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Usefullness of Glycemic Gap to Predict ICU Mortality in Critically ILL Medical Patient

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Abstract

Glycemic gap has been independently associated with an increased risk of mortality in critically ill Patients. However, it is also necessary to consider pre existing hyperglycemia when investigating the relationship between Glycemic gap and mortality in critically ill patients. We therefore assessed whether the gap between admission glucose and A1C-derived average glucose (ADAG) levels could be a predictor of mortality in critically ill patients with diabetes. We prospectively study the Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores & Sequential Organ Failure Assessment score and clinical outcomes of critically ill patients admitted in medical intensive care unit (ICU) . The glycosylated hemoglobin (HbA1c) levels were converted to the ADAG by the equation, ADAG = [(28.7*HbA1c)-46.7]. We also used receiver operating characteristic (ROC) curves to determine the optimal cut-off value for the glycemic gap when predicting ICU mortality and used the net reclassification improvement (NRI) to measure the improvement in prediction performance gained by adding the glycemic gap to the APACHE-II score & SOFA score. We enrolled 100 patients, of which 87 (17.0%) died during their ICU stay. Nonsurvivors had significantly higher APACHE-II scores and SOFA score glycemic gaps than survivors (P<0.001). Critically ill patients and a glycemic gap >84mg/dL had significantly higher ICU mortality and adverse outcomes than those with a glycemic gap <84mg/dL (P<0.001). Combining the glycemic gap with the APACHE-II score significantly increased its discriminative ability to predict ICU mortality, increasing the AUC from 0.91 (95% CI: 0.84-0.94) to 0.98 (95%: 0.96 -0.99) (p < 0.001) (NRI-13.9%)While combining the glycemic gap with the SOFA score significantly increased its discriminative ability to predict ICU mortality, increasing the AUC from 0.91 (95% CI: 0.84-0.94) to 0.99 (95%: 0.97 -1.00) (p < 0.001) (NRI-14.1%). The glycemic gap can be used to assess the severity and prognosis of critically ill patients admitted in medical ICU. The addition of the glycemic gap to the APACHE-II score & SOFA score significantly improved its ability to predict ICU mortality.

Keywords: Glycemic Gap, ADAG, APACHE, SOFA, ICU Mortality.

Introduction

Emergency department (ED) hyperglycemia has been observed to be a strong predictor of in hospital outcomes.[1] Glycemic gap is common in patients with critical illness, including sepsis, multiple trauma, major surgery, and acute myocardial infarction (AMI).[2-5] Glycemic gap occurs secondary to an increase in the levels of counter-regulatory hormones (cortisol, catecholamines, glucagon, and growth hormone), which results in increased gluconeogenesis and decreased glycogenolysis. Notably, the phenomenon occurs in individuals with and without a history of diabetes. The Acute Physiology and Chronic Health Evaluation II (APACHE-II) score is a commonly used for predicting mortality in the intensive care unit (ICU). However, glucose levels are not included; despite the growing evidence of the negative effect of

hyperglycemia on ICU mortality.[6] In patients without diabetes, not only is there evidence of a stronger association between ICU mortality and elevated levels of mean serum glucose and glucose variability[7-8] but also the mortality risk is reater.[6] Conversely, acute hyperglycemia in patients with diabetes could result from acute physiological stress, a high baseline blood glucose, or both, which confounds the assessments. A strong correlation between glycosylated hemoglobin (HbA1c) and mean plasma glucose levels in the preceding 3 months was found in an international multicenter A1C-derived average glucose (ADAG) study, which allows long-term average glucose levels to be estimated using HbA1c values. We hypothesize that glycemic gap which is calculated by subtracting the ADAG from the admission time glucose levels may eliminate the influence of chronic hyperglycemia on the disease severity assessments in patients with diabetes. In this study, ours aims and objectives were to determine whether the glycemic gap could be used to predict ICU mortality and whether incorporation of the glycemic gap into the APACHE-II score and SOFA score could increase the discriminative performance for predicting ICU mortality.

Material and Methods

We conducted a prospective observational study of consecutive patients admitted to our medical ICU between June 2016 and December 2017.The institutional Ethics Committee approved this study and waived the need for informed consent. We included 100 consecutive critically ill patients. Patients were excluded based on the following criteria: age <18 years, hypoglycemia (blood glucose<70mg/dL) at initial presentation in the ED, an admission diagnosis of diabetic ketoacidosis or hyperosmolar hyperglycemic state, treatment with corticosteroids and death within 1 day of admission. Included patients were classified into several categories according to their primary diagnosis as follows: Cardiac and vascular, Thoracic and Respiratory, Neurological, Gastrointestinal, and others. The medical reports of included patients were collected for the following data: age; sex; underlying comorbidities; laboratory data, including plasma glucose level at initial ED presentation and HbA1c levels, adverse outcomes; length of mechanical ventilation; and the length of stay in the ICU and hospital. The following adverse outcomes were recorded: mortality during admission; multiple organ dysfunction syndrome; acute respiratory distress. syndrome; acute respiratory failure, Days on ventilators, shock, acute kidney injury The admission glucose level was defined as the initial glucose recorded in the ED. HbA1c assays were performed using a blood analyzer

equipped with a high-performance liquid chromatography system. To convert HbA1c levels to chronic average blood glucose levels, we used the following equation: ADAG=[(28.7×HbA1c)−46.7].[11]The glycemic gap was calculated from the glucose level on admission, as follows: glycemic gap=[admission time glucose−ADAG].

Statistical Analysis: Continuous data are expressed as the mean±standard deviation and categorical data are expressed as frequencies (percentage). Analyses were performed by the 2-tailed Student *t* test and the Chi-square test or Fisher exact test as applicable. A receiver operating characteristic (ROC) curve was plotted to analyze the discriminative power of the prediction tools, and the area under the ROC curve (AUC) and 95% confidence internal (CI) was calculated. The log-rank test was used to determine the statistical significance on survival curves. The net reclassification improvement (NRI), a function of MATLAB (Math Works, Natick, MA), was used to assess the improvement in model performance after adding parameters.[12] Otherwise, data were analyzed using SPSS statistics for Windows, Version 17.0 (SPSS Institute, Inc., Chicago, IL). Differences with *P* values of <0.05 were considered statistically significant.

Observation and Results:100 critically ill patients who were admitted to the ICUs during study period. Out of which 31 died during their ICU stay. Most mortalities were from the Bronchopneumonia (40.6%), genitourinary 7 (21.7%), Cardiac and Vascular 3(10.1%),gastro Intestinal 3 (10.1%), Hepatobiliary 2 (6.4%). Compared with survivors, non-survivors had higher APACHE-II scores, SOFA scores admission glucose levels and glycemic gaps (*P*<0.001).

Table-I. Underlying Conditions of the ICU Survivors and Non-survivors

	Survived (n = 69)	**Died (n = 31)**	***P Value***
Age (years)	58.01±17.03	61.61±15.91	0.32
Patients Comorbidities			
DM	32 (46.4)	15 (48.4)	0.85
HTN	33 (47.8)	13 (41.9)	0.58
IHD	17 (24.6)	9 (29.0)	0.64
CKD	11 (15.9)	6 (19.4)	0.67
COPD	6 (8.7)	3 (9.7)	0.87
CLD	5 (7.2)	0 (0.0)	0.32
Diagnosis at admission			
Bronchopneumonia	22 (32.3)	12 (40.6)	0.72
Genitourinary	13 (19.4)	7 (21.7)	0.86
Cardiac and vascular	2 (3.2)	3 (10.1)	0.42
Gastro Intestinal	6 (8.7)	3 (10.1)	0.88
Hepatobiliary	2 (3.2)	2 (6.4)	0.74

Compared with survivor, non-survivors tended to be older while morbidity like HTN (47.8%) was more common in survivor group and the difference was not significant (p<0.01)

Table-II

Comparison of characteristics of survivor and non-survivors (n=100)						
	Survived (n = 69)		**Died (n = 31)**		**Difference in mean (95% CI)**	**p value***
	Mean	**SD**	**Mean**	**SD**		
HR	107.4	10.64	103.5	9.24	3.8(0.5-8.2)	0.08
RR	25.38	5.05	25.71	3.96	0.33 (-2.37-1.30)	0.74
SBP	96.38	13.23	99.94	19.02	3.55 (-10.1-2.98)	0.28
DBP	60.46	12.42	59.74	9.97	0.72(-4.70-5.75)	0.77
S. Creatinine	2.55	2.01	3.91	3.36	1.36 (0.04-2.67)	**0.01**
Total Bilirubin (mg/dl)	2.20	2.86	2.21	3.67	0.01(1.35- 1.33)	0.98
Temperature	100.64	1.21	100.58	1.23	0.43 (0.08-0.94)	0.81
Platelets (Lakh)	1.60	1.08	1.52	1.05	-0.45 (-0.90-0.11)	0.74
ESR	33.14	26.67	42.87	31.38	-1.35 (-13.73-11.02)	0.11

Serum creatinine was found to be significantly higher among those who did not survive when compared to those who survived (p value < 0.05) while other variables were not different significantly between survivors and non-survivors.

Table-III. Comparison of the Characteristic of Critically ill ICU survivor and non-survivor

	Survival (n = 69)	Non-Survival (n = 31)	p value*
Age (years)	58.01±17.03	61.61±15.91	0.32
HR	107.4±10.64	103.5±9.24	0.08
RR	25.38±5.05	25.71±3.96	0.74
SBP	96.38±13.23	99.94±19.02	0.28
DBP	60.46±12.42	59.74±9.97	0.77
S. Creatinine	2.55±2.01	3.91±3.36	0.01
Total Bilirubin (mg/dl)	2.2±2.86	2.21±3.67	0.98
Temperature	100.64±1.21	100.58±1.23	0.81
Platelets (Lakh)	1.6±1.08	1.52±1.05	0.74
ESR	33.14±26.67	42.87±31.38	0.11
Admission Glucose (mg/dl)	229.84±42.85	317.61±51.13	<0.001
ADAG (mg/dl)	145.12±35.11	176.97±33.84	<0.001
Glycemic Gap	84.58±22.88	140.63±33.34	<0.001
HbA1C	6.68±1.12	7.79±1.17	<0.001
APACHE II Score	18.46 ± 4.65	31.84 ± 4.48	<0.001
SOFA Score	7.83 ± 2.98	17.74 ± 1.99	<0.001

Predictors of ICU Mortality

Figure 1: ROC curves for glucose parameters and the APACHE-IIscore for predicting ICU mortality. Glycemic parameters includedadmission glucose levels, glycemic gap, and HbA1c. The AUC of the APACHE-II score was larger than that of glycemic gap oradmission glucose levels (P<0.001).

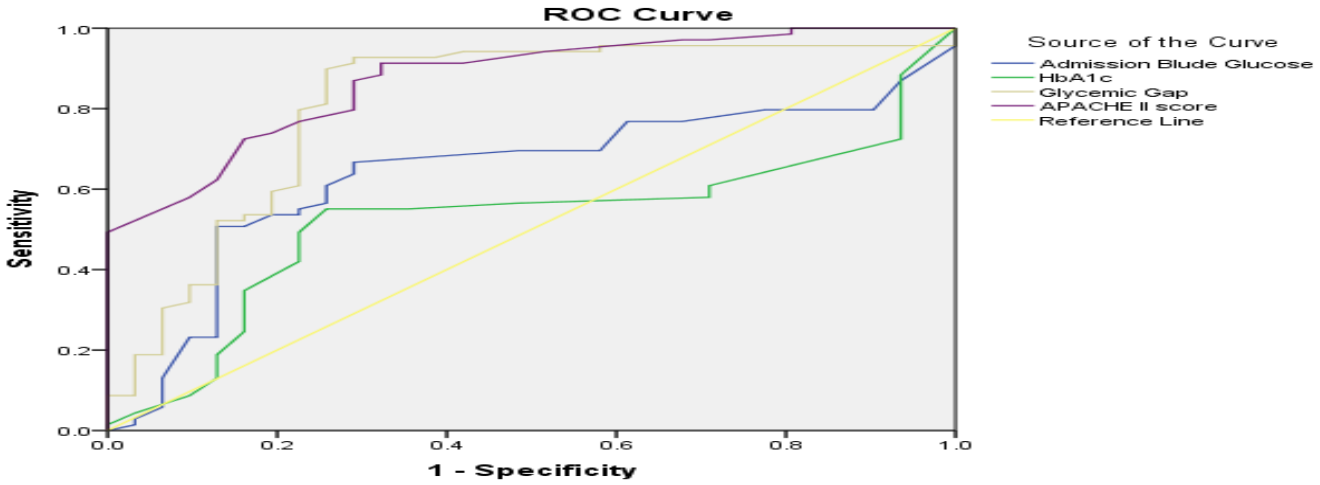


Table IV: AUC for different variable with 95% CI for predicting mortality

Test Variable	AUC	95% Confidence Interval
Admission Blood Glucose	.88	0.79-0.95
HbA1c	.73	0.62-0.84
Glycemic Gap	.91	0.84-0.98
APACHE II score	.96	0.94-0.99

Glycemic Gap in Critically Ill Patients: The optimal cut-off for the glycemic gap to predict ICUmortality in patients with diabetes was 84 mg/dl (using the Youden index), which provided a sensitivity and specificity of 89.9% and 74.2%, respectively.

Table-V

ICU mortality according to glycemic gap categories among critically ill patients				
Glycemic gap	**Final Outcome**		**Total n (%)**	**p value**
	Survived n (%)	**Died n (%)**		
0-40	0 ((0.0)	1 (100.0)	1 (1.0)	<0.001
41-80	38 (100.0)	0 (0.0)	38 (38.0)	
81-120	26 (81.2)	6 (18.8)	32 (32.0)	
>120	5 (17.2)	24 (82.8)	29 (29.0)	
Total	69(69.0)	31(31.0)	100(100.0)	

There was an upward trend for ICU mortality with increasing glycemic gaps. The ICU mortality rate was increased markedly when the glycemic gap exceeded 80 mg/dl.

Table-VI. Clinical Outcome versus Glycemic Gap in critically ill ICU patients

	Glycemic Gap (n=43)	Glycemic Gap (n=57)	p value*
	<84	≥84	
Age (years)	56.16 ± 16.35	61.35 ± 16.79	P =0.1253
S. Creatinine	2.87 ± 2.35	3.04 ± 2.74	P =0.7519
Total Bilirubin (mg/dl)	2.44 ± 3.68	2.02 ± 2.64	P = 0.5044
Platelets (Lakh)	157771 ± 111529	158056.3 ± 104926.8	P = 0.9896
ESR	30.02± 26.38	42.49 ± 31.78	P = 0.0396
ICU Mortality	1(2.32%)	30(52.63%)	
ICU stay (Days)	8.41 ± 3.04	11.12 ± 3.37	P < 0.0001
Ventilator (Days)	3.69 ± 3.43	8.52 ± 4.59	P < 0.0001

Figure 2: Kaplan–Meier survival curve of the glycemic gap in critically ill patients. The ICU mortality was statically significant between diabetic patients with high (>84 mg/dl) and low (<84 mg/dl) glycemic gaps. (log rank p =0.64)

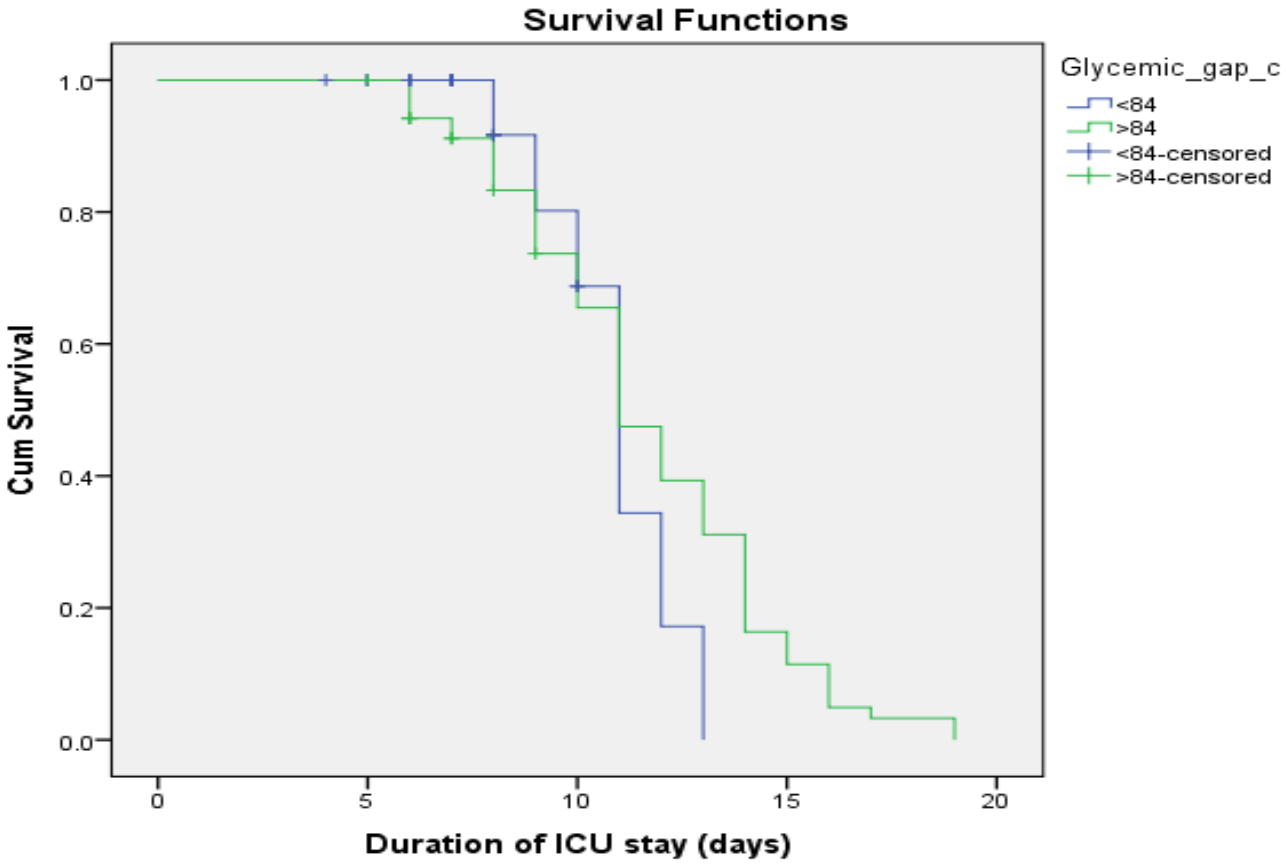
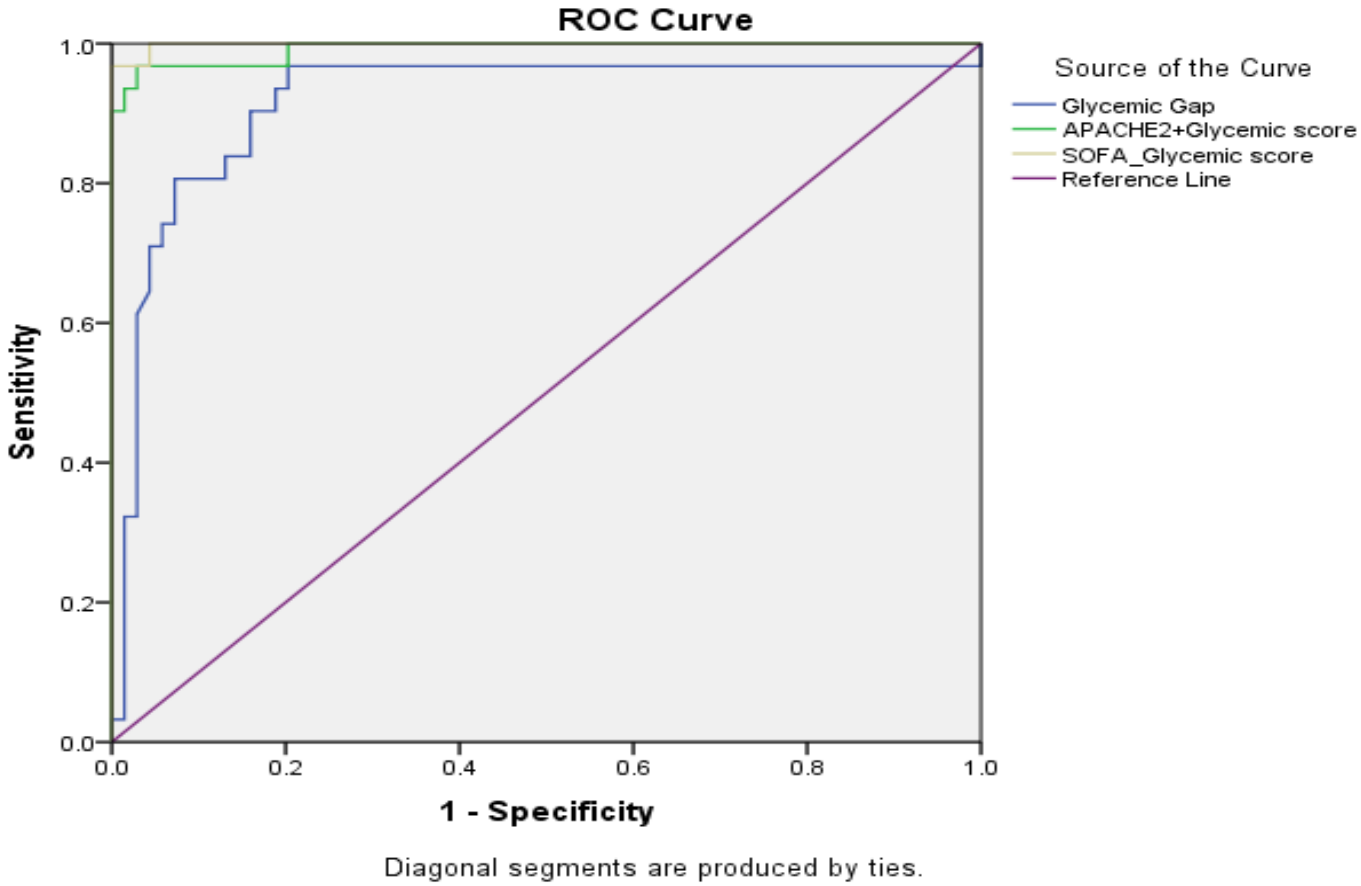


Figure 3. ROC curves after integrating the glycemic gap into the APACHE-II and SOFA scores.



Combining the glycemic gap with the APACHE-II score significantly increased its discriminative ability to predict ICU mortality, increasing the AUC from 0.91 (95% CI: 0.84-0.94) to 0.98 (95%: 0.96 -0.99) ($p < 0.001$) (NRI-13.9%)While combining the glycemic gap with the SOFA score significantly increased its discriminative ability to predict ICU mortality, increasing the AUC from 0.91 (95% CI: 0.84-0.94) to 0.99 (95%: 0.97 -1.00) ($p < 0.001$) (NRI-14.1%)

Discussion

Our major findings in patients with diabetes were as follows: compared with other blood glucose-based parameters, the glycemic gap was able to predict ICU mortality; a glycemic gap ≥84mg/dL was associated with significantly higher ICU and in-hospital mortality rates and adverse outcomes compared with those with a glycemic gap <84mg/dL and adding the glycemic gap to the APACHE-II score and SOFA score could significantly increase its discriminative power. Thus, the glycemic gap could be successfully incorporated into future clinical scoring systems to enhance their discriminative performance.Researchers have suggested that SIH could predict outcomes in critically ill patients because the severity of SIH correlates to disease severity. SIH forms a part of the adaptive response to critical illness, in which excessive cytokine and counter-regulatory hormone release results in insulin resistance. Hyperglycemia and insulin resistance could be evolutionarily preserved responses that increase the chances of survival from acute illness. Therefore, attempts to interfere with this

exceedingly complex multisystem adaptive response could be harmful.[13]On the other hand, because hyperglycemia is the cardinal feature of diabetes, preexisting hyperglycemia must be considered when investigating the association between SIH and adverse outcomes in patients with diabetes. When acutely ill, the epiphenomenon of admission hyperglycemia could result from a combination of acute physiological stress or higher baseline blood glucose (HbA1c and ADAG).[14] Because of the discordance between these phenomena, the fundamental question with regard to acute hyperglycemia in nondiabetic and diabetic patients is complicated. We observed that an elevated glycemic gap (≥84 mg/dL) could predict several adverse outcomes and ICU mortality in this patient group.We also confirmed that the APACHE-II score was a good predictor of ICU mortality in critically ill patients with diabetes than either the glycemic gap or the admission glucose level. It is unlikely that any single biochemical variable would have a sufficiently high AUC to be useful for early prognostication when used in isolation. When a novel biomarker becomes available to facilitate risk prediction, it should be compared against existing best practice tool.[15] By incorporating the glycemic gap into the APACHE-II score, we found better discriminative performance for predicting ICU mortality in our cohort. The American Diabetes Association recommends biannual evaluation of HbA1c levels in patients with stable treatment and glycemic control and recommends quarterly evaluation in patients with changes in therapy or who are not meeting glycemic targets. [16]We believe that incorporating the glycemic gap into other acute assessment tools is clinically feasible and could provide increased discriminative performance in critically ill patients with diabetes, without the need for additional laboratory examinations. However, a larger prospective cohort study is needed to confirm our hypothesis. The difference between the ICU and hospital mortality rates was smaller for patients with a glycemic gap ≥84 mg/dL than for those with a glycemic gap <84 mg. We speculate that patients with the former had greater disease severity than the latter. A high glycemic gap in the ICU was therefore associated with less chance of surviving to the general wards. Our results are consistent with previous studies where admission glucose, mean glucose, and maximum glucose levels were associated with adverse outcomes and ICU morality.[10,17,18] In addition, higher admission APACHE-II scores among critically ill patients with Glycemic gap.[2] For example, admission glucose levels, HbA1c, and Glycemic gap were significantly associated with ICU mortality in critically ill patients, with similar AUCs for each glycemic variable (0.88, 0.73, and 0.91, respectively).[9] A recent study of 194,772 patients showed that ICU mortality increased progressively with the severity of hyperglycemia [17] whereas another large multicenter study showed that admission hyperglycemia was associated with increased ICU mortality, including in patients with AMI, arrhythmia, unstable angina, and pulmonary embolism.[6,18]The presence of preexisting hyperglycemia in critically ill patients may be a confounding factor for predicting ICU mortality in patients with diabetes; indeed, several studies have reported a relatively weak relationship.[6-8,19] Egi et al observed that ICU mortality was not strictly associated with the diabetes, but with the chronic blood glucose control. They observed a stronger association between acute hyperglycemia and ICU mortality in patients without diabetes. However, poorer glycemic control has also been shown not to be associated with poorer outcomes. [9,10,11]

Conclusions

In this study, an elevated glycemic gap was associated with an increased risk of ICU mortality and it improved the discriminative performance of the APACHE-II score and SOFA score. The glycemic gap can be used to assess the severity and prognosis of patients presenting with critical illness. Compared with other blood glucose-based parameters, the glycemic gap could predict ICU mortality in patients with diabetes. A glycemic gap ≥84mg/dL in patients with diabetes was associated with significantly higher ICU and in-hospital mortality rates and adverse outcomes compared with those with a glycemic gap <84 mg/dL. The discriminative power of the APACHE-II score and SOFA could significantly increased after adding the glycemic gap into these score.

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