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Original Article

Effect of glycemic gap on short term outcome in critically ill patient: In zagazig university hospitals

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ABSTRACT

Both admission Blood glucose and previous glycemic state may affect critically ill patients; So Glycemic gap may be a good indicator of ICU outcomes. This study **investigated** the effect of glycemic gap on short term outcome in critically ill patient and the value of incorporation of the Glycemic Gap into the APACHE-II on its discriminative performance.

Subjects and Methods: This cross sectional study was conducted in medical ICU of Zagazig University Hospitals, March 2018 to September 2018; total numbers of 240 critically ill patients admitted to ICU were enrolled in. All of them were subjected to: full history taking, clinical examination, routine investigations, random blood sugar, hemoglobin A1c. ADAG, Glycemic Gap and APACHE II were calculated.

Results: Elevated glycemic gap was associated with an increased ICU mortality and APACHE-II score was a good predictor of ICU mortality in critically ill patients.

Conclusions: Elevated glycemic gap was significantly associated with an increased ICU mortality that the glycemic gap can be used to assess the severity and prognosis of critically ill patients and their incorporation into the APACHE II score has increased its performance as a predictor of mortality.

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1. Introduction

Both admission Blood glucose and previous glycemic state are associated with adverse ICU outcomes, may be due to elevated counter regulatory hormones and cytokines. Measuring the increase in blood glucose levels above the existing average (HbA1c) would help in assessing the stress levels in critical illness and to derive average ambient glucose levels, the formula from A1C-derived average glucose study (ADAG) may be used, The glycemic gap is calculated as a difference between the ADAG and the admission glucose and may be a better predictor of ICU outcome [1]. SIH is frequent in patients with acute illness, like sepsis, multiple trauma, major surgery, and acute myocardial infarction (AMI). APACHE-II score is a commonly used model for predicting mortality in the intensive care unit (ICU) However, blood glucose levels may also reflect different severities of stress depending on whether a patient has diabetes and in patients without diabetes, not only is there evidence of a stronger connection between ICU mortality and increased levels of mean serum glucose and glucose variability, but also the mortality risk is greater. Conversely, acute hyperglycaemia in patients with diabetes could result from acute physiological stress, high baseline blood glucose, or both, which confounds the assessments [2].

1.1. Subjects and methods

This cross sectional study was conducted in medical ICU of Zagazig University Hospitals, March 2018 to September 2018. Total numbers of 240 critically ill patients (119 male and 121 female). Patients with chronic anemia, renal failure, acute or chronic liver disease and Pregnant females were excluded. Written informed consent was obtained from all participants if oriented or their first degree relatives if not and all protocols were approved by Zagazig Institutional Review Board (IRB). All of them were subjected to: full history taking, clinical examination, routine investigations, random blood sugar, hemoglobin A1c. ADAG, Glycemic Gap and APACHE II were calculated.

1.2. Patients were classified to four groups

Group **I** (control): 60 patients (40 male and 20 females) with normal admission blood glucose (110.75 ± 14.5) and HbA1C

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(4.28 ± 0.539).

Group **II** (known Diabetic): 60 patients (36 male and 24 females) were known diabetic with high admission blood glucose (281.96 ± 70.65) and HbA1C (9.07 ± 1.54).

Group **III** (undiagnosed Diabetic): 60 patients (16 male and 44 females) presented with undiagnosed diabetes with high admission blood glucose (240.8 ± 41.52) and HbA1C (8.71 ± 1.47) with mean age (Mean ± SD) was 55.13 ± 8.66 and BMI (kg/m2) Mean ± SD was found to be 27.82 ± 1.69.

Group **IV** (stress hyperglycemia): 60 patients (27 male and 33 females) presented with high blood glucose (172.61 ± 25.89) with normal HgA1c (4.77 ± 0.411).

1.3. Statistical analysis of the results

After data collection, data were coded, entered and analyzed using SPSS (Statistical Package for Social Science) version 23. Numerical data were summarized using means and standard deviations. Categorical data were summarized as numbers and percentages. For numerical variables, differences between two groups were analyzed using Mann Whitney *U* test. For categorical variables, differences were analyzed with x2 (chi square) test or fisher exact when appropriate. ROC analysis was done for predictors of mortality in ICU patients. Best cutoff point and diagnostic indices for each predictor were calculated. All p-values are two-sided. P-values < 0.05 were considered significant. P value (≤0.05) was considered significant difference.

2. Results

Both Glycemic gap and APACHE II score was significantly higher in Stress Induced hyperglycemia group (P value < 0.0001) (Table 1).

Concerning outcome of the studied population it was found to be 52% for improved population while 48% for dead population. There is a highly significant difference between the two groups regarding APACHE II score, ICU stay and glycemic gap (P value < 0.05)but there were no significant difference between the two groups regarding age, sex, HB, urea, CRP, INR, RBS and HBA1C as P value were >0.05 (Table 2).

Regarding the effect of glycemic state on patient outcome it was found that in group I (control)75%improved and15% dead, for group II(diabetic)it was fond 33.3%improved and 66.7%dead, for group III(recent diagnosed)86.7%improved and 13.3% dead while for group IV(stress hyperglycemia)11.1% improved and 88.9%dead Fig. 1.

ROC curves for glucose parameters and the APACHE-II score for predicting ICU mortality explained that Glycemic parameters included glycemic gap, and HbA1c showed that the AUC of the APACHE-II score was larger than that of glycemic gap (P < 0.001) as the AUCs for key predictors of short term outcome of critical ill patients as the APACHE-II score had the highest AUC (0.928, 95% CI: 0.861–0.995) and the discriminative power of the glycemic gap for outcome was greater than that of HbA1c with AUCs of 0.838 (95% CI: 0.723–0.953) and p < 0.001 for patients glycemic gap and 0.439 (95% CI: 0.291–0.588) with p value of 0.420 for HbA1c. Fig. 2.

Table 1

	Group I (N = 60)	Group II (N = 60)	Group III (N = 60)	Group IV (N = 60)	F	P
Glycemic gap Mean ± SD	**33.09 ± 12.03**	**71.26 ± 41.78**	**102.72 ± 228.17**	**131.51 ± 212.24**	**60.01**	**.000**
APACHE II Mean ± SD	10.33 ± 3.45	15.2 ± 6.45	10.27 ± 4.64	17.22 ± 4.52	**7.807**	**.000**
ICU stay (day) Mean ± SD	9.5 ± 5.75	9.2 ± 5.63	7.6 ± 2.82	8.5 ± 4.67	.436	.728

Both Glycemic gap and APACHE II score was significantly higher in Stress Induced hyperglycemia group(P value < 0.0001).

Table 2
Comparison of the Characteristics of the ICU patients according to outcome.

		Improved (N = 124)	**Dead** (N = 116)	t/χ^2	**P**
Age (years) Mean ± SD		52.76 ± 11.99	51.94 ± 14.25	.241	.810
Sex	Male	56 (45.2%)	60 (51.7%)	.276	.599
	Female	68 (54.8%)	56 (48.3%)		
Hb Mean ± SD		12.52 ± 1.28	12.35 ± 2.12	.357	.723
Urea Mean ± SD		16.76 ± 7.3	18.20 ± 10.24	.625	.534
CRP Mean ± SD		48.97 ± 83.43	59.01 ± 95.2	.433	.667
INR Mean ± SD		1.39 ± 0.941	1.25 ± 0.336	.794	.430
RBS Mean ± SD		198.18 ± 74.5	219.07 ± 75.82	1.539	.129
HbA1c Mean ± SD		6.98 ± 2.31	6.49 ± 2.57	.757	.452
Glycemic gap Mean ± SD		70.04 ± 167.33	107.83 ± 162.57	**4.498**	**<0.001**
APACHE II Mean ± SD		9.28 ± 3.27	17.65 ± 4.41	**8.313**	**<0.001**
ICU stay Mean ± SD		7.21 ± 2.85	10.01 ± 5.71	**2.374**	**.021**

Concerning outcome of the studied population it was found to be 52% for improved population while 48% for dead population. There is a highly significant difference between the two groups regarding APACHE II score, ICU stay and glycemic gap (P value < 0.05)but there were no significant difference between the two groups regarding age, sex, HB, urea, CRP, INR, RBS and HBA1C as P value were >0.05.

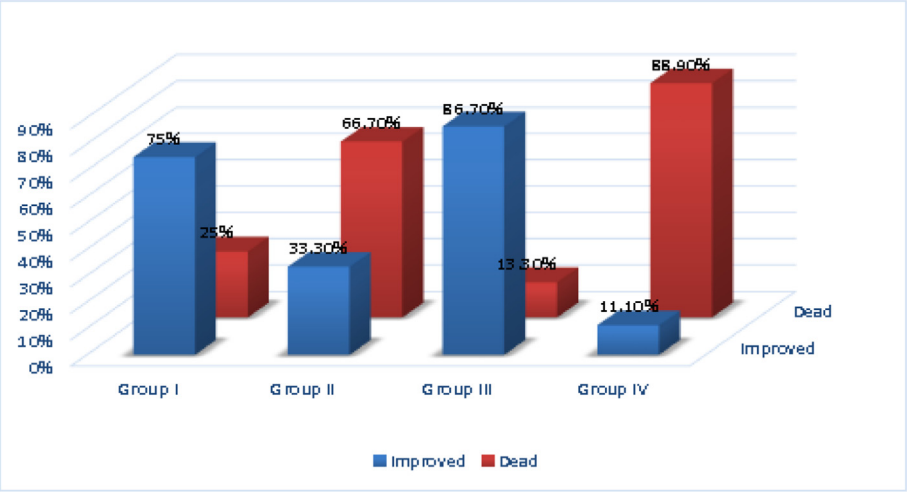
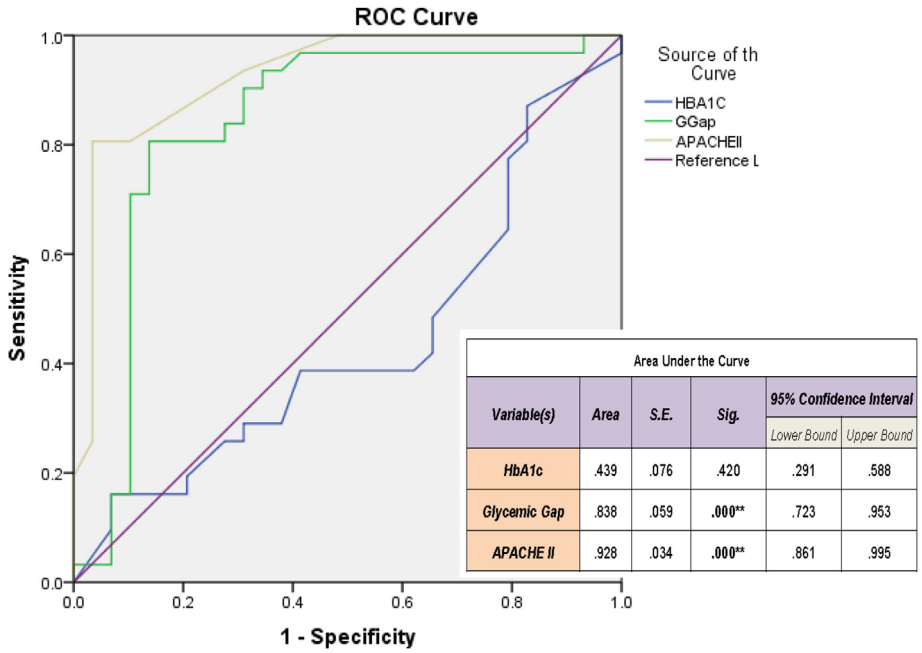


Fig. 1. Patient outcome according to Glycemic state. Regarding the effect of glycemic state on patient outcome it was found that in group I (control)75%improved and15% dead, for group II(diabetic)it was fond 33.3%improved and 66.7%dead, for group III(recent diagnosed)86.7%improved and 13.3% dead while for group IV(stress hyperglycemia)11.1% improved and 88.9%dead Fig. 1.



Area Under the Curve

Variable(s)	Area	S.E.	Sig.	95% Confidence Interval	
				Lower Bound	Upper Bound
HbA1c	.439	.076	.420	.291	.588
Glycemic Gap	.838	.059	.000**	.723	.953
APACHE II	.928	.034	.000**	.861	.995

Fig. 2. ROC curves for HbA1c, glycemic gap and the APACHE-II score for predicting ICU mortality. ROC curves for glucose parameters and the APACHE-II score for predicting ICU mortality explained that Glycemic parameters included glycemic gap, and HbA1c showed that the AUC of the APACHE-II score was larger than that of glycemic gap (P<0.001) as the AUCs for key predictors of short term outcome of critical ill patients as the APACHE-II score had the highest AUC (0.928, 95% CI: 0.861–0.995) and the discriminative power of the glycemic gap for outcome was greater than that of HbA1c with AUCs of 0.838 (95% CI: 0.723– 0.953) and p < 0.001 for patients glycemic gap and 0.439 (95% CI: 0.291–0.588) with p value of 0.420 for HbA1c. Fig. 2.

3. Discussion

The glycemic gap may be better reflector of outcome in critically ill patient as it consider both admission blood glucose and the pre-existing glycemic state.

In our study, all glycemic indicators including RBS, HbA1c and glycemic gap; were significantly different in the four studied groups as (P value < 0.05); as glycemic gap [glycemic gap = (admission glucose −ADAG)] was found to be higher in the stress hyperglycemia group because RBS for them was high and ADAG was normal because HbA1c was normal.

In our study high glycemic gap was associated with bad prognosis and increased ICU mortality, this agree with **Liao and his colleagues** [2,3] who observed that increased glycemic gaps >72 mg/dL can predict adverse outcomes. We found that glycemic gap of dead (107.83 ± 162.57) was significantly higher than that improved patients (70.04 ± 167.33) (p value < 0.05). And also ***Donagaon & Dharmalingam in 2018*** [1] found that higher glycemic gap levels were significantly associated with an increased risk of ICU mortality and concluded that Glycemic gap is a tool that can be used to detect the prognosis in patients with type 2 DM admitted with critical illness similarly **Yang et al., in 2017** [4] published that both the glycemic gap and stress hyperglycaemia ratio could be used to evaluate the prognosis of patients suffering

from Acute Ischemic Stroke.

In 2017 Galal et al [5] in their study claimed that an increased gycemic gap in critically ill patients with trauma and sepsis, was accompanied with an increased risk of ICU mortality and the glycemic gap can be used to evaluate the severity and prognosis of patients with diabetes presenting with critical illness.

Regarding **APACHE II** score and its correlation with patients outcome it was found that the mean for improved patients was (9.28 ± 3.27) less than the mean for dead patients (17.65 ± 4.41) and this difference was statistically significant (P value < 0.05) and this agree with **(Liao et al., 2015)** [2] as APACHE-II score had a high association with outcome and it was a good reflector of ICU mortality in critically ill patients Also our findings are in accordance with the findings of **Mohammed et al. in 2017** [6] as they found that; the difference of mean APACHE II scores between the survivors and dead was significant and was known as an independent predictor of mortality in severe sepsis, Also in APACHI II score there is high statistical significance between the four groups as (p value < 0.05) and this agree with **EL-Toony and her colleagues in 2018** [7]; in patients with hyperglycaemia it was found that the presence of more than 3 comorbidities including diabetes and APACHE II score more than 15 were independent predictors for hospital mortality of patients in groups of their study.

In our study stress hyperglycemia group had highest mortality (88.9%) this may be related to multiple causes that include inflammatory and neuro endocrine derangements in critically ill patients, which lead to insulin resistance and high hepatic glucose output also Hyperglycaemia has a negative impact on the function of the immune system, on the host response to illness or injury, and on infectious and overall outcomes [8] and this explain why stress hyperglycaemia group had high mortality than other group and this agree with **Robba and Bilotta in 2016** [9] they conclude that elevate blood glucose level in critically ill patients associated with increased mortality and the more the severity of the illness the more stress hyperglycaemia which affect immune system, host response to disease, susceptibility for sepsis and over all on outcome.

In our study ROC curves for glucose parameters and the APACHE-II score for predicting ICU mortality explained that Glycemic parameters included glycemic gap, and HbA1c showed that the AUC of the APACHE-II score was larger than that of glycemic gap ($P < 0.001$) as the AUCs for key predictors of short term outcome of critical ill patients as the APACHE-II score had the highest AUC (0.928, 95% CI: 0.861–0.995) and the discriminative power of the glycemic gap for outcome was greater than that of HbA1c with AUCs of 0.838 (95% CI: 0.723–0.953) and $p < 0.001$ for patients glycemic gap and 0.439 (95% CI: 0.291–0.588) with p value of 0.420 for HbA1c and In the current study, combining glycemic gap with APACHE-II score significantly increased its discriminative ability to predict ICU mortality, This is in concordance with **Liao et al. in 2015** [2]and **Galal and her colleagues in 2017** [5].

4. Conclusion

Elevated glycemic gap significantly associated with an increased risk of ICU mortality that glycemic gap can be used to assess the severity and prognosis of critically ill patients and their incorporation into the APACHE II score has increased its discriminative ability to predict ICU mortality.

Recommendations

Using the glycemic gap in addition to APACHE-II may give better prediction of prognosis in critically ill patients.

Conflicts of interest

There is no conflict of interest.

Acknowledgment

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