyperglycemia, insulin resistance, and impaired immunity [27]. These effects are bidirectional, since hyperglycemia, inflammation and cytokine release are also toxic to beta cells, contributing to beta cell impairment, reduced insulin secretion, dysfunction of the immune system, endothelial damage, and hypercoagulation [28]. This overall response appears to be both unique and exaggerated in people with diabetes with COVID-19[29]. It is possible, and perhaps likely, that the glycemic gap is a surrogate marker of this phenomenon.

Alternatively, the glycemic gap may primarily be an indicator of an acute impairment in insulin secretion. It has been postulated that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, can directly infect pancreatic beta cells, but this has not been proven. Angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) are needed for entry of SARS-CoV-2 into cells. ACE2 expression has been found in human pancreatic ductal epithelium and exocrine as well as islet vascular endothelium whereas TMPRSS2 expression was mostly detected in human acinar and ductal cells, suggesting that most if not all SARS-CoV-2-related beta cell damage is indirect [30,31]. Whether individuals with a high glycemic gap have a higher pancreatic viral load is unknown.

The concept that relative changes in glucose may be more deleterious than absolute glucose levels links the glycemic gap to the concept of glycemic variability (GV). GV may be measured in both the short- or long-term, and is associated with mortality from sepsis [32] and adverse cardiovascular events [33], among other negative outcomes. Glycemic gap and GV both measure deviations in blood

glucose from a mean and may share an underlying relationship to the body's response to severe illness, including the dysregulated production of reactive oxygen species [34]. No prospective randomized trial has been performed to determine whether reducing glycemic gap or GV improves outcomes, but insight into the relationship between these entities and adverse outcomes would provide more specific guidance on how acute illness may be managed in people with dysglycemia in the pre-admission or early-hospitalization period.

Importantly, we found that individuals who had previously been prescribed standard therapies for diabetes management (antihyperglycemics, statin therapy +/- ACE-I /ARB) overall fared better than those who had not been prescribed these therapies. One interpretation of this finding is that untreated cardiometabolic disease parameters in those at high risk, including lipids, blood pressure, and blood glucose, increases the likelihood of poor outcomes, including death, in the event of a serious illness. However, it is also possible that previously untreated individuals, likely mostly due to undiagnosed diabetes, are more likely to have acute hyperglycemia and higher glycemic gap, leading independently to the increased risk of mortality. In either case, this finding potentially uncovers a novel indication for diligent screening and management of diabetes and related conditions as soon as they are recognized.

Through exploratory analyses, we were interested in determining if glucocorticoid treatment altered the relationship between glycemic gap and mortality since the selection of this treatment could have been influenced by the glycemic gap [35]. Despite evidence of mortality benefit in prospective trials in severe pulmonary COVID-19, we found that glucocorticoid exposure was strongly associated with increased mortality, independent of the glycemic gap on admission. While this finding likely reflects the higher disease severity indication for the treatment with glucocorticoids, the relative effectiveness of this therapeutic approach in people with diabetes and/or with different degrees of hyperglycemia is unclear and should be considered for further study.

While our study has several strengths as a centrally coordinated, multicenter study of a large, diverse population, it also has several limitations. The available data were collected during routine care through electronic health record software; hence, while the data source was rich, it did not include several factors of potential interest, including symptoms reported by patients. The majority of comorbidities and conditions were identified based on ICD-10 coding and may have led to some inaccurate or incomplete attribution; however, whenever possible we utilized primary sources such as laboratory data to identify diagnoses (e.g. DKA and HHS). Additionally, due to the imprecision of diagnostic coding, particularly in the case of COVID-19 where many patients were transferred to our medical centers from other nonaffiliated institutions with unlinked electronic health records, we could not assign the prior diagnosis of diabetes with high accuracy. Therefore, the study group represents the larger population of individuals who generally require management for hyperglycemia during hospitalization including those with established diabetes, undiagnosed diabetes, and those with glucose ≥ 10mmol/L [180 mg/dl] without established diabetes, commonly known as stress hyperglycemia [14,36]. This may have impacted our results, although given the large percentage of undiagnosed diabetes in the US [37] our analysis of the impact of prior exposure to diabetes treatment may be more clinically relevant in hospital-based practice. Because our study used data obtained from electronic medical records, we were unable to ascertain whether any Level 3 (severe) hypoglycemia characterized by altered mental and/or physical status requiring assistance occurred. Lastly, in order to calculate the glycemic gap, all those in the cohort had an HbA_{1c} measurement either before or during hospitalization. This may have selected individuals who are either already engaged in care or those with unexpected hyperglycemia during the hospitalization and excluded many patients with stress hyperglycemia who did not have an HbA_{1c} measurement. However, these factors would not be expected to have biased results in one direction.

We conclude that the glycemic gap, defined as admission plasma glucose minus estimated average glucose based on HbA_{1c}, is a powerful predictor of poor clinical outcomes in hospitalized

people with COVID-19. A positive or elevated glycemic gap found at admission can be utilized as a marker to predict progression to severe illness and poor outcomes, including death. If applied as an easily calculated triage tool and employed similarly to scores such as APACHE, the glycemic gap could be used to assist with triage to different levels of care, e.g. floor or ICU, designed especially for people with diabetes or stress hyperglycemia. Whether the glycemic gap contributes to poor clinical outcomes, reflects the deleterious nature of untreated and/or unrecognized diabetes, is an indicator of more severe infection/inflammation, or remains an innocent bystander remains to be determined. Further studies to evaluate the potential benefit of utilizing a glycemic marker like glycemic gap to risk-stratify patients as well as to determine best approaches to the treatment of stress hyperglycemia are needed.

Acknowledgments

For the COVIDEastDM Consortium

We would like to thank Grace Cromwell[1] and Felipe Montero[5] and James Ruccio[1] for their assistance in data acquisition, dataset design and maintenance.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

References

1. Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, Lei F, Wang H, Xie J, Wang W, Li H, Zhang P, Song X, Chen X , Xiang M, Zhang C, Bai L, Xiang D, Chen MM, Liu Y, Yan Y, Liu M, Mao W , Zou J, Liu L, Chen G, Luo P, Xiao B, Zhang C, Zhang Z, Lu Z, Wang J, Lu H, Xia X, Wang D, Liao X, Peng G, Ye P, Yang J, Yuan Y, Huang X, Guo J, Zhang BH, Li H. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab. 2020;31(6):1068-1077.e3.

2. Song S, Zhang S, Wang Z, Wang S, Ma Y, Ma P, Luo H, Wang M, Jin Y. Association between longitudinal change in abnormal fasting blood glucose levels and outcome of COVID-19 patients without previous diagnosis of diabetes. Front Endocrinol (Lausanne). 2021;12:640529.

3. Mazori AY, Bass IR, Chan L, Mathews KS, Altman DR, Saha A, Soh H, Wen HH, Bose S, Leven E, Wang JG, Mosoyan G, Pattharanitima P, Greco G, Gallagher EJ. Hyperglycemia is associated with increased mortality in critically ill patients with COVID-19. Endocr Pract. 2021;27(2):95-100.

4. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab. 2002;87(3):978-982.

5. Fakhry SM, Morse JL, Wilson NY, Waswick W, Garland JM, Chipko JM, Wyse RJ, Elkbuli A, Dunne J, Litow KJ, Duane TM, Fisher C, Shillinglaw W, Banton K, Biswas S, Plurad D, Watts DD. Hyperglycemia in non-diabetic adult trauma patients is associated with worse outcomes than diabetic patients: an analysis of 95,764 patients. J Trauma Acute Care Surg. 2022. Mar 1. doi: 10.1097/TA.0000000000003576. Online ahead of print.

6. Klein SJ, Mayerhofer T, Fries D, Preuss Hernandez C, Joannidis M, Collaborators. Elevated HbA1c remains a predominant finding in severe COVID-19 and may be associated with increased mortality in patients requiring mechanical ventilation. Crit Care. 2021;25(1):300.

7. Agarwal S, Schechter C, Southern W, Crandall JP, Tomer Y. Preadmission diabetes-specific risk factors for mortality in hospitalized patients with diabetes and coronavirus disease 2019. Diabetes Care. 2020;43(10):2339-2344.

8. Patel AJ, Klek SP, Peragallo-Dittko V, Goldstein M, Burdge E, Nadile V, Ramadhar J, Islam S, Rothberger GD. Correlation of hemoglobin A1C and outcomes in patients hospitalized with COVID-19. Endocr Pract. 2021;27(10):1046-1051.

9. Liao WI, Wang JC, Chang WC, Hsu CW, Chu CM, Tsai SH. Usefulness of glycemic gap to predict ICU mortality in critically ill patients with diabetes. Medicine (Baltimore). 2015;94(36):e1525.

10. Liao WI, Wang JC, Lin CS, Yang CJ, Hsu CC, Chu SJ, Chu CM, Tsai SH. Elevated glycemic gap predicts acute respiratory failure and in-hospital mortality in acute heart failure patients with diabetes. Sci Rep. 2019;9(1):6279.

11. McDonnell ME, Simonson DC, Lebastchi J, Palermo NE, Radhakrishnan R, Westcott GP, Cromwell G, Greenfield M, Johnson M, Gopalakrishnan G, Weinstock RS, Mitri J, Garg R. Glycemic gap predicts mortality in a large multicenter diabetes cohort hospitalized with COVID-19. American Diabetes Association 82nd Scientific Sessions. Abstract #263-OR. June 2022.

12. Ramon J, Llaurado G, Guerri R, Climent E, Ballesta S, Benaiges D, López-Montesinos I, Navarro H, Fernández N, Carrera MJ, Mauricio D, Flores-Le Roux JA, Chillarón JJ. Acute-to-chronic glycemic ratio as a predictor of COVID-19 severity and mortality. Diabetes Care. 2022;45(1):255-258.

13. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J, Duda SN, REDCap Consortium. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.

14. American Diabetes Association Professional Practice Committee; Draznin B, Aroda VR, Bakris G, Benson G, Brown FM, Freeman R, Green J, Huang E, Isaacs D, Kahan S, Leon J, Lyons SK, Peters AL, Prahalad P, Reusch JEB, Young-Hyman D, Das S, Kosiborod M. 16. Diabetes care in the hospital: Standards of medical care in diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S244-S253.

15. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med. 2015 Jan 6;162(1):55-63.

16. Coppelli A, Giannarelli R, Aragona M, Penno G, Falcone M, Tiseo G, Ghiadoni L, Barbieri G, Monzani F, Virdis A, Menichetti F, Del Prato S, Pisa COVID-19 Study Group. Hyperglycemia at hospital admission is associated with severity of the prognosis in patients hospitalized for COVID-19: The Pisa COVID-19 Study. Diabetes Care. 2020;43(10):2345-2348.

17. Yang Y, Cai Z, Zhang J. Hyperglycemia at admission is a strong predictor of mortality and severe/critical complications in COVID-19 patients: a meta-analysis. Biosci Rep. 2021;41(2):BSR20203584.

18. Hartmann-Boyce J, Rees K, Perring JC, Kerneis SA, Morris EM, Goyder C, Otunla AA, James OA, Syam NR, Seidu S, Khunti K. Risks of and from SARS-CoV-2 infection and COVID-19 in people with diabetes: a systematic review of reviews. Diabetes Care. 2021;44(12):2790-2811.

19. Lou R, Jiang L, Zhu B. Effect of glycemic gap upon mortality in critically ill patients with diabetes. J Diabetes Investig. 2021;12(12):2212-2220.

20. Chen PC, Tsai SH, Wang JC, Tzeng YS, Wang YC, Chu CM, Chu SJ, Liao WI. An elevated glycemic gap predicts adverse outcomes in diabetic patients with necrotizing fasciitis. PLoS One. 2019;14(10):e0223126.

21. Jensen AV, Egelund GB, Andersen SB, Petersen PT, Benfield T, Witzenrath M, Rohde G, Ravn P, Faurholt-Jepsen D. The glycemic gap and 90-day mortality in community-acquired pneumonia. A prospective cohort study. Ann Am Thorac Soc. 2019 Dec;16(12):1518-1526.

22. Donagaon S, Dharmalingam M. Association between glycemic gap and adverse outcomes in critically ill patients with diabetes. Indian J Endocrinol Metab. 2018;22(2):208-11.

23. Bellaver P, Schaeffer AF, Dullius DP, Viana MV, Leitao CB, Rech TH. Association of multiple glycemic parameters at intensive care unit admission with mortality and clinical outcomes in critically ill patients. Sci Rep. 2019;9(1):18498.

24. Fawzy F, Saad MSS, ElShabrawy AM, Eltohamy MM. Effect of glycemic gap on short term outcome in critically ill patient: In zagazig university hospitals. Diabetes & metabolic syndrome. 2019;13(2):1325-8.

25. Garg R, Hurwitz S, Turchin A, Trivedi A. Hypoglycemia, with or without insulin therapy, is associated with increased mortality among hospitalized patients. Diabetes Care. 2013;36(5):1107-1110.

26. Guo JY, Chou RH, Kuo CS, Chao TF, Wu CH, Tsai YL, Lu YW, Kuo MR, Huang PH, Lin SJ. The paradox of the glycemic gap: Does relative hypoglycemia exist in critically ill patients? Clin Nutr. 2021;40(7):4654-4661.

27. Roy S, Demmer RT. Impaired glucose regulation, SARS-CoV-2 infections and adverse COVID-19 outcomes. Transl Res. 2022;241:52-69.

28. Drucker DJ. Diabetes, obesity, metabolism, and SARS-CoV-2 infection: the end of the beginning. Cell Metab. 2021;33(3):479-498.

29. Vasbinder A, Anderson E, Shadid H, Berlin H, Pan M, Azam TU, Khaleel I, Padalia K, Meloche C, O'Hayer P, Michaud E, Catalan T, Feroze R, Blakely P, Launius C, Huang Y, Zhao L, Ang L, Mikhael M, Mizokami-Stout K, Pennathur S, Kretzler M, Loosen SH, Chalkias A, Tacke F, Giamarellos-Bourboulis EJ, Reiser J, Eugen-Olsen J, Feldman EL, Pop-Busui R, Hayek SS, ISIC Study Group. Inflammation, hyperglycemia, and adverse outcomes in individuals with diabetes mellitus hospitalized for COVID-19. Diabetes Care. 2022;45(3):692-700.

30. Kusmartseva I, Wu W, Syed F, Van Der Heide V, Jorgensen M, Joseph P, Tang X, Candelario-Jalil E, Yang C, Nick H, Harbert JL, Posgai AL, Paulsen JD, Lloyd R, Cechin S, Pugliese A, Campbell-Thompson M, Vander Heide RS, Evans-Molina C, Homann D, Atkinson MA. Expression of SARS-CoV-2 entry factors in the pancreas of normal organ donors and individuals with COVID-19. Cell Metab. 2020;32(6):1041-1051.e6.

31. Coate KC, Cha J, Shrestha S, Wang W, Goncalves LM, Almaca J, Kapp ME, Fasolino M, Morgan A, Dai C, Saunders DC, Bottino R, Aramandla R, Jenkins R, Stein R, Kaestner KH, Vahedi G, HPAP Consortium, Brissova M, Powers AC. SARS-CoV-2 cell entry factors ACE2 and TMPRSS2 are expressed in the microvasculature and ducts of human pancreas but are not enriched in β cells. Cell Metab. 2020;32(6):1028-1040. e4.

32. Ali NA, O'Brien JM, Jr., Dungan K, Phillips G, Marsh CB, Lemeshow S, Connors AF, Preiser JC. Glucose variability and mortality in patients with sepsis. Crit Care Med. 2008;36(8):2316-2321.

33. Gerbaud E, Darier R, Montaudon M, Beauvieux MC, Coffin-Boutreux C, Coste P, Douard H, Ouattara A, Catargi B. Glycemic variability is a powerful independent predictive factor of midterm major adverse cardiac events in patients with diabetes with acute coronary syndrome. Diabetes Care. 2019;42(4):674-681.

34. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA. 2006;295(14):1681-1687.

35. RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693-704.

36. Moyer ED, Lehman EB, Bolton MD, Goldstein J, Pichardo-Lowden AR. Lack of recognition and documentation of stress hyperglycemia is a disruptor of optimal continuity of care. Sci Rep. 2021 Jun 1;11(1):11476.

37. Cheng YJ, Kanaya AM, Araneta MRG, Saydah SH, Kahn HS, Gregg EW, Fujimoto WY, Imperatore G. Prevalence of diabetes by race and ethnicity in the United States, 2011-2016. JAMA. 2019;322(24):2389-2398.

Table 1. Baseline Characteristics of Study Population (n = 1,786)

Variable	N (%) or mean ± SD
Demographics	
Age (yrs)	65.6 ± 14.4
Sex	
Male	917 (51.3%)
Female	869 (48.7%)
Race	
White / Caucasian	952 (53.3%)
Black / African-American	335 (18.8%)
Asian	53 (3.0%)
Other [a]	400 (22.4%)
Missing	46 (2.6%)
Ethnicity	
Hispanic / Latino	518 (29.0%)
Not Hispanic / Latino	1250 (70.0%)
Missing	18 (1.0%)
Clinical / Laboratory	
Criteria for Cohort Inclusion	
Diagnosed diabetes by ICD-10 code	1464 (82.0%)
HbA_{1c} > 6.4% without diagnosed diabetes	169 (9.5%)
HbA_{1c} ≤ 6.4% with two glucoses > 10 mmol/l	153 (8.6%)
BMI (kg/m²)	31.5 ± 7.9

HbA_{1c} (%)	8.07 ± 2.25
Admission Glucose (mmol/l)	12.0 ± 7.5
Estimated Average Glucose (mmol/l) [b]	10.3 ± 3.6
Glycemic Gap (mmol/l) [c]	1.7 ± 6.2
Estimated GFR (ml/min/1.73 m²)	56 ± 29
Urine albumin/creatinine (mg/mmol)	4.1 (1.2, 22.1) [d]
Lactate (mmol/l)	2.0 ± 1.4
Beta-hydroxybutyrate (mmol/l)	1.8 ± 2.4
Diabetes History	
Any Diabetes Medication Use [e]	49.4%
Insulin	35.2%
Metformin	24.2%
Sulfonylureas	10.1%
GLP-1 agonists	4.3%
DPP-4 inhibitors	3.6%
SGLT-2 inhibitors	3.2%
Thiazolidinediones	0.7%
Hypoglycemia on Admission (< 3.9 mmol/l)	1.8%
DKA on Admission	2.4%
Comorbidities [f]	
Any comorbidity	76.9%
Hypertension	62.3%
Coronary Artery Disease	27.7%
Chronic Kidney Disease	25.4%
Congestive Heart Failure	18.4%
Chronic Obstructive Pulmonary Disease	15.2%

Cancer	13.1%
Liver Disease	12.6%
Asthma	11.7%
Stroke	11.1%
Use of ACE-I or ARB	31.4%
Use of Statins	37.6%

[a] Multiracial, American-Indian or Alaska-Native, Hawaiian or Pacific Islander, or other

[b] Estimated average glucose = 28.7 × HbA_{1c} - 46.7 mg/dl; (18 mg/dl = 1 mmol/l)

[c] Glycemic Gap = Admission glucose - estimated average glucose

[d] Median (interquartile range)

[e] Patients may be taking more than one medication

[f] Patients may have more than one comorbidity

Table 2. Associations (by univariate logistic regression) of predictors with primary and secondary outcomes. Significant associations shown in bold. (OR = odds ratio)

	Death during Hospitalization		**Mechanical Ventilation**		**Intensive Care Unit**	
Variable	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Age (yr)	**1.040 (1.028, 1.053)**	**<0.001**	**0.990 (0.982, 0.998)**	**0.013**	0.994 (0.988, 1.001)	0.102
Sex (male)	1.11 (0.82, 1.50)	0.495	0.89 (0.71, 1.11)	0.302	0.86 (0.71, 1.05)	0.138
Race						
White	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Black	0.84 (0.56, 1.26)	0.395	1.31 (0.96, 1.78)	0.089	1.04 (0.80, 1.36)	0.774
Asian	0.77 (0.30, 1.98)	0.593	1.38 (0.73, 2.59)	0.322	1.27 (0.73, 2.21)	0.407
Other	0.67 (0.44, 1.00)	0.052	1.15 (0.86, 1.53)	0.339	0.80 (0.63, 1.02)	0.076
Ethnicity (Hispanic)	0.85 (0.60, 1.20)	0.350	**1.64 (1.28, 2.10)**	**<0.001**	**1.45 (1.16, 1.80)**	**0.001**
BMI (kg/m^2)	1.010 (0.991, 1.029)	0.290	**1.017 (1.003, 1.032)**	**0.018**	1.007 (0.994, 1.020)	0.292
HbA_{1c} (%)	0.940 (0.875, 1.010)	0.090	0.974 (0.926, 1.025)	0.318	1.004 (0.962, 1.048)	0.853
Glucose (mmol/l)	**1.022 (1.005,**	**0.014**	**1.018 (1.003,**	**0.019**	**1.035 (1.020,**	**<0.001**

	1.040)		**1.033)**		**1.049)**	
Glycemic Gap (mmol/l)	**1.040 (1.019, 1.061)**	**<0.001**	**1.032 (1.013, 1.050)**	**0.001**	**1.053 (1.034, 1.072)**	**<0.001**
DKA on Admission	**3.45 (1.26, 9.48)**	**0.016**	**11.53 (4.14, 32.09)**	**<0.001**	∞ [a]	
Hypoglycemia on Admission (< 3.9 mmol/l)	0.27 (0.04, 1.97)	0.195	0.66 (0.25, 1.74)	0.401	0.46 (0.20, 1.07)	0.073
eGFR (ml/min/1.73m^2)	**0.984 (0.978, 0.991)**	**<0.001**	1.001 (0.997, 1.005)	0.616	1.003 (0.999, 1.007)	0.198
CKD stage						
eGFR ≥ 60	1.00 (ref)		1.00 (ref)		1.00 (ref)	
eGFR 30-59	**2.67 (1.75, 4.08)**	**<0.001**	1.03 (0.77, 1.37)	0.860	0.86 (0.66, 1.11)	0.250
eGFR 15-29	**2.82 (1.66, 4.80)**	**<0.001**	0.94 (0.62, 1.43)	0.783	0.70 (0.49, 1.02)	0.066
eGFR < 15	**2.49 (1.32, 4.68)**	**0.005**	1.03 (0.63, 1.69)	0.909	1.04 (0.67, 1.62)	0.852
Any DM Medication	**0.74 (0.54, 1.00)**	**0.050**	**0.64 (0.50, 0.80)**	**<0.001**	**0.81 (0.66, 0.98)**	**0.034**
Insulin	0.96 (0.68, 1.36)	0.822	**0.74 (0.57, 0.97)**	**0.027**	0.85 (0.69, 1.05)	0.142
Metformin	0.71 (0.48, 1.03)	0.073	0.82 (0.62, 1.09)	0.170	0.82 (0.65, 1.04)	0.107
Use of ACE-I or ARB	0.71 (0.50, 1.02)	0.066	**0.63 (0.48, 0.83)**	**0.001**	**0.79 (0.63, 0.99)**	**0.040**
Use of statin	0.81 (0.58, 1.14)	0.230	**0.70 (0.55, 0.91)**	**0.006**	0.82 (0.66, 1.01)	0.066

[a] All patients with DKA were admitted to the ICU

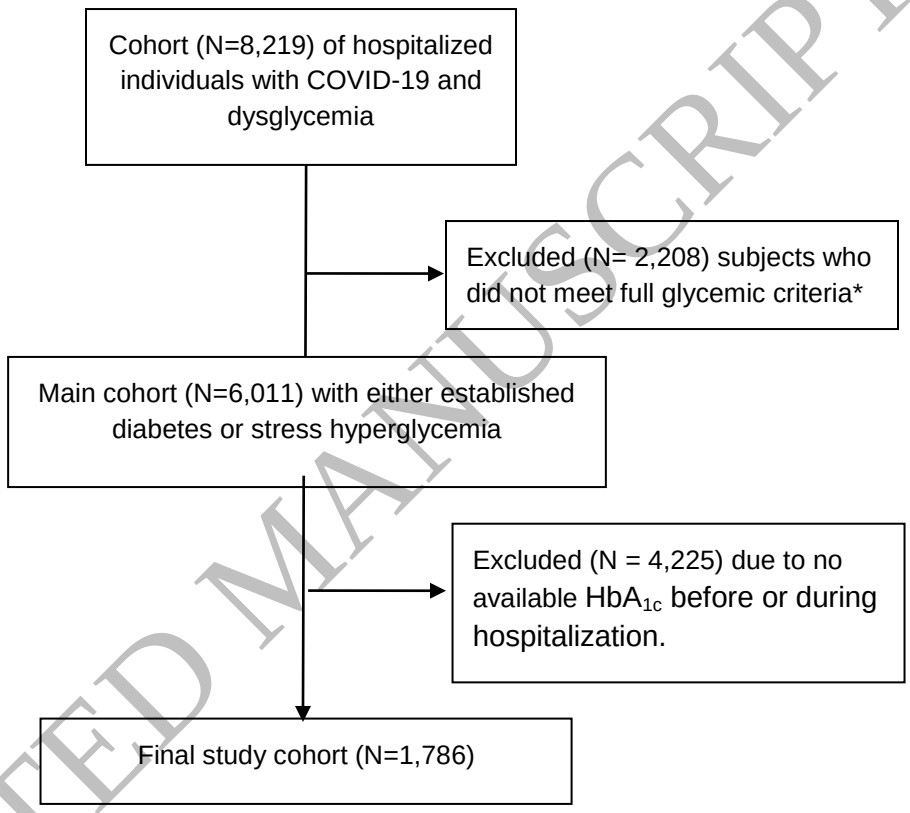
Table 3. Adjusted models (by multivariable logistic regression) of associations of predictors with primary and secondary outcomes. (OR = odds ratio)

Outcome	Predictor Variable	OR (95% CI)	p value
Death during Hospitalization	Age (yrs)	1.026 (1.004, 1.049)	0.021
	Glycemic Gap (mmol/l)	1.055 (1.017, 1.095)	0.004
	BMI (kg/m^2)	1.040 (1.004, 1.078)	0.030
	DKA on Admission	3.56 (1.08, 11.71)	0.037
	eGFR (ml/min/1.73m^2)	0.986 (0.976, 0.997)	0.010
	Any Diabetes Medication	0.41 (0.23, 0.73)	0.002
Mechanical Ventilation	Age (yrs)	0.987 (0.976, 0.998)	0.021
	Glycemic Gap (mmol/l)	1.056 (1.026, 1.087)	< 0.001
	Sex (male)	0.63 (0.45, 0.87)	0.005
	BMI (kg/m^2)	1.025 (1.003, 1.048)	0.017
	DKA on Admission	13.60 (3.82, 48.45)	< 0.001
	Use of ACE-I or ARB	0.54 (0.35, 0.84)	0.006
ICU Admission	Glycemic Gap (mmol/l)	1.060 (1.032, 1.089)	< 0.001
	Sex (male)	0.72 (0.55, 0.95)	0.019
	DKA on Admission	∞ [a]	
	Any Diabetes Medication	0.69 (0.52, 0.92)	0.011

[a] All patients with DKA were admitted to the ICU

Figure 1. Flow diagram outlining the development of the study cohort

.



* Established diabetes by ICD-10 code or HbA_{1c} ≥ 6.5% or glucose > 10 mmol/l (180 mg/dl) twice in the same 24 hr. period

Figure 2. Graphical display of multivariable logistic regression of the primary outcome (mortality in the hospital, expressed as a probability) as a function of glycemic gap, adjusted for age, BMI, DKA on admission, eGFR, and diabetes medication use (model $\chi^2_{(6)} = 45.02$, $p < 0.001$).