Glycemic Gap versus Admission Plasma Glucose Level as a Mortality Predictor of ICU Outcomes in Type 2 Diabetic Patients with Acute Heart Failure

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Abstract:

Background*:* Hyperglycemia is a prevalent issue among patients experiencing acute heart failure and constitutes an autonomous determinant of short-term mortality among non-diabetic patients but is comparatively insignificant in diabetic patients. Glycemic variables adjusted based on hemoglobin A1c (HbA1c), encompassing the glycemic gap, have been the subject of recent studies. This study evaluates the association between a glycemic gap and unfavorable clinical consequences within diabetic patients hospitalized with AHF.

Patients and Methods: This is a cross-sectional study, which encompassed 140 type-2 diabetic patients who were hospitalized in the intensive care unit at Assiut University during the period from October 2021 to November 2022. These patients met the criteria outlined in the 2021 European Society of Cardiology guidelines for AHF. Calculating the glycemic gap involved subtracting the A1C-derived average glucose (ADAG) level from the admission blood glucose level. The ADAG was determined utilizing the formula: ADAG = 28.7 × HbA1c − 46.72.

Results: Glycemic gap and admission blood glucose level were able to predict all-cause mortality among the studied participants. However, the glycemic gap was superior to admission plasma glucose level with a maximum AUC of 0.71 for all-cause mortality at a cut-off value of ≥ 57mg/dl better than admission blood glucose.

Conclusion: The glycemic gap demonstrated enhanced discriminatory ability in predicting death in patients with diabetes presenting with AHF. Thus, the glycemic gap levels could potentially serve as an indicator of critical illness intensity and overall prognosis in diabetic individuals experiencing AHF.

Keywords: Acute heart failure (AHF), glycemic gap, ICU.

Introduction

Hyperglycemia is a prevalent issue among patients with acute heart failure (AHF). It is an additional risk element for near-term fatality in non-diabetic patients but not in those with diabetes (1). There is still debate about whether individuals with diabetes experiencing AHF or severe illness who exhibit admission hyperglycemia are at risk of mortality or not. (1). Researchers have shown an inverse (2), direct (3), and U-shaped (4) correlation between HbA1c levels and fatality in chronic HF (4). A recent study investigated how HbA1c influenced mortality in patients with acute HF and found no correlation (5).

Stress hyperglycemia has emerged as a noteworthy predictor of in-hospital morbidity and mortality (6). This phenomenon can be

observed in diabetic and non-diabetic patients (7). Conversely, the occurrence of intense hyperglycemia in diabetic patients may stem from either an acute state of physiological stress or elevated initial blood glucose levels. This situation presents difficulties when attempting to evaluate and assess the condition.

One intriguing aspect under investigation is the concept of the glycemic gap among diabetic individuals experiencing AHF. The glycemic gap is a marker of glycemic aberration in patients with diabetes admitted to ICU. It is calculated by subtracting the A1C-derived average glucose (ADAG) level from the admission blood glucose level**.** The ADAG was determined utilizing the formula: ADAG = 28.7 × HbA1c − 46.727.

The current research aims to evaluate the relationship between the glycemic gap, admission of random blood glucose levels, and negative clinical consequences in diabetic AHF patients.

Patients and Methods

Study Participants:

The Ethical Review Board of our college provided approval (**IRB No.: 17101380**) for the study's protocol. All participants provided informed written consent, and measures were taken to ensure the confidentiality of information throughout the study.

One hundred forty patients with type-2 diabetes who were hospitalized in the ICU at Assiut University during the period spanning from October 2021 to November 2022 and were diagnosed with AHF were recruited for inclusion in this work, as per the criteria outlined in the 2021 recommendations of the European Society of Cardiology (ESC) (8), by clinical history, systemic examination, and echocardiography results.

Patients who were under the age of 18, patients presented with hypoglycemia (plasma glucose levels below 70 mg/dl), patients presented with hyperosmolar hyperglycemic state or diabetic ketoacidosis, or patients who had hemoglobin disorders, hematologic, or conditions with acute or chronic blood loss that could potentially affect the HbA1c assay accuracy were omitted from the study.

The main outcomes observed were mortality from any cause during the initial hospitalization.

Study Design:

This cross-sectional study was conducted in the ICU of the Internal Medicine Department at Assiut University Hospital.

All participants were subjected to the following:

1. Full history taking including underlying comorbidities, duration, type, treatment of DM, controlled or not, etiology of AHF as history of coronary artery disease, hypertension, exposure to cardiovascular medications, and systemic examination including chest, cardiac, neck vines and lower limbs and detecting New York Heart Association (NYHA) functional class to evaluate heart failure intensity.
2. Laboratory investigation comprising: (CBC), serum creatinine, AST, ALT, random blood glucose (RBG) at admission, and (HbA1C). In addition, the study also involved measuring HbA1c-based adjusted glycemic gap:
   - The A1C-derived average glucose level (ADAG) was determined utilizing the formula: ADAG = 28.7 × HbA1c − 46.727.
   - The glycemic gap was determined by subtracting the ADAG level from the level of glucose recorded upon admission (9).
3. ECG and echocardiography are used to assess the function of the right and left ventricles through trans-thoracic echocardiography using the Phillips HD 11 XE echocardiography machine.

Statistical Analysis:

All statistical calculations were conducted utilizing SPSS (statistical package for the social sciences; SPSS Inc., Chicago, IL, USA) version 22. The quantitative variables were compared with the student t-test for data with normal distribution and the Mann-Whitney U test for non-normally distributed data. The Chi-square ($\chi 2$) test was employed to compare categorical data. In cases where the expected frequency was less

than 5, the exact test was utilized. The correlation between various variables was assessed utilizing the Pearson correlationtest. To validate the prediction of death, the Receiver Operating Characteristic Curve (ROC) analysis was employed to identify the optimal cut-off values. Death prediction was assessed by calculating the odds ratio (OR) with a 95% Confidence Interval (CI) and Logistic Regression. The significance level was adjusted at a p-value of less than 0.05 for all tests.

Results:

We enrolled 140 diabetic patients admitted to the Internal Medicine Department's ICU at our tertiary hospital, diagnosed with AHF. Among this cohort, 60% were females, while 40% were males. No statistically significant disparity was observed between survivors and non-survivors regarding diabetes management. **Table (1)** summarizes the research participants' baseline characteristics, allowing for a direct comparison of hospital stays between survivors (96 patients) and non-survivors (44 patients).

Table 1: Demographic and Clinical Characteristics of Diabetic HF Survivors and Non-survivors

Variable name	Total (n=140)		Survivors (n=96)		Non-survivors (n=44)		P value
Age (years)							0.285
Mean ± SD	63.48 ± 11.89		64.21 ± 11.19		61.89 ± 13.28		
Sex							0.372
Male	56	(40.0)	36	(37.5)	20	(45.5)	
Female	84	(60.0)	60	(62.5)	24	(54.5)	
Comorb idities							
Hypertension	60	(61.9)	44	(71.0)	16	(45.7)	0.014
Chronic kidney disease	36	(38.3)	28	(45.9)	8	(24.2)	0.039
History of HF	132	(94.3)	88	(91.7)	44	(100.0)	0.056

Numbers (percentages %) represent qualitative data, whereas quantitative data is shown as mean ± SD and median (range). $P < 0.05$ is used to determine significance.

In non-surviving patients, the glycemic gap and admission blood glucose levels were considerably higher (124.9 mg/dl, 311.5 mg/dl) than in surviving patients (31.3mg/dl, 237.5mg/dl). Nevertheless, no significant differences were noted in HbA1c levels between the two groups **(Table 2).**

Table 2: Comparison of random blood glucose, HBA1c, and glycemic gab, APACHE score among Diabetic-associated HF Survivors and Non-survivors.

	Survivors (n=96)	Non-survivors (n=44)	P value
Admission BG (g/dl)			**< 0.001**
Median (range)	237.5 (110.0 - 500.0)	311.5 (189.0 - 621.0)	
HbA1c			**0.545**
Mean ± SD	8.80 ± 2.08	8.88 ± 1.78	
Glycemic gap			**< 0.001**
Median (range)	31.3 (-61.6 to 273.3)	124.9 (-102.96 to 308.95)	
APACHE score			**< 0.001**
Mean ± SD	15.57 ± 4.60	19.59 ± 4.92	

AST: aspartate transaminase. Quantitative data are displayed as mean ± SD, with a p-value < 0.05, significance isestablished.

We used an ROC analysis to find the glycemic gap cut-off values to obtain the most accurate prediction for the all-cause mortality rate. Both analyses showed that the optimal glycemic gap cut-off value was 57 mg/dl (Table 3), with a maximum AUC of 0.71 (sensitivity 88.6% and 52.1%) for all-cause mortality. Furthermore, the glycemic gap predicted all-cause mortality better than admission glucose (Fig. 1).

Table 3: The best cut-off, sensitivity, and specificity for death prediction within the examined participants (n=140)

Markers	Cut off	95%CI	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC	P value
Admission BG	≥ 256	0.600 – 0.778	77.3%	54.2%	43.6%	83.9%	61.4%	0.689	<0.001
Glycemic gap	≥ 57	0.628 – 0.809	88.6%	52.1%	45.9%	90.9%	63.6%	0.718	<0.001
APACHE	≥19.5	0.627 – 0.810	61.4%	77.1%	55.1%	81.3%	72.1%	0.719	<0.001

PPV: Positive predictive value; **NPV:** negative predictive value; **AUC:** Area under the curve; **CI:** Confidence interval. * p < 0.05 indicate significance

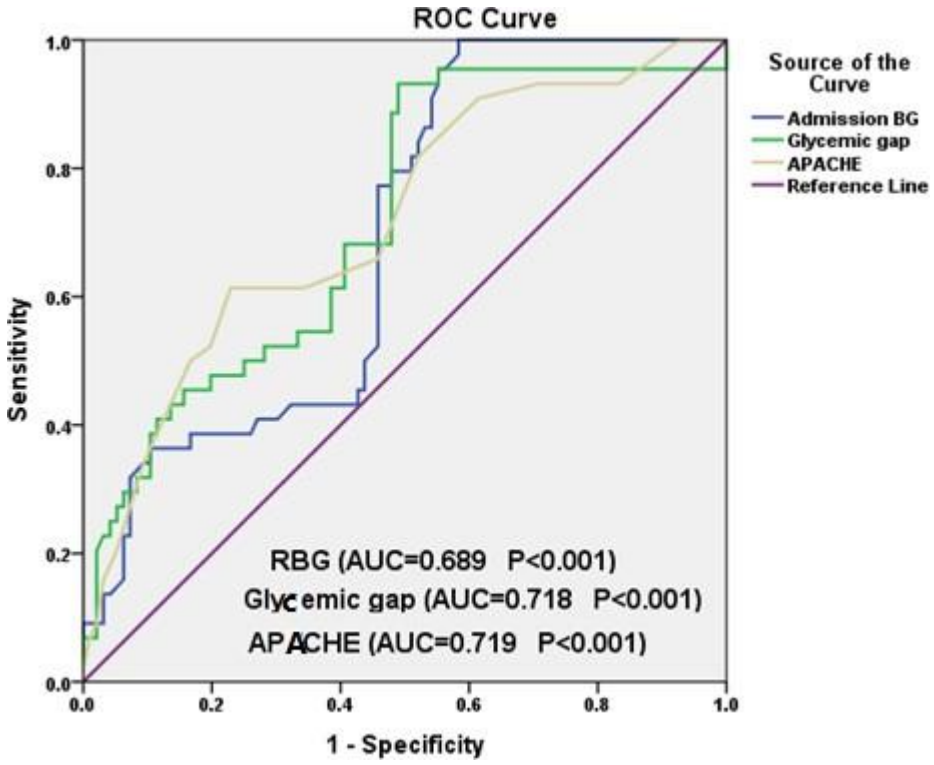

Figure (1): ROC curves for death prediction within the studied participants. RBG (blue), Glycemic gap (green), APACHE (brown), and reference line (purple). Area under the curve (AUC)= 0.689 (0.600 to 0.778) P-value < 0.001 for RBG, AUC = 0.718 (0.628 to 0.809), P value < 0.001 for Glycemic gap, and AUC = 0.719 (0.627 to 0.810), P-value < 0.001 for APACHE score.

In patients with diabetes, a glycemic gap of ≥ 57mg/dl was identified as the optimal threshold for predicting ICU mortality. This threshold yielded a sensitivity of 88.6% and a specificity of 52.1%. Patients with a glycemic gap ≥ 57mg/dl exhibited significantly increased rates of major complications compared to those with a glycemic gap < 57mg/dl. Individuals experiencing increased glycemic gap likely exhibit elevated risks of acute kidney injury (P=0.006), sepsis (P=0.023), acute liver cell failure (P < 0.001), arrhythmia (P=0.020), shock (P=0.004), and longer hospital stay (≥ 7 days, P < 0.001), and also have lower rate of improvement (P < 0.001) compared to those with glycemic gap <57mg/dl (Table 4).

Table 4: Clinical Outcome of Diabetic ICU Patients according to Glycemic Gap.

Variable name	Glycemic gap (n=55)	< 57	Glycemic gap (n=85)	< 57	P value
Improvement					**< 0.001**
- No	36	(65.5%)	77	(90.60%)	
- Yes	19	34.5%	8	(9.4%)	
Acute kidney injury					**0.006**
- No	29	(52.7%)	25	(29.4%)	
- Yes	26	47.3%)	60	(70.6%)	
Sepsis					**0.023**
- No	36	(65.5%)	39	(45.9%)	
- Yes	19	(34.5%)	46	(54.1%)	
Acute liver cell failure					**<0.001**
- No	53	(96.4%)	57	(67.1%)	
- Yes	2	(3.6%)	28	(32.9%)	
Arrhythmia					**0.020**
- No	50	(90.9%)	64	(75.3%)	
- Yes	5	(9.1%)	21	(24.7%)	
Shock					**0.004**
- No	54	(98.2%)	70	(82.4%)	
- Yes	1	(1.8%)	15	(17.6%)	

Qualitative data are presented as numbers (percentages); $p < 0.05$ indicates significance.

Univariate logistic regression analysis for death prediction within the investigated cohort showed that patients complicated by sepsis, acute liver injury, arrhythmia, or shock, those with APECHE score ≥ 19.5, RBG ≥ 256 g/dl, and those with Glycemic gap ≥ 57 mg/dl were riskier to die compared to their counterparts. This finding was confirmed on multivariate logistic regression analysis, which showed that patients complicated with shock, those with APECHE score≥ 19.5, and those with a high Glycemic gap ≥ 57mg/dl were more likely to die compared to their counterparts. As we observed that shocked patients were about twenty-one times more likely to die compared to non-shocked cases (OR=21.343, 95%CI 2.546 – 178.906, P=0.005), patients with APECHE score ≥ 19.5 triple the risk of death compared to patients with APECHE score < 19.5 (OR=3.438, 95%CI 1.382 – 8.552, P=0.008), and patients with high Glycemic gap ≥ 57 mg/dl about six times were more likely to die in comparison with patients experiencing low Glycemic gap < 57 mg/dl (OR=6.397, 95%CI 2.105-19.439, P=0.001), as shown in (Table 5).

Table 5: Multivariate logistic regression analysis for prediction of death among the studied participants.

	Multivariate analysis		
Variables	**OR**	**95% CI**	**P value**
Shock			
- **No**	Ref		
- **Yes**	21.343	2.546 – 178.906	0.005
APATCH			
- **< 19.5**	Ref		
- **≥ 19.5**	3.438	1.382 – 8.552	0.008
Glycemic gap			
- **< 57**	Ref		
- **≥ 57**	6.397	2.105 – 19.439	0.001

RBG: random blood glucose; **CI:** Confidence interval; **OR:** Odds ratio. The p-value is significant ≤ατ 0.05.

Discussion

Hyperglycemia is a prevalent issue in AHF patients and increases the risk of short-term mortality in patients without diabetes rather than diabetic patients (1). Nevertheless, there is ongoing debate regarding the correlation between high levels of blood glucose upon admission and the likelihood of death in diabetic patients with AHF (1).

Admission hyperglycemia is linked to in-hospital mortality and negative cardiac outcomes in several prior studies (10). Prior research has demonstrated a correlation between elevated blood glucose levels at admission and higher death rates in cases of acute coronary syndrome (ACS) and acute heart failure (12). However, in another retrospective observational study measuring glycosylated hemoglobin (HbA1c) as a marker of premorbid glycaemia in the 3 months before intensive care unit (ICU) admission, the authors believed that acute hyperglycemia was accompanied by a decrease rather than an increase in mortality in patients with "inadequately controlled" diabetes. (11). So**,** it is crucial to identify a marker that can serve as a prognostic predictor rather than relying on admission hyperglycemia.

In the current observational cross-sectional study, we aimed to assess the relation between random blood glucose levels and glycemic gap and severe clinical consequences in diabetic individuals diagnosed with heart failure and admitted to the ICU of the Internal Medicine Department at Assiut University.

The key results of our study revealed that the glycemic gap in diabetic patients can predict ICU mortality compared to other blood glucose-based metrics. Furthermore, individuals with a glycemic gap of ≥57 mg/dl showed significantly higher incidence of ICU and in-hospital mortality, as well as unfavorable outcomes in terms of acute kidney injury, sepsis, acute liver cell failure, shock, in comparison to those with a glycemic gap less than 57 mg/dl.

Our data indicated that both admission blood glucose level and glycemic gap have a discriminative power for predicting in-hospital mortality; however, the glycemic gap was superior to admission BG with greater ROC values 68.9% (95%CI: 0.600 – 0.778, P < 0.001) for death prediction, and also shown to be a risk factor for death as determined by logistic regression analysis as we observed that patients with glycemic gap ≥ 57 (g/dl) are about 22 times more likely to die compared to those with Glycemic gap < 57(g/dl) (OR=21.787, 95%CI 3.932 - 120.719, P < 0.001).

Our finding agrees with Laio et al. (13), who reported that non-survivors exhibited a significantly increased glycemic gap and

maximal blood glucose during the first 48 hours compared to survivors. The same authors showed that by using the Kaplan–Meier survival curve, a glycemic gap > 42 mg/dl was linked to a significantly shorter survival rate compared to a gap <42 mg/dl (log-rank test $p < 0.05$) (14). However, both studies showed that the glucose levels upon admission were higher in non-survivors than survivors, although the difference was not statistically significant (14).

Also, Itzhaki Ben Zadok et al. (15) reported that among DM patients, Kaplan–Meier survival curves revealed no significant variances in mortality risk according to the admission BG level. Similarly, multivariable analysis revealed no significant differences in mortality risk and admission BG level (16). Likewise, in the current study, the multivariable analysis demonstrated no role in predicting mortality for admission to BG level.

Similar results were disclosed in diabetic patients with subsequent variables comorbidities such as liver abscess (17), community-acquired pneumonia (18), acute ischemic stroke, chronic obstructive lung disease with acute exacerbation (20), and acute myocardial infarction (22). Employing the glycemic gap might explain the "diabetes paradox" and the conflicting viewpoints surrounding the correlation between chronic glycemic control, admission hyperglycemia, and unfavorable outcomes (21).

Based on the current study's findings, we recommend using glycemic gap rather than admission BG level to predict outcomes among diabetic individuals experiencing HF.

Conclusion

The glycemic gap demonstrated a more discriminatory ability in predicting mortality among diabetic individuals with acute heart failure. Therefore, the glycemic gap levels can be utilized to assess the extent of critical disease and clinical results in diabetic individuals experiencing AHF.

List of Abbreviations

ADAG: A1C-derived average glucose study
ALT: Alanine transaminase
APATCHI: Acute Physiology and Chronic Health Evaluation
AST: Aspartate Transferase
CBC: Complete blood count
DM: Diabetes mellitus
HbA1: Hemoglobin A1c
AHF: Acute Heart Failure
ICU: Intensive Care Unit
NYHA: New York Heart Association
T2DM: Type 2 diabetes mellitus

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