

Glycemic lability index and mortality in critically ill patients—A multicenter cohort study

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Abstract

Background: Emerging evidence indicates a relationship between glycemic variability during intensive care unit (ICU) admission and death. We assessed whether mean glucose, hypoglycemia occurrence, or premonitory glycemic control modified this relationship.

Methods: In this retrospective, multicenter cohort study, we included adult patients admitted to five ICUs in Australia and Sweden with available preadmission glycated hemoglobin A1c (HbA1c) and three or more glucose readings. We calculated the glycemic lability index (GLI), a measure of glycemic variability, and the time-weighted average blood glucose (TWA-BG) from all glucose readings. We used logistic regression analysis with adjustment for hypoglycemia and admission characteristics to assess the independent association of GLI (above vs. below cohort median) and TWA-BG (above vs. below cohort median) with hospital mortality.

Results: Among 2305 patients, 859 (37%) had diabetes, median GLI was 40 [mmol/L]²/h/week, median TWA-BG was 8.2 mmol/L, 171 (7%) developed hypoglycemia, and 371 (16%) died. The adjusted odds ratio for death was 1.61 (95% CI, 1.19–2.15; $P = .002$) for GLI above versus below median and 1.06 (95% CI, 0.80–1.41; $P = .67$) for TWA-BG above versus below median. The relationship between GLI and mortality was not modified by TWA-BG (P [interaction] = 0.66), a history of diabetes (P [interaction] = 0.89) or by HbA1c ≥ 52 mmol/mol (vs. < 52 mmol/mol) (P [interaction] = 0.29).

Conclusion: In adult patients admitted to an ICU in Sweden and Australia, a high GLI was associated with increased hospital mortality irrespective of the level of mean glycemia, hypoglycemia occurrence, or premonitory glycemic control. These findings support the assessment of interventions to reduce glycemic variability during critical illness.

1 | INTRODUCTION

Stress-hyperglycemia, a ubiquitous feature of critical illness, is associated with increased mortality in intensive care unit (ICU) patients.^{1–3} Consequently, the majority of ICU patients receive

insulin to control blood glucose within a target range. Current ICU guidelines^{4,5} recommend targeting blood glucose within the mild hyperglycemia range (6–10 mmol/L) to prevent the harmful effects of hypoglycemia associated with exposure to normoglycemic targets (4.5–6 mmol/L).⁶

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Although insulin therapy effectively reduces the mean blood glucose concentration toward a desired target range, it may also induce unnecessary and large glucose fluctuations (high glycemic variability).⁷ Experimental human data suggest that such fluctuations trigger endothelial dysfunction and oxidative stress.^{8,9} Furthermore, clinical studies suggest that high glycemic variability is independently associated with higher mortality in ICU patients.^{10,11} They also suggest that this association may be related to the mean glycemic level around which glucose fluctuates.¹² Finally, emerging data also demonstrate that chronic pre-morbid glycemic control (ie, diabetes and level of glycosylated hemoglobin A1c [HbA1c]) significantly alters the relationship between glycemic variability and outcome.^{13,14}

Unfortunately, no previous studies have provided data on the combined impact of HbA1c and mean blood glucose in ICU on glycemic variability exposure and on its association with mortality. Moreover, previous studies have used unweighted measures of variability and/or mean blood glucose. This may have introduced surveillance bias as more frequent glucose sampling typically occurs in sicker patients with more severe dysglycemia.

Accordingly, we aimed to assess the independent association of time-weighted measures of glycemic variability and mean blood glucose with hospital mortality in critically ill patients. In addition, we aimed to investigate whether these associations were modified by the presence of diabetes or by the level of chronic glycemic control (expressed as HbA1c).

2 | MATERIALS AND METHODS

The study was approved by the Swedish Ethical Review Authority (approval number 2016/1745-31) and the Austin Health Human Research Ethics Committee (LNR/16/Austin/430) with a waiver of informed consent. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

2.1 | Study population

We conducted a retrospective observational binational multicenter study including adult (>16 y) ICU patients included in two existing HbA1c databases. Patients were admitted to four ICUs in Sweden (between March and August 2016)¹⁵ and one ICU in Australia (between October 2012 and September 2015). We excluded patients with less than three blood glucose readings, patients with unknown admission diagnosis, and patients without mortality or illness severity data. We also excluded patients admitted with diabetic ketoacidosis or hyperosmolar hyperglycemic state. Target blood glucose was 5-10 mmol/L in the Swedish cohort. In the Australian cohort, target blood glucose was 6-10 mmol/L for all patients until February 2015. Thereafter, target blood glucose was 6-10 mmol/L for patients without diabetes and 10-14 mmol/L for patients with diabetes.¹⁶

Editor Comments

This international cohort study of 2305 adult ICU patients suggests that glycemic variability is associated with increased risk of death. Whether this effect is causal or can be explained by confounding by indication remains to be determined.

2.2 | Data collection

The databases contained all available arterial and venous blood glucose concentrations obtained in ICU. Blood glucose was measured by the Radiometer ABL825 (Australia) or ABL800 Flex (Sweden) blood gas analyzer (Radiometer Medical A/S, Brønshøj, Denmark). Demographic data, admission characteristics, ICU mortality, hospital mortality, and HbA1c obtained within 3 mon before admission to the ICU were also included. Diabetes diagnosis was determined by assessing electronic medical records for an International Classification of Diseases, 10th edition (ICD-10) code of diabetes or by an HbA1c level of ≥ 48 mmol/mol (cutoff recommended by the World Health Organization). In addition, a history of diabetes was obtained by chart review of the patient's medical records (notes, chronic diabetes medication) in the Swedish cohort. The Simplified Acute Physiology Score (SAPS) 3¹⁷ was used to assess illness severity in Sweden, and the Acute Physiology and Chronic Health Evaluation (APACHE) III score¹⁸ was used to assess illness severity in Australia. To obtain a combined measure of illness severity for the entire study cohort, we calculated the percentage estimated risk of death from SAPS 3 (Swedish patients) and APACHE III score (Australian patients) using published Equations^{17,18}

2.3 | Operational definitions

To avoid surveillance bias, we calculated each patient's time-weighted average blood glucose (TWA-BG) concentration and glycemic lability index (GLI) from all recorded blood glucose concentrations in the ICU. GLI was used to quantify glycemic variability and was calculated according to the following formula¹⁹:

$$\text{GLI} \left(\frac{\text{mmol/L}^2}{\text{h}} \right) / \text{week} = \sum_{n=1}^N (\text{Glu}_n - \text{Glu}_{n+1})^2 / (h_{n+1} - h_n)$$

in which h = time, Glu_n (mmol/L) = the n th reading taken at time h_n , and N = total number of readings. To create a weekly average measure of GLI (in $[\text{mmol/L}]^2/\text{h}/\text{week}$) as reported in previous publications,^{12,14} we multiplied GLI with the number of hours in 1 wk (168) divided by the number of hours under observation. A detailed example of the GLI calculation is provided in Table S1.

Patients were allocated into four groups according to whether their TWA-BG and GLI levels were above or below the whole study

cohort medians. Group 1 contained patients with both TWA-BG and GLI below median. Group 2 contained patients with TWA-BG below median and GLI above median. Group 3 contained patients with TWA-BG above median and GLI below median. Group 4 contained patients with both TWA-BG and GLI above median. We defined hypoglycemia as a blood glucose level ≤ 3.9 mmol/L, moderate hypoglycemia as a blood glucose level >2.2 and ≤ 3.9 mmol/L, and severe hypoglycemia as a blood glucose level ≤ 2.2 mmol/L.²⁰

2.4 | Outcomes

The primary outcome was hospital mortality.

2.5 | Statistical analysis

Data were analyzed using STATA version 15.1 (Stata Corp., College Station, TX). The final dataset of included patients contained no missing data. Categorical variables were summarized as numbers (%) and compared using the chi-square test. Continuous variables were assessed for normality by visual inspection of histograms. Variables with normal distribution were summarized as mean (standard deviation) and compared using analysis of variance. Variables with non-normal distribution were summarized as median (interquartile range) and compared using the Kruskal–Wallis test. The association between GLI and TWA-BG, respectively, with mortality was assessed using multivariable logistic regression analysis. In the analysis, both variables were dichotomized at the median for the cohort. In addition, we considered the occurrence of hypoglycemia and the following baseline variables for inclusion in the multivariable model: age (years), estimated risk of death (in quartiles), ICU admission source, sex, diabetes, HbA1c ≥ 52 mmol/mol (vs. below 52 mmol/mol) and country (Australia vs. Sweden). We also assessed the potential interaction between TWA-BG and GLI. Variables were included in the multivariable model if they were statistically significant at $P < .10$ in the univariable analyses. Goodness of fit and model discrimination were determined using the Hosmer–Lemeshow test and area under the curve, respectively. The final model was assessed for multicollinearity.

To test the robustness of any association between GLI, TWA-BG, and mortality, we repeated the analysis using early GLI and TWA-BG calculated from blood glucose values obtained during the first 24 h. Additionally, we assessed these associations using GLI and TWA-BG as continuous variables. GLI and TWA-BG were found to be well approximated by log-normal distributions so were log-transformed before inclusion in the model. We performed sensitivity analyses to assess the association between GLI above (vs. below) median and hospital mortality adjusted for estimated risk of death and TWA-BG in the following subgroups: diabetes versus no diabetes, HbA1c greater or equal to 52 mmol/mol versus less than 52 mmol/mol, admission from the emergency department versus admission from other locations, sepsis versus no sepsis, and country (Sweden vs. Australia).

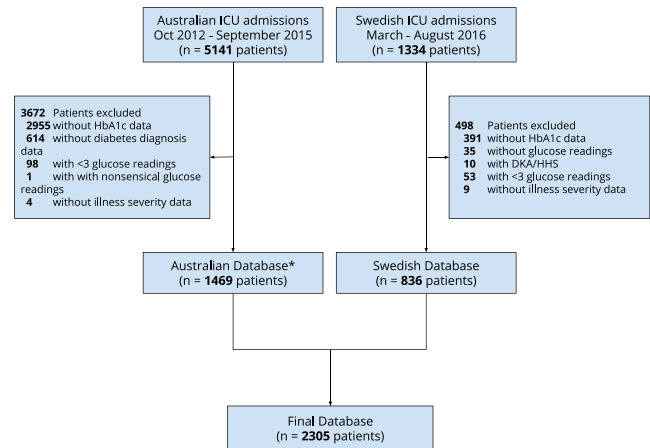


FIGURE 1 Patient selection. DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state; HbA1c, glycated hemoglobin A1c. *None of the remaining patients in the Australian Database had DKA or HHS [Colour figure can be viewed at wileyonlinelibrary.com]

We determined heterogeneity by fitting an interaction between GLI above (vs. below) median and subgroup. In a similar sensitivity analysis, we assessed the association between TWA-BG above (vs. below) median and hospital mortality across subgroups. A two-sided P value less than 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Patients

The selection of study patients is shown in Figure 1. We included 2305 patients in the final analysis. Number of patients included in each participating ICU is presented in Table S2. Baseline characteristics of patients stratified according to median TWA-BG (8.2 mmol/L) and median GLI (40 [mmol/L]²/h/week) are presented in Table 1. Patients with TWA-BG above median (Groups 3 and 4) had higher HbA1c levels, were more likely to have diabetes and were more likely to be admitted due to cardiovascular causes than patients with TWA-BG below median (Groups 1 and 2). Conversely, patients with GLI above median (Groups 2 and 4) were more likely to be immunosuppressed and were more likely to be admitted due to liver failure, ARDS, and septic shock than patients with GLI below median (Groups 1 and 3). Irrespective of the TWA-BG, the estimated risk of death was greater in patients with GLI above the median than in patients with GLI below the median.

3.2 | Glucose metrics

We analyzed 60 574 glucose concentrations (median 8 [IQR 6–11] concentrations/day). Blood glucose was measured more frequently in patients with GLI above median (Groups 2 and 4, median 9–10 measurements/day) than in patients with GLI below

TABLE 1 Baseline characteristics

Characteristic	Time-weighted average blood glucose below cohort median		Time-weighted average blood glucose above cohort median		Overall P value
	Group 1 (glycemic lability index below median)	Group 2 (glycemic lability index above median)	Group 3 (glycemic lability index below median)	Group 4 (glycemic lability index above median)	
N (%)	810 (35.1%)	342 (14.8%)	343 (14.9%)	810 (35.1%)	
Age, years	62 (17)	60 (18)	67 (12)	65 (13)	<0.001
Male sex	546 (67.4%)	208 (60.8%)	236 (68.8%)	540 (66.7%)	0.11
HbA1c, mmol/mol	38 (6)	40 (10)	44 (12)	51 (17)	<0.001
Diabetes	108 (13.3%)	78 (22.8%)	145 (42.3%)	528 (65.2%)	<0.001
Immunosuppression	48 (5.9%)	27 (7.9%)	21 (6.1%)	71 (8.8%)	0.13
ICU admission source					<0.001
Emergency department	192 (23.7%)	105 (30.7%)	43 (12.5%)	183 (22.6%)	
Other ICU	29 (3.6%)	17 (5.0%)	13 (3.8%)	15 (1.9%)	
OR/HDU/Trauma room	412 (50.9%)	129 (37.7%)	232 (67.6%)	431 (53.2%)	
Ward	177 (21.9%)	91 (26.6%)	55 (16.0%)	181 (22.3%)	
ICU admission diagnosis					<0.001
Metabolic/intoxication	56 (6.9%)	37 (10.8%)	2 (0.6%)	24 (3.0%)	
Neurologic	60 (7.4%)	17 (5.0%)	26 (7.6%)	50 (6.2%)	
Cardiovascular	264 (32.6%)	103 (30.1%)	148 (43.1%)	350 (43.2%)	
Gastrointestinal	107 (13.2%)	46 (13.5%)	69 (20.1%)	113 (14.0%)	
Respiratory	72 (8.9%)	33 (9.6%)	28 (8.2%)	65 (8.0%)	
Sepsis	109 (13.5%)	54 (15.8%)	36 (10.5%)	112 (13.8%)	
Trauma	91 (11.2%)	34 (9.9%)	13 (3.8%)	40 (4.9%)	
Other	51 (6.3%)	18 (5.3%)	21 (6.1%)	56 (6.9%)	
Selected admission diagnoses					
Liver failure	12 (1.5%)	18 (5.3%)	5 (1.5%)	31 (3.8%)	<0.001
ARDS	17 (2.1%)	19 (5.6%)	3 (0.9%)	31 (3.8%)	0.001
Septic shock	40 (4.9%)	30 (8.8%)	17 (5.0%)	44 (5.4%)	0.06
Country					<0.001
Sweden	287 (35.4%)	191 (55.8%)	78 (22.7%)	280 (34.6%)	
Australia	523 (64.6%)	151 (44.2%)	265 (77.3%)	530 (65.4%)	
Estimated risk of death, % ^a	11 (4-30)	21 (6-48)	9 (2-29)	19 (4-44)	<0.001

Note: Data are presented as mean (SD) or median (IQR) for continuous measures, and n (%) for categorical measures.

Abbreviations: ARDS, acute respiratory distress syndrome; HbA1c, glycated hemoglobin A1c; HDU, high dependency unit; ICU, intensive care unit; OR, operating room.

^aThe percentage estimated risk of death from SAPS 3 (Swedish patients) and APACHE III score (Australian patients) was calculated using published equations^{15,16}.

median (Groups 1 and 3, median 7 measurements/day). Moreover, the proportion of patients exposed to at least one episode of hypoglycemia was higher in patients with GLI above median. Hypoglycemia was particularly common among those patients with GLI above median in combination with a TWA-BG below median (19.9%) (Table 2).

3.3 | Outcomes

Compared with patients with GLI below median (Group 1 and 3), patients with GLI above median (Groups 2 and 4) had a longer ICU stay ($P < .001$). In addition, patients with GLI above median had significantly higher ICU and hospital mortality (Table 2). The

TABLE 2 Glycemic characteristics and outcomes

Variable	Time-weighted average blood glucose below cohort median		Time-weighted average blood glucose above cohort median		Overall P value
	Group 1 (Glycemic lability index below median)	Group 2 (Glycemic lability index above median)	Group 3 (Glycemic lability index below median)	Group 4 (Glycemic lability index above median)	
Number of glucose measurements/d	7 (5-9)	10 (7-13)	7 (5-9)	9 (7-12)	<0.001
Time-weighted average blood glucose, mmol/L	7 (1)	7 (1)	9 (1)	10 (2)	<0.001
Glycemic lability index, [mmol/L] ² /h/wk	13 (6-23)	85 (55-157)	22 (12-32)	100 (63-177)	<0.001
At least one blood glucose value >10 mmol/L	162 (20.0%)	203 (59.4%)	250 (72.9%)	785 (96.9%)	<0.001
Hypoglycemia ^a	28 (3.5%)	68 (19.9%)	4 (1.2%)	71 (8.8%)	<0.001
Moderate hypoglycemia ^b	27 (3.3%)	60 (17.5%)	4 (1.2%)	63 (7.8%)	<0.001
Severe hypoglycemia ^c	1 (0.1%)	8 (2.3%)	0	8 (1.0%)	<0.001
ICU length of stay, d	1.9 (0.9-3.8)	2.2 (1.1-4.9)	1.8 (1.0-3.7)	2.1 (1.0-4.7)	<0.001
ICU mortality	21 (2.6%)	46 (13.5%)	19 (5.5%)	96 (11.9%)	<0.001
Hospital mortality	89 (11.0%)	72 (21.1%)	35 (10.2%)	175 (21.6%)	<0.001

Note: Data are presented as mean (SD) or median (IQR) for continuous measures, and n (%) for categorical measures.

^aHypoglycemia was defined as a blood glucose level ≤ 3.9 mmol/L.

^bModerate hypoglycemia was defined as a blood glucose level >2.2 and ≤ 3.9 mmol/L.

^cSevere hypoglycemia was defined as a blood glucose level ≤ 2.2 mmol/L

probability of death increased with increasing level of GLI and TWA-BG, respectively (Figure 2). On multivariable logistic regression analysis adjusted for TWA-BG, age, estimated risk of death, hypoglycaemia, ICU admission source, and country, we found an independent association between GLI above (vs. below) median and hospital mortality (adjusted odds ratio for GLI above median: 1.60 [95% CI, 1.19-2.15]; $P = .002$). In contrast, we found no significant association between TWA-BG and mortality on multivariable analysis (Table 3). The relationship between GLI and mortality was not significantly modified by the level of TWA-BG (P value for interaction = 0.66). The association of GLI and TWA-BG with mortality remained when restricting GLI and TWA-BG calculations to the first 24 h (Table S3). Similarly, log-transformed GLI but not log-transformed TWA-BG was associated with mortality on multivariable analysis (Table S4). The association between GLI and mortality did not differ significantly when comparing patients with and those without diabetes ($P = .89$), patients with HbA1c above or equal to 52 mmol/mol and those with HbA1c below 52 mmol/mol ($P = .29$), patients who were or were not admitted from the emergency department ($P = .18$), patients with and those without sepsis ($P = .47$), and patients admitted to ICU in Sweden and patients admitted to ICU in Australia ($P = .25$) (Figure 3). We also found no association between TWA-BG and mortality in any of the predefined subgroups (Figure S1).

4 | DISCUSSION

4.1 | Key findings

We conducted a retrospective observational multicentre study to evaluate the association between the glycemic lability index (GLI), a marker of glycemic variability, and hospital mortality in ICU patients and to assess whether this potential association was modified

by the time-weighted average blood glucose (TWA-BG) level in ICU or by pre-morbid chronic glycemia (HbA1c) or the presence of diabetes. We found that high glycemic variability, as determined by the GLI, was associated with increased hospital mortality independent of TWA-BG, age, diabetes, a high HbA1c, hypoglycaemia, and illness severity.

4.2 | Relationship to previous studies

Early studies demonstrated an independent association between glycemic variability, expressed as the standard deviation of blood glucose concentration during ICU stay, and mortality. However, these studies did not consistently consider mean blood glucose, hypoglycaemia, diabetes, and HbA1c levels in the analyses.^{10,11} In addition, since the standard deviation is correlated with the mean glucose,²¹ it is uncertain if mean glucose, glycemic variability, or both these metrics were responsible for the effect on mortality.

In a single center study of almost 6000 ICU patients, Hermanides et al found an association between higher glycemic variability (expressed as mean absolute glucose change) and increased hospital mortality after adjusting for illness severity, diabetes, mean blood glucose, and severe hypoglycemia.²² Unfortunately, because covariate regression coefficients were not reported, their significance in the multivariable model remained uncertain. Furthermore, mean absolute glucose change and mean blood glucose are not time weighted and hence are subject to surveillance bias.

Ali et al used GLI to quantify glycemic variability in 1200 hospitalized patients with sepsis.¹² In contrast to our results, they found a significant interaction between GLI and average hospital glucose level; GLI was associated with mortality only among patients with mean glucose below the cohort median (<7.4 mmol/L) suggesting that this subgroup was exposed to hypoglycemia. Although this

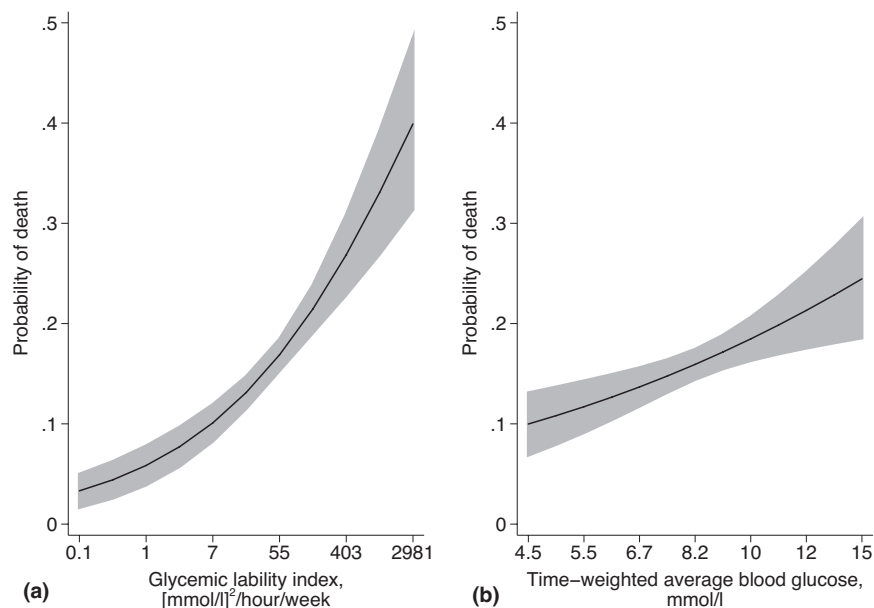


FIGURE 2 Unadjusted relationship between glycemic lability index (A), time-weighted average blood glucose (B) and probability of death. Independent continuous values (x-axis) are presented on a logarithmic scale

TABLE 3 Univariable and multivariable logistic regression analysis showing the association with hospital mortality

Variable	Univariable		Multivariable ^a	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Time-weighted average glucose				
Below median	1.0		1.0	
Above median	1.37 (1.10-1.71)	0.006	1.06 (0.80-1.41)	0.67
Glycemic lability index				
Below median	1.0		1.0	
Above median	2.26 (1.79-2.86)	<0.001	1.60 (1.19-2.15)	0.002
Age, per year	1.03 (1.02-1.04)	<0.001	1.01 (1.00-1.02)	0.07
Estimated risk of death ^b				
Q1	1.0		1.0	
Q2 vs. Q1	3.10 (1.44-6.65)	0.004	2.96 (1.37-6.41)	0.006
Q3 vs. Q1	10.95 (5.45-21.99)	<0.001	8.10 (3.91-16.80)	<0.001
Q4 vs. Q1	48.40 (24.55-95.42)	<0.001	33.75 (16.30-69.89)	<0.001
Hypoglycemia ^c				
No	1.0		1.0	
Yes	2.90 (2.06-4.07)	<0.001	1.50 (1.01-2.24)	0.04
ICU admission source				
Emergency Department	1.0		1.0	
Other ICU	1.00 (0.54-1.86)	>0.99	1.21 (0.61-2.39)	0.59
OR/HDU/Trauma room	0.38 (0.28-0.52)	<0.001	1.09 (0.77-1.55)	0.62
Ward	1.97 (1.48-2.63)	<0.001	1.87 (1.35-2.59)	<0.001
Country				
Sweden	1.0		1.0	
Australia	0.57 (0.46-0.72)	<0.001	0.97 (0.74-1.28)	0.84
Sex				
Female	1.0			
Male	0.83 (0.66-1.04)	0.11		
Diabetes				
No	1.0			
Yes	1.03 (0.82-1.31)	0.78		
HbA1c \geq 52 mmol/mol				
No	1.0			
Yes	0.93 (0.70-1.24)	0.63		

Abbreviations: HDU, high dependency unit; ICU, intensive care unit; OR, operating room; Q, quartile.

^aHosmer–Lemeshow goodness-of-fit test, $P = .75$. Model area under the receiver operating characteristics curve 0.84.

^bThe percentage estimated risk of death from SAPS 3 (Swedish patients) and APACHE III score (Australian patients) was calculated using published equations^{15,16}.

^cHypoglycemia was defined as a blood glucose level \leq 3.9 mmol/L.

association was independent of hypoglycemia and insulin administration, the regression coefficients for these covariates were not reported.

It has been suggested that ICU patients with diabetes tolerate large glucose fluctuations better than those without diabetes.²³ For example, in a cohort of 1600 ICU patients, risk of death progressively increased by quartiles of GLI but only in the diabetes subgroup.¹⁴ In addition, Plummer et al found a significant interaction between

HbA1c level and the relationship between glycemic variability and hospital mortality.¹³ Specifically, an association between the coefficient of variation and mortality was only seen among those patients with an HbA1c of 8.5% (69 mmol/mol) or lower.

In accord with most previous studies, our analysis of ICU patients from five ICUs in Sweden and Australia suggest that higher glycemic variability is associated with mortality independent of both the average glucose level and the occurrence of hypoglycemia. As

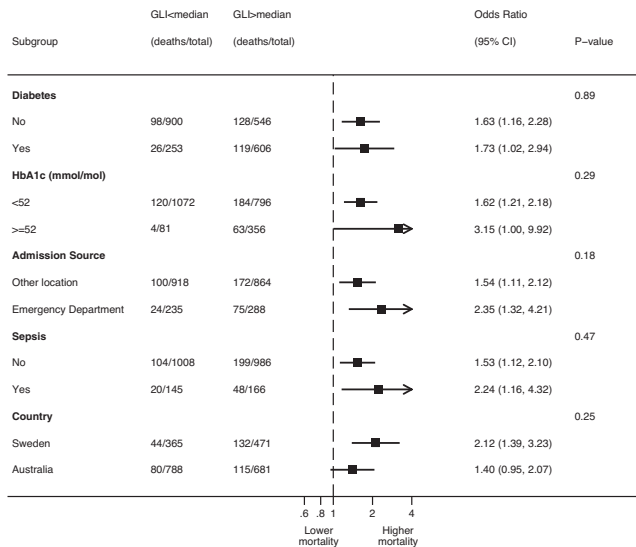


FIGURE 3 Odds ratio of hospital mortality with adjustment for estimated risk of death and time-weighted average blood glucose above (vs. below) cohort median according to diabetes diagnosis, glycated hemoglobin A1c (HbA1c) level, admission source, sepsis on admission, and country. Odds ratio greater than 1 indicates higher mortality with glucose lability index (GLI) above (vs. below) cohort median. P-values represent test for heterogeneity. HbA1c, glycated hemoglobin A1c

consistently demonstrated in the literature,^{3,20,24} hypoglycemia was an independent mortality predictor in our analysis. However, the association was markedly weakened after adjustment for variability in our multivariable model. In contrast to previous data, the association between variability and mortality was seen in patients with and without diabetes and in patients with higher (≥ 52 mmol/mol) and lower (< 52 mmol/mol) HbA1c.

4.3 | Study implications

Our findings imply that high levels of glycemic variability may be harmful irrespective of whether such variability occurs above or below average glucose levels. Moreover, they imply that the harmful effects of such variability is unrelated to the presence of pre-existing diabetes or the level of pre-morbid chronic glycemia (ie, level of HbA1c). In addition, our findings imply that exposure to a higher average glucose level is safe if variability around that level is avoided. Accordingly, our results support the notion that strategies targeting a low GLI may be more valuable to patients than strategies targeting a given blood glucose level. Such strategies may include the use of more liberal glucose targets in patients with diabetes who are typically exposed to high glycemic variability in the ICU,¹⁶ the avoidance of insulin boluses, the avoidance of large increments in insulin therapy from hour to hour, the use of more frequent or even continuous blood glucose monitoring,²⁵ or a combination of these interventions. Finally, our results imply that glycemic variability should be an important outcome measure in future randomized trials of glycemic management.

4.4 | Strengths and limitations

Our study has several strengths. We included > 2 000 patients admitted to five ICUs in two countries, thus providing a high degree of external validity with generalizability to similar populations. Additionally, we analyzed > 60 000 blood glucose concentrations obtained in the ICU and used time-weighted metrics, which increases the robustness of the key exposure variables. Moreover, the assessment of GLI and TWA-BG as both continuous and binary variables produced consistent results. Finally, our findings are coherent with previous studies, a characteristic that further increases the validity of our results.

Our study has some limitations. It is an observational study and does not account for unmeasured confounders or imply causation. Therefore, our results should be considered exploratory. However, at this stage, ethical concern prevents randomizing patients to different glycemic variability levels. We lacked data on insulin and corticosteroid therapy and were therefore unable to assess their role in inducing glucose fluctuations. However, the prevalence of immunosuppression, ARDS, and septic shock was greater among patients with GLI above median. This suggests that these patients might have been exposed to corticosteroids to a greater extent. Additionally, liver failure, a risk factor for hypoglycemia and glucose variability, was more common among patients with GLI above median. Australian and Swedish patients were included during different time periods. Selection bias can therefore not be ruled out. However, country was accounted for in the multivariable analyses.

5 | CONCLUSIONS

In adult patients admitted to five ICUs in Sweden and Australia, high glycemic variability during ICU admission was associated with increased hospital mortality irrespective of the level of mean glycemia, the occurrence of hypoglycemia, and the degree of acute illness severity. The observed association between glycemic variability and mortality was not modified by the presence of diabetes or by the level of chronic glycemic control. Our findings support further assessment of strategies to reduce blood glucose fluctuations during critical illness.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

MH and JM had full access to all of the data in the study and take responsibility for the integrity of the data, the accuracy of the

data analysis, and the decision to submit for publication. Study concept and design: JM, MH. Data acquisition: AB, ML, NG, JM, GE. Analysis and interpretation of the data: JM, MH, RB, AB, ML, NG, AO, GE. Drafting of the manuscript: JM, MH, RB. Critical revision of the manuscript: JM, MH, RB, AB, ML, NG, AO, GE. All authors approved the final version of the manuscript submitted for publication.

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REFERENCES

- Whitcomb BW, Pradhan EK, Pittas AG, et al. Impact of admission hyperglycemia on hospital mortality in various intensive care unit populations. *Crit Care Med*. 2005;33:2772-2777.
- Falciglia M, Freyberg RW, Almenoff PL, et al. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med*. 2009;37:3001-3009. <https://doi.org/10.1097/CCM.0b013e3181b083f7>
- Krinsley JS, Egi M, Kiss A, et al. Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. *Crit Care*. 2013;17:R37. <https://doi.org/10.1186/cc12547>
- Nolan JP, Soar J, Cariou A, et al. European resuscitation council and European society of intensive care medicine guidelines for post-resuscitation care 2015: section 5 of the European resuscitation council guidelines for resuscitation 2015. *Resuscitation*. 2015;95:202-222. <https://doi.org/10.1016/j.resuscitation.2015.07.018>
- Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43:304-377. <https://doi.org/10.1007/s00134-017-4683-6>
- Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *New Engl J Med*. 2009;360:1283-1297. <https://doi.org/10.1056/NEJMoa0810625>
- Al-Dorzi HM, Tamim HM, Arabi YM. Glycaemic fluctuation predicts mortality in critically ill patients. *Anaesth Intensive Care*. 2010;38:695-702. <https://doi.org/10.1177/0310057X1003800413>
- Ceriello A, Esposito K, Piconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes*. 2008;57:1349-1354. <https://doi.org/10.2337/db08-0063>
- Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA*. 2006;295:1681-1687. <https://doi.org/10.1001/jama.295.14.1681>
- Egi M, Bellomo R, Stachowski E, et al. Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology*. 2006;105:244-252.
- Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med*. 2008;36:3008-3013. <https://doi.org/10.1097/CCM.0b013e31818b38d2>
- Ali NA, O'Brien JM, Dungan K, et al. Glucose variability and mortality in patients with sepsis. *Crit Care Med*. 2008;36:2316-2321. <https://doi.org/10.1097/CCM.0b013e3181810378>
- Plummer MP, Finnis ME, Horsfall M, et al. Prior exposure to hyperglycaemia attenuates the relationship between glycaemic variability during critical illness and mortality. *Crit Care Resusc*. 2016;18:189-197.
- Donati A, Damiani E, Domizi R, et al. Glycaemic variability, infections and mortality in a medical-surgical intensive care unit. *Crit Care Resusc*. 2014;16:13-23.
- Balintescu A, Palmgren I, Lipcsey M, et al. Prevalence and impact of chronic dysglycemia in intensive care unit patients—a retrospective cohort study. *Acta Anaesthesiol Scand*. 2021;65:82-91. <https://doi.org/10.1111/aas.13695>
- Luethi N, Cioccarri L, Biesenbach P, et al. Liberal glucose control in ICU patients with diabetes: a before-and-after study. *Crit Care Med*. 2018;46:935-942. <https://doi.org/10.1097/CCM.00000000000003087>
- Moreno RP, Metnitz PGH, Almeida E, et al. SAPS 3—from evaluation of the patient to evaluation of the intensive care unit. Part 2: development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med*. 2005;31:1345-1355. <https://doi.org/10.1007/s00134-005-2763-5>
- Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. risk prediction of hospital mortality for critically ill hospitalized adults. *Chest*. 1991;100:1619-1636. <https://doi.org/10.1378/chest.100.6.1619>
- Ryan EA, Shandro T, Green K, et al. Assessment of the severity of hypoglycemia and glycemic lability in type 1 diabetic subjects undergoing islet transplantation. *Diabetes*. 2004;53:955-962. <https://doi.org/10.2337/diabetes.53.4.955>
- Finfer S, Liu B, Chittock DR, et al. Hypoglycemia and risk of death in critically ill patients. *New Eng J Medicine*. 2012;367:1108-1118. <https://doi.org/10.1056/NEJMoa1204942>
- Rodbard D. The challenges of measuring glycemic variability. *J Diabetes Sci Technol*. 2012;6:712-715.
- Hermanides J, Vriesendorp TM, Bosman RJ, et al. Glucose variability is associated with intensive care unit mortality. *Crit Care Med*. 2010;38:838-842. <https://doi.org/10.1097/CCM.0b013e3181cc4be9>
- Balintescu A, Mårtensson J. Hemoglobin A1c and permissive hyperglycemia in patients in the intensive care unit with diabetes. *Crit Care Clin*. 2019;35:289-300. <https://doi.org/10.1016/j.ccc.2018.11.010>
- Krinsley JS, Schultz MJ, Spronk PE, et al. Mild hypoglycemia is independently associated with increased mortality in the critically ill. *Crit Care*. 2011;15:R173. <https://doi.org/10.1186/cc10322>
- Ancona P, Eastwood G, Lucchetta L, et al. The performance of flash glucose monitoring in critically ill patients with diabetes. *Crit Care Resusc: J Aus Acad Crit Care Med*. 2017;19:167-174.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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