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The Predictive Performance of Blood Glucose Prognosticators And There's Correlations With Major Clinical Outcomes In Critically Ill Patients Who Are Taking Cryst-Insulin Infusion

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Abstract

Objectives: Stress hyperglycemia is commonly encountered in critically ill patients and is associated with increased morbidity and mortality. Primarily, we aim to investigate the predictive efficacies of percentage variation in blood glucose ($\%BG_{var}$), average blood glucose (BG_{avg}), and maximum blood glucose (BG_{max}) as prognosticators of overall 28-day ICU mortality. Also, we intend to evaluate the optimal cutoff points of these three tested prognosticators.

Methods: A retrospective analysis was conducted for 188 eligible patients admitted to our adult ICU between April 2017 and Sep 2018. Patients who died or were discharged before completing at least 1 week after ICU admission were excluded. An Independent and One Sample T-tests were conducted to analyze the continuous variables; while Chi Square was conducted to analyze the ordinal variables. A Receiver Operating Characteristic (ROC) and Sensitivity Analysis were conducted to compare the prognostic abilities and optimal cutoff points of the three tested prognosticators on the overall 28-day ICU mortality.

Results: The Means±SDs of BG_{max}, BG_{avg}, and $\%BG_{var}$ were significantly lower in Survivors than in Non-survivors (227.6±10.2 mg/dl, 185.5±3.52 mg/dl, and 45.4%±11.3% **vs.** 250.0±26.7 mg/dl, 193.4±7.51 mg/dl, and 58.1%±20.3%). The best cut-off values for $\%BG_{var}$, BG_{avg}, and BG_{max} were 55.6%, 188.5 mg/dl, and 241.5 mg/dl for overall 28-day ICU mortality. The AUROC curve of $\%BG_{var}$ (0.923; 95%CI, 0.877-0.969) in this study was significantly greater than that of BG_{avg} (0.874; 95% CI, 0.802-0.947) and BG_{max} (0.865; 95% CI, 0.791-0.939).

Conclusion: $\%BG_{var}$ is more predictive effective prognosticator with high sensitivity, specificity, performance, and accuracy when compared with BG_{avg}, and BG_{max} to forecast overall 28-day ICU mortality in hyperglycemic critically ill patients receiving a crystal-insulin infusion.

Keywords: Blood glucose, Critically, Cryst-Insulin infusion, Mortality, Stress hyperglycemia.

Introduction

Hyperglycemia during stress is precipitated by a congregate of cytokine, hormonal and nervous effects on

glucose metabolism.[1,2] Hence, it's unsurprising that hyperglycemia is routinely encountered in critically ill patients admitted to the intensive care unit (ICU), irrespective of the reason behind admission.[3-5]This phenomenon was first explained by the French physiologist Claude Bernard in 1855 and is described as stress hyperglycemia.[2] A blood glucose level >140 mg/dL in non-diabetic patients or glycated hemoglobin (HBA1c)>6.5% are the defining characteristics of stress hyperglycemia.[5] Notably, stress hyperglycemia appears to be a marker of disease severity and is an established predictor of morbidity and mortality.[6] Stress hyperglycemia can be explained by the surge of counter-regulatory hormone levels associated with stressful conditions.[7,8] Among other factors, β-2 adrenergic stimulation secondary to elevated catecholamine levels, stimulates gluconeogenesis and hepatic glycogenolysis, which is thought to be a substantial factor engendering stress hyperglycemia.[9,10]

Mortality is the worst clinical consequence in the ICU setting. Early prediction of mortality in critically ill patients can help stratify patients and promptly provide the best treatment. Therefore, predicting mortality risk is a major priority of ICU care. Several prognostic indices have been suggested to predict the risk of critically ill patient's mortality, but some predictive indices are too complicated to calculate the mortality probability. As a result, there has been an increasing need to establish simplified clinical mortality indicators while maintaining the prognostic accuracy and performance of the prognosticator. In clinical practice, several aspects must be taken into account in the management of critically ill patients with stress hyperglycemia: including average BG targets (BG_{avg}), acceptable maximum BG (BG_{max}), maximum allowable percentage variation in BG ($\%BG_{var}$), and route of nutrition (enteral or parenteral), which substantially increases the workload of providers involved in the patients' care. The aim of our study is to investigate the predictive efficacy of BG_{max}, BG_{avg}, and $\%BG_{var}$ on the overall 28-day ICU mortality. Additionally, we aim to evaluate the optimal cut-off points of these three tested prognosticators.

Material and Methods

This was a single-center observational retrospective study conducted in the departments of King Hussein Medical Center (KHMC) at Royal Medical Services (RMS) in Jordan. This study was approved by our Institutional Review Board (IRB), and a requirement for consent was waived owing to its retrospective design. This study included 188 hyperglycemic critically ill patients. Flow chart of our studied patients' selection and data collection process is fully illustrated in **Figure 1.**

An Independent and One Sample T-tests were conducted to analyze the continuous variables and to express them as Mean±SD in Survivors group, Nonsurvivors group, and overall tested critically ill patients while Chi Square test was conducted to analyze the ordinal variables and to express them as a number of participants (percentage). Furthermore, an independent T-test was conducted to express the Mean differences±SEMs for the tested continuous variables between Survivors group and Nonsurvivors group. A Receiver Operating Characteristic (ROC) curve followed by sensitivity analysis was used to determine the area under the ROC (AUROC) curves, predictive performances, and the optimal cut-off values for BG_{max}, BG_{avg}, and $\%BG_{var}$. Youden indices, sensitivities, specificities, positive and negative predictive values, and accuracy indices were also calculated. Statistical analyses were performed using IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA) and P-values ≤ 0.05 were considered statistically significant.

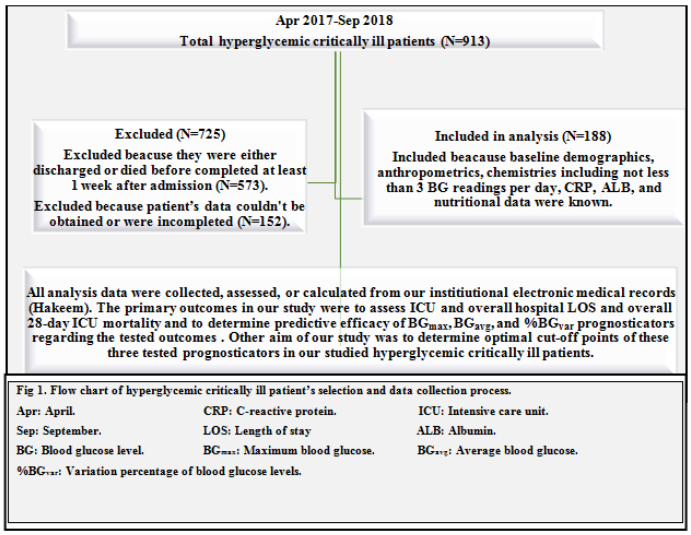

Fig 1. Flow chart of hyperglycemic critically ill patient's selection and data collection process.

Apr: April. CRP: C-reactive protein. ICU: Intensive care unit.
Sep: September. LOS: Length of stay ALB: Albumin.
BG: Blood glucose level. BG_{max}: Maximum blood glucose. BG_{avg}: Average blood glucose.
$\%BG_{var}$: Variation percentage of blood glucose levels.

Results

The mean age of our 188 studied hyperglycemic critically ill patients was 58.94±10.4 years in which 131 patients (69.7%) of the eligible sample were male and 57 patients (30.3%) were female. The overall 28-day ICU mortality was 40.4% (76 patients). The ICU and overall hospital LOS were 12.76±4.95 days and 17.07±6.98 days with Mean differences±SEM of -8.58±0.39 days and -13.6±0.29 days, respectively. The Means±SDs of albumin level (ALB), total calorie input (TCI), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), total corrected calcium (cCa), total magnesium level (Mg), and phosphate level (P) were significantly higher in Survivors than in Nonsurvivors (2.45±0.14 g/dl, 676.8±77.9 Cal/day, 111.8±3.15 mmHg, 66.7±3.20 mmHg, 81.8±3.15 mmHg, 8.14±0.24 mg/dl, 1.99±0.09 mg/dl, and 3.29±0.28 mg/dl **vs** 2.27±0.16 g/dl, 614.7±67.1 Cal/day, 96.4±16.1 mmHg, 51.0±16.5 mmHg, 66.8±14.7 mmHg, 7.91±0.29 mg/dl, 1.77±0.24 mg/dl, 3.39±0.49 mg/dl, and 3.00±0.38 mg/dl, respectively). While the Means±SDs of c-reactive protein (CRP) and CRP to ALB ratio (CRP: ALB) were significantly higher in Nonsurvivors than in Survivors (15.9±4.93 mg/dl and 7.26±2.95 **vs** 11.3±2.39 mg/dl and 4.69±1.25). The Means±SDs of BG_{max}, BG_{avg}, and $\%BG_{var}$ were significantly lower in Survivors than in Nonsurvivors (227.6±10.2 mg/dl, 185.5±3.52 mg/dl, and 45.4%±11.3% **vs** 250.0±26.7 mg/dl, 193.4±7.51 mg/dl, and 58.1%±20.3%) with Mean differences±SEM between Survivors group and Nonsurvivors group of -22.5±2.78 mg/dl, -7.90±0.82 mg/dl, and -12.7%±2.31%, respectively. Demographics, anthropometrics, and follow-up comparison data of the study's hyperglycemic critically ill patients are fully summarised in **Table 1**.

Table 2 shows the optimal cut-off point, sensitivity (TPR), specificity (TNR), Youden index (YI), positive and negative predictive values (PPV and NPV), accuracy index (AI), and AUROC curves. We demonstrated that the best cut-off values for $\%BG_{var}$, BG_{avg}, and BG_{max} in our study were 55.6%, 188.5 mg/dl, and 241.5 mg/dl for overall 28-day ICU mortality. The AUROC curve of $\%BG_{var}$ (0.923; 95%CI, 0.877-0.969) in this study was significantly greater than that of BG_{avg} (0.874; 95% CI, 0.802-0.947) and BG_{max} (0.865; 95% CI, 0.791-0.939). The ROC curve analysis of our three tested prognosticators for the overall 28-day ICU mortality is fully illustrated in **Figure 2.**

Discussion

Both hyperglycemia and hypoglycemia have been associated with an increased risk of mortality in specific cases.[3,7,11] Hyperglycemia is linked to a continuum of deleterious mechanisms, including: inflammation, thrombosis, and an increment in oxidative stress, which is attributed to a higher risk of mortality.[12] While Furukawa *et al*[3] linked hypoglycemia to increased mortality along with hypoalbuminemia in septic patients. Accumulating data suggest the importance of $\%BG_{var}$ as a prognosticator of mortality.[13-15] We reiterate this claim while going a step further by conducting what is, to the best of our knowledge, the first study to address the correlation between the three tested hyperglycemic parameters and

mortality. Bearing in mind the scarce resources, we believe that early stratification with highly accessible, reliable, and discriminative predictive tools is imperative to the unstable and high acuity status of the critically ill: to avoid under-triaging or delays in appropriately assigning a higher priority to patients requiring the most care.

In summary, we found $\%BG_{var}$ to be a more predictive effective prognosticator with high sensitivity, specificity, performance, and accuracy when compared with BG_{avg}, and BG_{max} to forecast overall 28-day ICU mortality in hyperglycemic critically ill patients receiving Cryst-insulin infusion (the overall average rate of Cryst-insulin infusion in the present study was 4.17±2.01 IU/hr which is equivalent to 99.9±48.2 IU/day). Our analysis justifies the potential use of $\%BG_{var}$ as an additional, readily available red flag bedside assessment tool for critically ill patients while considering the appropriate cutoff point demonstrated in **Table 2**. The present study is limited by its retrospective design, using single-center data, and including only hyperglycemic ICU patients. Nonetheless, our center is an experienced and high-volume unit, so our data may be useful to other centers. A larger, multisite, and prospective study is needed to control for multiple confounders and to clarify the causation between variables, including $\%BG_{var}$, and mortality.

Table 1. Baseline and follow-up comparison data of 28-day ICU survival and mortality for the study's hyperglycemic critically ill patients.

Variables		Total (N=188)	Survivors (N=112)	Nonsurvivors (N=76)	Mean difference ± SEM	P-Value
Age (Yrs)		58.94±10.4	58.91±9.85	58.99±11.2	-0.08±1.55	0.961 (NS)
Gender	Female	57 (30.3%)	34 (30.4%)	23 (30.3%)		0.560 (NS)
	Male	131 (69.7%)	78 (69.6%)	53 (69.7%)		
BW (Kg)		74.05±10.2	75.27±10.4	72.25±9.79	3.02±1.51	0.047 (S)
BMI (Kg/m^2)		25.90±3.97	26.4±3.91	25.1±3.97	1.29±0.58	0.028 (S)
CRP (mg/dl)		13.19±4.27	11.3±2.39	15.9±4.93	-4.59±0.54	0.000 (S)
ALB (g/dl)		2.37±0.18	2.45±0.14	2.27±0.16	0.19±0.02	0.000 (S)
CRP: ALB		5.73±2.45	4.69±1.25	7.26±2.95	-2.57±0.31	0.000 (S)
TCI (Cal/kg/day)		9.49±0.70	9.81±0.55	9.03±0.64	0.79±0.09	0.000 (S)
TCI (Cal/day)		651.7±79.6	676.8±77.9	614.7±67.1	62.0±10.9	0.000 (S)
Carb Cal (Cal/day)		613.4±74.0	635.8±73.0	580.3±62.5	55.5±10.2	0.000 (S)
% Carb Cal_TCI		94.2%±2.72%	94.0%±2.68%	94.5%±2.76%	-0.44%±0.40%	0.275 (NS)
NNC_D5 (Cal/day)		306.7±37.0	317.9±36.5	290.2±31.2	27.8±5.12	0.000 (S)
PD (g/100 Cal)		1.45±0.68	1.49±0.67	1.39±0.69	0.11±0.10	0.275 (NS)
SBP (mmHg)		105.6±12.9	111.8±3.15	96.4±16.1	15.4±1.56	0.000 (S)
DBP (mmHg)		60.34±13.2	66.7±3.20	51.0±16.5	15.6±1.59	0.000 (S)

MAP (mmHg)	75.70±12.1	81.8±3.15	66.8±14.7	15.0±1.43	0.000 (S)
BG_{min} (mg/dl)	140.8±15.2	143.5±12.1	136.9±18.3	6.62±2.21	0.003 (S)
BG_{max} (mg/dl)	236.7±21.7	227.6±10.2	250.0±26.7	-22.5±2.78	0.000 (S
BG_{avg} (mg/dl)	188.7±6.72	185.5±3.52	193.4±7.51	-7.90±0.82	0.000 (S)
$\%BG_{var}$	50.5%±16.7%	45.4%±11.3%	58.1%±20.3%	-12.7%±2.31%	0.000 (S)
Cryst-Insulin infusion rate (IU/hr)	4.17±2.01	3.06±0.71	5.80±2.18	-2.74±0.22	0.000 (S)
Cryst-Insulin infusion dose (IU/day)	99.9±48.2	73.2±17.2	139.2±52.3	-65.9±5.31	0.000 (S)
Ca (mg/dl)	6.77±0.33	6.92±0.23	6.55±0.34	0.38±0.04	0.000 (S)
cCa (mg/dl)	8.05±0.29	8.14±0.24	7.91±0.29	0.23±0.04	0.000 (S)
Mg (mg/dl)	1.90±0.20	1.99±0.09	1.77±0.24	0.23±0.03	0.000 (S)
K (mEq/l)	3.78±0.46	4.05±0.14	3.39±0.49	0.66±0.05	0.000 (S)
P (mg/dl)	3.18±0.35	3.29±0.28	3.00±0.38	0.29±0.05	0.000 (S)
Pre-ICU admission days	4.32±3.95	2.29±1.14	7.32±4.65	-5.03±0.46	0.000 (S)
ICU stay days	12.76±4.95	9.29±1.14	17.9±3.83	-8.58±0.39	0.000 (S)
Overall hospital stay days	17.07±6.98	11.6±2.29	25.2±1.41	-13.6±0.29	0.000 (S)
28-day ICU survival	112 (59.6%)				0.000 (S)
28-day ICU overall mortality	76 (40.4%)				

Values are presented as Mean±SD by using independent T-test and one sample T-test or as number (%) by using Chi square test.

Yrs: Years.

Kg: Kilogram.

BW: Actual body weight.

BMI: Body mass index.

S: Significant (P-Value <0.05).

NS: Nonsignificant (P-Value >0.05).

N: Number of study's patients.

CRP: C-reactive protein.

CRP: ALB ratio: C-reactive protein to albumin level ratio.

ALB: Albumin level.

TCI: Total calorie Input.

PD: Protein density.

Car Cal: Carbohydrate calorie.

NNC: Non nutritional calorie.

D5: Dextrose 5%.

SBP: Systolic blood pressure.

DBP: Diastolic blood pressure.

MAP: Mean arterial pressure.

BG_{min}: Minimum Blood glucose level.

BG_{max}: Maximum blood glucose level.

BG_{avg}: Average of blood glucose level.

$\%BG_{var}$: Percentage variation in blood glucose level.

IU: International unit.

Ca: Total calcium level.

cCa: Corrected total calcium level.

Mg: Total magnesium level.

K: Corrected potassium level.

P: Total phosphate level.

Table 2. The optimal cut-off point, sensitivity, specificity, positive and negative predictive values, Youden and accuracy indices, and AUROC of the three tested prognosticators for overall 28-day ICU mortality.

Prognostic Indicators		Optimal Cut-off	TPR	FPR	YI	TNR	PPV	NPV	AI	AUROC curve (95% CI)
Overall 28-day ICU mortality	$\%BG_{var}$	55.6%	86.8%	0.00%	86.8%	100.0%	100.0%	91.8%	94.66%	0.923 (0.877-0.969)
	BG_{avg} (mg/dl)	188.5	94.7%	8.90%	85.8%	91.1%	87.8%	96.2%	92.56%	0.874 (0.802-0.947)
	BG_{max} (mg/dl)	241.5	85.5%	0.00%	85.5%	100.0%	100.0%	91.0%	94.14%	0.865 (0.791-0.939)

%BGvar: Percentage variation in blood glucose level.

BGavg: Average of blood glucose level.

BGmax: Maximum blood glucose level.

ICU: Intensive care unit.

TPR: True positive rate (sensitivity)

FPR: False positive rate.

YI: Youden index.

PPV: Positive predictive value.

NPV: Negative predictive value.

AI: Accuracy index.

TNR: True negative ratio (specificity).

AUROC: Area under receiver operating characteristic.

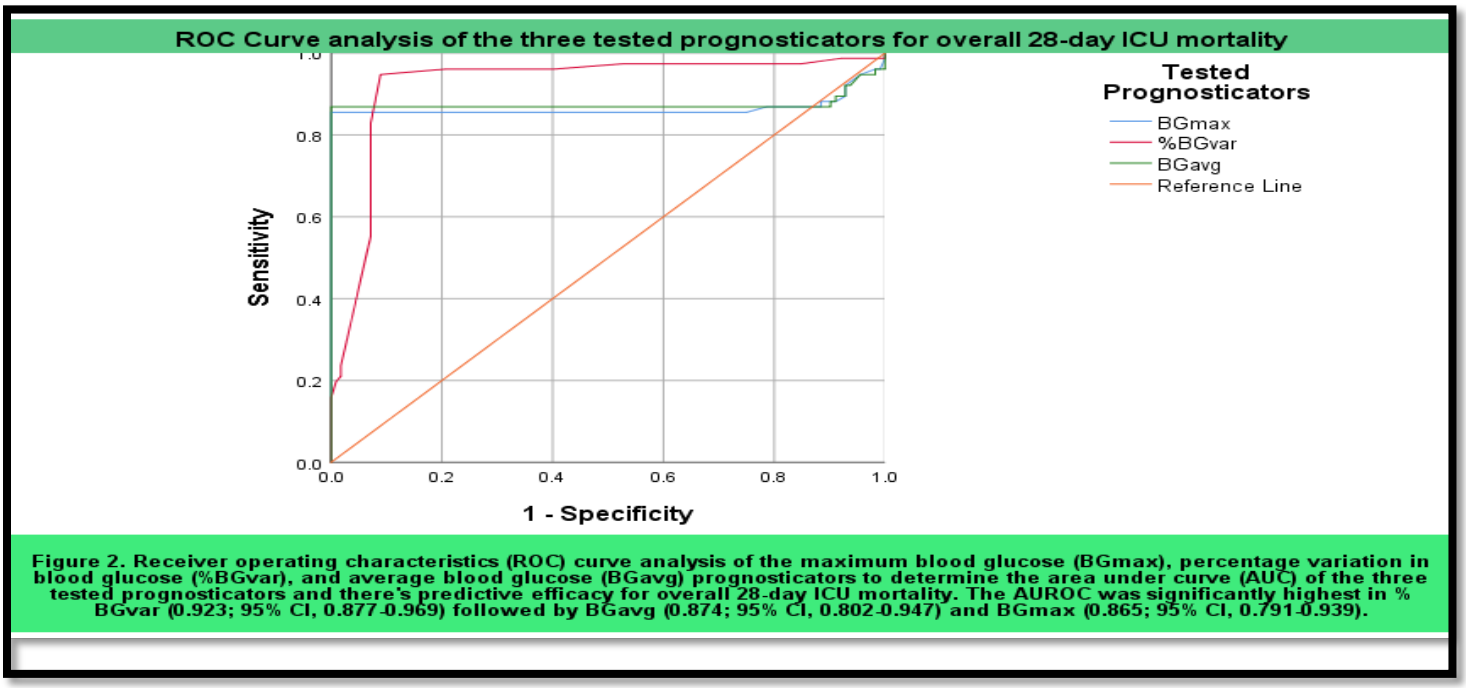

Figure 2. Receiver operating characteristics (ROC) curve analysis of the maximum blood glucose (BGmax), percentage variation in blood glucose (%BGvar), and average blood glucose (BGavg) prognosticators to determine the area under curve (AUC) of the three tested prognosticators and there's predictive efficacy for overall 28-day ICU mortality. The AUROC was significantly highest in % BGvar (0.923; 95% CI, 0.877-0.969) followed by BGavg (0.874; 95% CI, 0.802-0.947) and BGmax (0.865; 95% CI, 0.791-0.939).

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