International Journal of Gerontology 19 (2025) 211–216
https://doi.org/10.6890/IJGE.202510_19(4).0003

International Journal of Gerontology

journal homepage: http://www.sgecm.org.tw/ijge/

Original Article

Influence of Stress Hyperglycemia on In-Hospital Mortality in Older Patients with Sepsis: A Retrospective Analysis

You-Cheng Lin [a], Tsong-Yih Ou [b,c], Shu-Fen Liao [d,e], Shih-Chang Hsu [a,f], Shau-Ku Huang [g,h], Wen-Cheng Huang [a,f,i,j], Chin-Wang Hsu [a,f *]

[a] *Emergency Department, Taipei Municipal Wan-Fang Hospital, Taipei, Taiwan,* [b] *Division of Infectious Diseases, Department of Internal Medicine, Taipei Municipal Wan-Fang Hospital, Taipei, Taiwan,* [c] *Department of Nursing, Cardinal Tien Junior College of Healthcare and Management, New Taipei City, Taiwan,* [d] *Department of Medical Research, Taipei Municipal Wan-Fang Hospital, Taipei, Taiwan,* [e] *School of Public Health, College of Public Health Taipei Medical University, Taipei, Taiwan,* [f] *Department of Emergency, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan,* [g] *National Health Research Institutes, National Institute of Environmental Health Sciences,* [h] *The Johns Hopkins University School of Medicine, Johns Hopkins Asthma and Allergy Center,* [i] *Department of Clinical Education, Taipei Municipal Wan-Fang Hospital, Taipei, Taiwan,* [j] *Center for Education in Medical Simulation, Taipei Medical University, Taipei, Taiwan*

ARTICLE INFO

Accepted 2 May 2025

Keywords:
hyperglycemia,
geriatrics,
sepsis,
critical care

SUMMARY

Background: Stress hyperglycemia, a critical illness response, is linked to poor outcomes. Its impact on geriatric sepsis patients remains unclear. This study investigates stress hyperglycemia's influence in geriatric sepsis patients.

Methods: These patients were identified by searching the 10th revision of the International Classification of Diseases codes that were sepsis-related diagnoses, and they were categorized into two age groups: 18–65 years and over 65 years. Stress hyperglycemia was assessed using the glycemic gap (the difference between admission glucose and estimated average glucose (eAG)) and glycemic ratio (the ratio of admission glucose to eAG). Mortality risk during hospitalization was assessed using logistic regression and ROC analysis.

Results: The study analyzed 16,582 sepsis patients, with 9,602 in the older group (≥ 65 years) and 6,980 in the younger group. The diabetic patients were 29.5% in the younger group and 37.7% in the older group. Comorbidities, except obesity, were more prevalent in the older group. The older group had higher initial glucose levels, while younger patients had higher HbA1C levels. In younger patients, a higher glycemic ratio was significantly associated with increased in-hospital mortality (p = 0.0492). In contrast, among older diabetic patients, both the glycemic gap and ratio were lower in non-survivors than in survivors, and a higher glycemic ratio was independently associated with reduced mortality (adjusted RR = 0.67, 95% CI = 0.451–0.996, p = 0.048).

Conclusion: Stress hyperglycemia in older sepsis patients may indicate preserved endocrine function and a better prognosis, warranting age-specific hyperglycemia management strategies.

1. Introduction

Sepsis, a critical condition, induces life-threatening multiple organ dysfunction by a dysregulated host response to infection. It is a common, costly, and lethal condition in hospitals worldwide. Hyperglycemia frequently occurs in critically ill patients, including those without pre-existing diabetes. This stress-induced hyperglycemia results from excessive counterregulatory hormones, such as catecholamines, cortisol, growth hormones, and cytokines, which promote gluconeogenesis and insulin resistance.[1] Large glucose fluctuations could trigger endothelial dysfunction and oxidative stress responses, leading to multiple organ failure.[1] Previous studies suggest that stress hyperglycemia is related to poor outcomes among critical patients.[2–20]

A meta-analysis by Wang et al. indicated that blood glucose levels were related to mortality among patients with sepsis, irrespective of their diabetes status.[21] Though diabetes is a common comorbidity in patients with sepsis, it is not associated with the mortality of sepsis.[22,23] Instead, stress hyperglycemia was indicated as an independent mortality factor in patients with sepsis.[24]

Those aged greater than 65 years comprise more than 60% of patients with sepsis.[25] This demographic is more vulnerable to sepsis due to factors such as comorbidities and age-related physiological changes, including endocrine dysfunction.[26] Aging is associated with a progressive decline in endocrine function — such as reduced adrenal reserve, decreased thyroid hormone levels, and impaired growth hormone secretion — which may influence the body's response to critical illness.[27,28] While stress hyperglycemia has been identified as a predictor of adverse outcomes in critically ill patients, it remains unclear whether older patients are more susceptible to stress-induced hyperglycemia than younger populations. Nevertheless, age-related endocrine changes may affect glucose metabolism under stress, potentially influencing the prognostic significance of hyperglycemia in older patients with sepsis.[28] Despite the prevalence of

* Corresponding author. Emergency Department, Wan Fang Hospital, Taipei Medical University, No. 111, Sec. 3, Shing Long Rd., Wenshan Dist., Taipei 11696, Taiwan.
E-mail address: wan11119@gmail.com (C.-W. Hsu)

sepsis in this population, little is known about how age-related endocrine changes interact with stress hyperglycemia to influence clinical outcomes. This knowledge gap highlights the importance of evaluating the glycemic response in older patients with sepsis.

To ensure clarity, we explicitly define key terms in this study. Stress hyperglycemia refers to the elevation of blood glucose levels in response to acute illness, independent of pre-existing diabetes. Glycemic gap is calculated as the difference between admission glucose and estimated average glucose (eAG), where eAG is derived using the formula AG (mg/dl) = 28.7 * HbA1c – 46.7.[29] Glycemic ratio is defined as the ratio of admission glucose to estimated average glucose. The glucose value mentioned in the study was according to the report from initial blood examination after admission. These two metrics quantify the discrepancy between acute and baseline glucose levels, reflecting the extent of stress hyperglycemia. This approach allows for adjusting glucose metrics based on the patient's baseline glycemic control, a critical factor in sepsis-related studies. The choice of these metrics is justified by previous studies indicating their validity in predicting outcomes in critically ill patients.[1–21,24]

This study investigates stress hyperglycemia's influence on in-hospital mortality among geriatric sepsis patients. By analyzing the relationship between glucose fluctuations and outcomes, we aim to understand whether stress hyperglycemia reflects preserved endocrine function and serves as a prognostic biomarker in this population. Understanding this relationship could lead to age-specific management strategies for hyperglycemia in sepsis patients, potentially improving survival rates in older adults.

2. Materials and methods

2.1. Data source

Our data were extracted from the Medical Information Mart for Intensive Care (MIMIC)-IV database, which contains detailed clinical data from over 40,000 ICU admissions at Beth Israel Deaconess Medical Center (BIDMC) between 2008 and 2019.[30] Patients' information was collected, including gender, age, date of death, final diagnosis, chronic systemic disorders, antibiotics administration, and laboratory values. Liao, one of our authors, had full access to the database and performed the data extraction (certificate number: 45984821). Since the patient identifiers were removed and the data were obtained from publicly available sources, the requirement for informed consent was waived. Authorization was obtained from the Massachusetts Institute of Technology Affiliates to use the data. This study was approved by the expedited review process of the TMU-Joint Institutional Review Board and monitored by TMU-JIRB (TMU-JIRB No.: N202209084).

2.2. Patient selection

Patients aged 18 or older who were admitted with a diagnosis of sepsis were eligible for inclusion. Sepsis was defined according to the Sepsis-3 criteria.[31] These patients were identified by searching the 10th revision of the International Classification of Diseases (ICD-10) codes that were sepsis-related diagnoses (Supplement). We then reviewed the associated data of the identified patients and selected those who had their blood glucose levels measured at their initial presentation. HbA1c level data were also collected within three months before or after admission. The participants were divided into two age groups: the younger group (aged 18–65) and the older group (aged over 65). The age cutoff of 65 years was chosen because it is a commonly accepted threshold for defining geriatric populations in sepsis studies.

Patients lacking HbA1c data when admission were excluded. The rationale for excluding these patients was that the calculation of stress hyperglycemia, such as the glycemic gap and glycemic ratio, requires both admission glucose and baseline glycemic control data derived from HbA1c values. Since the MIMIC-IV database does not allow retrospective supplementation of missing data, these values are essential for the analysis.

The date of death was collected if the patient expired during hospitalization and was applied to measure the in-hospital mortality rate.

2.3. Stress hyperglycemia

Stress hyperglycemia is defined as the glycemic gap (the difference between admission glucose and eAG) and the glycemic ratio (the ratio of admission glucose to eAG). The admission glucose value and the eAG value were collected in the initial blood examination after admission. The eAG was calculated by Glycated hemoglobin (HbA1c) with the formula: (AG (mg/dl) = 28.7 * A1C – 46.7).[29] These metrics were selected based on their ability to account for both acute glucose changes and baseline glycemic control. Previous research supports their utility in reflecting stress-induced glucose changes and their impact on outcomes in critical care.[1–21,24] The rationale for utilizing these specific metrics lies in their capacity to distinguish the acute stress response from pre-existing glycemic conditions, ensuring a nuanced analysis of the effects of stress hyperglycemia in sepsis outcomes.

2.4. Statistical analysis

We used medians and quartiles to present the distribution of variables. The distribution of baseline characteristics between young patients and older patients was examined by t-tests and chi-squared tests. Logistic regression models were used to estimate the risk ratios (RRs) and 95% confidence intervals (CIs) of mortality of the glycemic gap and ratio, adjusted by other variables. Logistic regression was chosen as it is well-suited for binary outcome variables such as mortality and allows for the adjustment of potential confounders. Although logistic regression traditionally yields odds ratios (ORs), we reported risk ratios to enhance interpretability, given that the mortality rate in our cohort was relatively high (> 10%), which can cause ORs to substantially overestimate effect sizes. This approach allows for a more clinically intuitive interpretation of relative risk, especially in the context of outcome incidence in critical care populations.

The selection of covariates was guided by their clinical relevance and potential impact on stress hyperglycemia or mortality, as identified in previous studies.[1–21,24] Age was included due to its role as both an effect modifier and independent predictor of mortality and endocrine response during critical illness. Diabetes mellitus (DM) was adjusted for given its direct impact on baseline glycemic status and its potential to confound glycemic gap and ratio calculations. In addition to age and DM, we adjusted for sex and common comorbidities — including coronary artery disease, hypertension, pulmonary disease, cerebrovascular accident, malignancy, chronic kidney disease, hyperlipidemia, heart failure, and obesity — to minimize residual confounding in the multiple regression models.

We also performed receiver operating characteristic (ROC) analysis of stress glycemia for predicting in-hospital mortality. The predictive performance was evaluated with the area under ROC curve (AUROC), and the optimal cutoff value with the best discrimination ability was estimated by the Youden index. ROC analysis was selected because it provides a robust framework for evaluating the dis-

criminatory power of predictive variables.

For the subgroup analyses, we implemented stratified analyses based on age to control for within-group variance. This approach allowed us to assess whether the association between stress hyperglycemia and mortality differed across younger and older patient groups. Additionally, multiple adjustments were applied in the logistic regression models to account for potential confounders, including age, sex, and comorbidities (coronary artery disease, diabetes mellitus, hypertension, pulmonary disease, cerebrovascular accident, malignancy, chronic kidney disease, hyperlipidemia, heart failure, and obesity). By including these covariates, we aimed to minimize the influence of confounding factors on the observed relationships within each subgroup. Furthermore, we examined interactions between glycemic metrics and age to identify modifying effects that could impact the association between stress hyperglycemia and mortality in different age groups. These steps ensured a more precise and reliable analysis of subgroup-specific outcomes.

Stratified analyses were conducted to assess the modifying effect of age on the glycemic gap on mortality. We set the significance level at 0.05. All the statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

We identified 16,582 adult patients diagnosed with sepsis after admission (Table 1). There were 9,602 patients aged 65 years and older (the older group), and 6,980 patients were younger (the younger group). The diabetic patients were 29.5% in the younger group and 37.7% in the older group. The comorbidities were listed. Compared to the younger group, all comorbidities, except obesity, comprised a higher percentage in the older group, and obesity was more common in the younger group (14.17% in the younger group; 9.43% in the older group, $p < 0.0001$). Stress hyperglycemia was analyzed through the initial glucose level, HbA1C, the glycemic ratio, and the glycemic gap of the older and the younger groups. The median initial glucose level was higher in the older group (younger group: 116.0 (Q1 = 95.0, Q3 = 155.0); older group: 122.0 (Q1 = 99.0, Q3 = 163.0); $p = 0.0097$). The median HbA1C level was higher in the younger group (younger group: 6.3 (Q1 = 5.5, Q3 = 8.4); older group: 6.2 (Q1 = 5.6, Q3 = 7.2); $p = 0.0097$). The glycemic gap and ratio medians were not significantly different between the two groups, but both were higher in the younger group.

The in-hospital mortality analysis is presented in Table 2. Survivors had higher HbA1c either in young and older patients. Higher glycemic gap and glycemic ratio associated with mortality in younger patients, while lower glycemic gap and glycemic ratio associated with mortality in older patients. However, the glycemic ratio was significantly related to mortality only in the younger group ($p = 0.0492$). After multiple adjustments, the glycemic gap and ratio had similar risks associated with mortality in both groups.

In the younger group, the ROC analysis showed that the AUROC of the glycemic gap was 0.5963 (95% CI = 0.5361, 0.6566, $p = 0.0017$), and the AUROC of the glycemic ratio was 0.6064 (95% CI = 0.5431, 0.6696, $p = 0.0010$) (Table 3). There was no distinguishing value of glycemic gap or glycemic ration in the analyses of all patients and the older group.

In the subgroup analysis of diabetic patients (Table 4), both the glycemic gap and glycemic ratio were significantly lower in non-survivors than in survivors within the older age group (gap: 29.9 vs.

Table 1
Basic characteristics of the patients and their comorbidities.

	Age < 65, n = 6980	Age ≥ 65, n = 9602	p value
Sex			0.011
Female	3113 (44.6%)	4475 (46.6%)	
Male	3867 (55.4%)	5127 (53.4%)	
Comorbidities			
CAD	1077 (15.4%)	3752 (39.1%)	< 0.001
DM	2061 (29.5%)	3617 (37.7%)	< 0.001
Hypertension	3117 (44.7%)	7130 (74.3%)	< 0.001
Pulmonary disease	1319 (18.9%)	2462 (25.6%)	< 0.001
CVA	468 (6.7%)	1077 (11.2%)	< 0.001
Malignancy	1456 (20.9%)	2386 (24.9%)	< 0.001
CKD	1246 (17.9%)	3170 (33.0%)	< 0.001
Hyperlipidemia	1647 (23.6%)	4470 (46.6%)	< 0.001
Heart failure	1125 (16.1%)	3640 (37.9%)	< 0.001
Obesity	989 (14.2%)	905 (9.4%)	< 0.001
Glucose	116.0 (95.0, 155.0)	122.0 (99.0, 163.0)	0.010
HbA1C	6.3 (5.5, 8.4)	6.2 (5.6, 7.2)	0.010
Glycemic gap	12.71 (-19.9, 62.2)	10.5 (-16.2, 56.0)	0.802
Glycemic ratio	1.09 (0.9, 1.4)	1.08 (0.9, 1.4)	0.894

Data are presented as number (percentage) for sex and comorbidities, and as median (interquartile range, IQR) for glucose, HbA1C, glycemic gap, and glycemic ratio.

Table 2
Stress hyperglycemia and in-hospital mortality.

	Survivors	Non-survivors	p value	Multiple adjusted RR (95% CI)	p value
All					
Glucose	141.8 (82.4)	147.0 (87.9)	0.003*	1.001 (1.000, 1.001)	0.002*
HbA1C	7.1 (2.3)	6.5 (1.8)	< 0.001*	0.86 (0.80, 0.92)	< 0.001*
Glycemic gap	33.7 (111.7)	32.7 (81.4)	0.858	1.000 (0.999, 1.001)	0.884
Glycemic ratio	1.2 (0.7)	1.2 (0.5)	0.669	1.03 (0.86, 1.24)	0.721
Age < 65 yr					
Glucose	141.5 (91.3)	144.6 (91.8)	0.316	1.001 (1.000, 1.001)	0.107
HbA1C	7.4 (2.6)	6.6 (2.1)	0.001*	0.96 (0.83, 1.10)	0.530
Glycemic gap	31.7 (119.4)	46.8 (82.7)	0.143	1.001 (0.999, 1.003)	0.260
Glycemic ratio	1.2 (0.8)	1.4 (0.6)	0.049*	1.13 (0.90, 1.43)	0.306
Age ≥ 65 yr					
Glucose	142.0 (74.7)	148.2 (85.8)	0.003*	1.001 (1.001, 1.002)	< 0.001*
HbA1C	6.8 (1.9)	6.4 (1.6)	0.011*	0.90 (0.80, 1.01)	0.085
Glycemic gap	35.7 (103.7)	26.3 (80.2)	0.194	0.999 (0.997, 1.001)	0.347
Glycemic ratio	1.2 (0.6)	1.2 (0.5)	0.404	0.90 (0.67, 1.21)	0.487

Data are presented as mean (standard deviation, SD). p values were calculated using the Mann-Whitney U test for continuous variables and chi-square test for categorical variables. Multiple adjusted risk ratios (RRs) were estimated using multivariable logistic regression models. Covariates included in the model: age, sex, diabetes mellitus, coronary artery disease, hypertension, pulmonary disease, cerebrovascular accident, malignancy, chronic kidney disease, hyperlipidemia, heart failure, and obesity. A p value < 0.05 was considered statistically significant (*).

55.0, p = 0.0348; ratio: 1.18 vs. 1.33, p = 0.0335). After adjusting for age, sex, and comorbidities, a higher glycemic ratio was independently associated with a lower risk of in-hospital mortality in this group (adjusted RR = 0.67, 95% CI = 0.451–0.996, p = 0.048).

4. Discussion

We used data from the MIMIC-IV database to investigate the relationship between stress hyperglycemia and sepsis in older patients. This study showed that the two age groups had no difference in stress hyperglycemia levels. Higher stress hyperglycemia levels (shown by glycemic ratio) were significantly related to higher mortality in the younger group. Stress hyperglycemia did not affect mortality in the older group, but it showed a trend of elevation in the survivors.

The comorbidity analysis showed high consistency in that the older group had significantly higher proportions of chronic illnesses, but patients in the younger group were significantly more obese (Table 1). Previous literature showed a similar feature: the older group had a higher percentage of these chronic diseases.[26] The reason may be that these comorbidities were age-related chronic diseases.

Stress hyperglycemia levels had no difference between the two age groups in our study but had relatively lower levels among older people. Stress hyperglycemia is described as the reaction to acute illness, which causes the production of excessive counterregulatory hormones and leads to gluconeogenesis and insulin resistance.[1] The result can be indirectly observed by glucose fluctuations.[1] Older adults have been found to have a decrease in hormone activities, such as hypoadrenalism, hypothyroidism, and hypogonadism.[27,28] Declines in growth hormone and insulin pulses are also well known.[28] This may be why stress hyperglycemia levels were relatively lower among older people with sepsis in our study (Table 1). However, the exact mechanism needs more evidence.

Our in-hospital mortality data demonstrated opposite results between both groups (Table 2). In the younger population, the survivors had lower glycemic gap and glycemia ratio. This finding was comparable to previous studies that stress hyperglycemia was related to poor outcomes among critical patients.[2,7,8,11,16] In the geriatric population, we demonstrated that the survivors had stress hyperglycemia (higher glycemic gap and glycemic ratio). There is a novel strategy that suggests treating endocrine deficiency in older adults with acute illness may result in a better prognosis.[28,32–34] Blood glucose level is a direct reflex to endocrine functions.[32] Stress hyperglycemia in older adults may indicate effective endocrine function. Therefore, we hypothesized that stress hyperglycemia is a potential prognostic predictor in older patients with sepsis.

Stress hyperglycemia is quantified using the glycemic ratio or glycemic gap. Many studies have used one of both methods.[1–21,24] We used the receiver operating characteristic curve (ROC) to predict in-hospital mortality by stress hyperglycemia (Table 3). The results showed that we could use both methods to predict mortality only in the younger group (AUROC = 0.6). Since there is little benefit in clinical application, a better method or application should be investigated.

Subgroup analysis of diabetic patients demonstrated that the survivors in the older group had higher stress hyperglycemia (Table 4). Previous sepsis studies have shown no association between diabetes and mortality, while stress hyperglycemia is an independent mortality factor.[23,24] Endocrine deficiency is relatively common in older adults.[27,28] In older patients, β-cell dysfunction and hormonal insufficiency are considered major contributors to glucose dysregulation.[28] Interestingly, our findings revealed that a higher glycemic ratio was associated with lower in-hospital mortality in older diabetic patients. While this may seem counterintuitive, one possible explanation is that stress hyperglycemia in older patients reflects preserved neuroendocrine responsiveness to critical illness. Aging is associated with a decline in stress hormone secretion, including cortisol and growth hormone, which can impair the metabolic adaptation to acute physiological stress.[27,28] In this context, measurable

Table 3
Prediction of in-hospital mortality by stress hyperglycemia.

	AUROC (95% CI)	p value	Cutoff (Youden)
All patients			
Glucose	0.51 (0.50, 0.52)	0.060	136.85
HbA1C	0.57 (0.54, 0.61)	< 0.001*	7.40
Glycemic gap	0.48 (0.44, 0.52)	0.265	124.00
Glycemic ratio	0.53 (0.49, 0.57)	0.160	1.26
Age < 65 yr			
Glucose	0.49 (0.47, 0.51)	0.531	155.00
HbA1C	0.60 (0.54, 0.67)	0.002*	6.20
Glycemic gap	0.60 (0.54, 0.66)	0.002*	18.70
Glycemic ratio	0.61 (0.54, 0.67)	0.001*	1.37
Age ≥ 65 yr			
Glucose	0.52 (0.50, 0.53)	0.034*	132.03
HbA1C	0.55 (0.50, 0.59)	0.031*	7.60
Glycemic gap	0.52 (0.47, 0.57)	0.423	-18.35
Glycemic ratio	0.51 (0.46, 0.56)	0.632	0.82

AUROC = area under the receiver operating characteristic curve; CI = confidence interval. Optimal cutoff values were determined by the Youden index. Stress hyperglycemia metrics (glucose, HbA1c, glycemic gap, glycemic ratio) were tested for their ability to discriminate in-hospital mortality. Statistical significance was defined as p < 0.05 (*).

Table 4
Stress hyperglycemia and in-hospital mortality of DM patients.

	Survivors	Non-survivors	p value	Multiple adjusted RR (95% CI)	p value
Age < 65 yr					
Glucose	198.0 (114.4)	186.8 (108.5)	0.123	0.999 (0.998–1.000)	0.156
HbA1C	8.7 (2.7)	8.1 (2.3)	0.201	0.91 (0.77–1.07)	0.267
Glycemic gap	37.6 (132.0)	63.9 (97.7)	0.166	1.001 (0.999–1.004)	0.357
Glycemic ratio	1.2 (0.7)	1.4 (0.6)	0.122	1.41 (0.84–2.35)	0.194
Age ≥ 65 yr					
Glucose	176.5 (96.7)	181.1 (111.8)	0.301	1.001 (1–1.001)	0.207
HbA1C	7.6 (2.1)	7.1 (2.0)	0.029*	0.88 (0.78–1.01)	0.070
Glycemic gap	55.0 (129.5)	29.9 (92.6)	0.035*	0.998 (0.996–1)	0.062
Glycemic ratio	1.3 (0.7)	1.2 (0.5)	0.034*	0.67 (0.45–1.00)	0.048*

Data are presented as mean (standard deviation, SD). p values were calculated using Mann-Whitney U tests. Multiple adjusted risk ratios (RRs) were estimated using multivariable logistic regression models. Covariates included: age, sex, coronary artery disease, hypertension, pulmonary disease, cerebrovascular accident, malignancy, chronic kidney disease, hyperlipidemia, heart failure, and obesity. This table presents the subgroup analysis for diabetic patients only. A p value < 0.05 was considered statistically significant (*).

stress hyperglycemia may indicate that a patient retains sufficient endocrine reserve to mount a compensatory response.

Alternatively, patients who demonstrated stronger glycemic responses may have received earlier interventions or closer monitoring, factors which could have contributed to improved outcomes. As such, we interpret this finding with caution. Further prospective research is needed to clarify whether stress hyperglycemia truly functions as a marker of physiological resilience in older sepsis patients.

Therefore, our study suggests that stress hyperglycemia may serve as a prognostic biomarker in older adults, especially among diabetic patients. However, the underlying mechanisms require further validation.

Stress hyperglycemia may serve as a useful biomarker with different meanings for younger and older sepsis patients. In younger patients, higher stress hyperglycemia is linked to worse outcomes, which matches findings from earlier studies showing that poor glucose control leads to higher mortality in critically ill patients.[2,7,8,11,16] However, in older patients, higher stress hyperglycemia in survivors might suggest better-preserved endocrine function, showing that their bodies can still respond to stress. This is different from younger patients and might be due to age-related changes, like lower hormone activity in older adults. Comparing our results with previous studies on hormone changes in older sepsis patients, such as reduced adrenal and growth hormone function, supports the idea that stress hyperglycemia could reflect better body function in older patients.[27,28] Clinically, these findings suggest monitoring stress hyperglycemia in older patients to guide treatments, such as supporting hormone functions to improve outcomes. Further research is needed to confirm these results and explore how stress hyperglycemia works in older sepsis patients.

Our study has a few limitations. First, the MIMIC-IV database offers a comprehensive scope of data collection, encompassing patient demographics, vital signs, laboratory test results, medication records, and clinical outcomes. However, as a single-center database, its findings may not be generalizable to broader populations outside the Boston region. Additionally, the dataset is focused on ICU patients, which may limit the representativeness of non-ICU hospitalized patients. Second, continuous glucose measurements were unavailable in the MIMIC-IV database, restricting our ability to assess dynamic glucose fluctuations and their potential prognostic implications. Stress hyperglycemia is inherently a dynamic process, and a single glucose measurement at admission may not fully capture its variability or peak values during the acute phase of sepsis. Future studies employing continuous glucose monitoring could provide a more comprehensive understanding of glycemic variability's role in sepsis outcomes. Third, we did not conduct stratified analyses for differences in glucose, HbA1c, glycemic ratio, and glycemic gap between diabetic and non-diabetic patients. While these analyses could provide additional insights, they fall beyond the scope of our current research. This limitation has been noted, and we recommend future studies to explore these differences more thoroughly. Fourth, we excluded patients without HbA1c data, as both admission glucose and HbA1c are required to calculate the glycemic gap and glycemic ratio. While this approach ensured the validity of stress hyperglycemia measurement, it may have introduced selection bias. Patients with available HbA1c data were more likely to have diabetes or suspected glucose dysregulation, potentially limiting the generalizability of our findings to the broader sepsis population. However, because HbA1c was routinely assessed in most ICU admissions, we believe the impact of this exclusion was minimized, although it should still be considered when interpreting the results.Lastly, the absence of detailed comorbidity data, particularly regarding the severity and duration of chronic conditions, introduces potential confounding factors. Although we included common comorbidities in the multivariate analyses, unrecorded conditions or missing severity data might obscure the nuanced interplay between pre-existing health conditions and stress hyperglycemia. These factors could significantly influence the stress response and its association with mortality, underscoring the need for future studies with more comprehensive data collection.[35]

In conclusion, our study highlights the distinct impact of stress hyperglycemia on sepsis outcomes in younger and older populations. In younger patients, elevated stress hyperglycemia is significantly associated with increased mortality, reinforcing the role of glucose dysregulation in poor outcomes for critically ill patients. In contrast, stress hyperglycemia did not correlate significantly with mortality in older patients, and elevated stress hyperglycemia was even observed among survivors, particularly in diabetic patients. The absence of elevated stress hyperglycemia in older septic patients suggests a poorer prognosis. However, further research is required to validate these findings and uncover the underlying mechanisms. Clinically, these insights emphasize the need for age-specific strategies in managing hyperglycemia in septic patients, as younger and older patients may require different therapeutic approaches to improve outcomes.

Acknowledgments

Not applicable' for that section.

Funding

This work was supported by Taipei Medical University [TMU 110-AE1-B17], Taiwan; Wan Fang Hospital [111-wf-eva-32] and [112-wf-swf-06], Taiwan; and in part by the National Science and Technology Council, R.O.C. [MOST 111-2314-B-038-022-MY3], Taiwan.

Declarations

The authors report no conflicts of interest. All named authors have seen and approved the final version of the manuscript. This study was approved by the expedited review process of the TMU-Joint Institutional Review Board and monitored by TMU-JIRB (TMU-JIRB No.: N202209084). Since the patient identifiers were removed and the data were obtained from publicly available sources, the requirement for informed consent was waived.

Supplementary materials

Supplementary materials for this article can be found at http://www.sgecm.org.tw/ijge/journal/view.asp?id=35.

References

1. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet*. 2009;373(9677):1798–1807. doi:10.1016/S0140-6736(09)60553-5
2. Bellaver P, Schaeffer AF, Dullius DP, Viana MV, Leitão CB, Rech TH. Association of multiple glycemic parameters at intensive care unit admission with mortality and clinical outcomes in critically ill patients. *Sci Rep*. 2019;9(1):18498. doi:10.1038/s41598-019-55080-3
3. Chen G, Li M, Wen X, et al. Association between stress hyperglycemia ratio and in-hospital outcomes in elderly patients with acute myocardial infarction. *Front Cardiovasc Med*. 2021;8:698725. doi:10.3389/fcvm.2021.698725
4. Chen PC, Liao WI, Wang YC, et al. An elevated glycemic gap is associated with adverse outcomes in diabetic patients with community-acquired

pneumonia. *Medicine (Baltimore)*. 2015;94(34):e1456. doi:10.1097/MD.0000000000001456
5. Chen PC, Tsai SH, Wang JC, et al. An elevated glycemic gap predicts adverse outcomes in diabetic patients with necrotizing fasciitis. *PLoS One*. 2019;14(10):e0223126. doi:10.1371/journal.pone.0223126
6. Gao S, Liu Q, Ding X, Chen H, Zhao X, Li H. Predictive value of the acute-to-chronic glycemic ratio for in-hospital outcomes in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention. *Angiology*. 2020;71(1):38–47. doi:10.1177/0003319719875632
7. Guo JY, Chou RH, Kuo CS, et al. The paradox of the glycemic gap: Does relative hypoglycemia exist in critically ill patients? *Clin Nutr.* 2021;40(7):4654–4661. doi:10.1016/j.clnu.2021.06.004
8. Lee TF, Drake SM, Roberts GW, et al. Relative hyperglycemia is an independent determinant of in-hospital mortality in patients with critical illness. *Crit Care Med*. 2020;48(2):e115–e122. doi:10.1097/CCM.0000000000004133
9. Liao WI, Lin CS, Lee CH, et al. An elevated glycemic gap is associated with adverse outcomes in diabetic patients with acute myocardial infarction. *Sci Rep*. 2016;6:27770. doi:10.1038/srep27770
10. Liao WI, Sheu WH, Chang WC, Hsu CW, Chen YL, Tsai SH. An elevated gap between admission and A1C-derived average glucose levels is associated with adverse outcomes in diabetic patients with pyogenic liver abscess. *PLoS One*. 2013;8(5):e64476. doi:10.1371/journal.pone.0064476
11. Liao WI, Wang JC, Chang WC, Hsu CW, Chu CM, Tsai SH. Usefulness of glycemic gap to predict ICU mortality in critically ill patients with diabetes. *Medicine (Baltimore)*. 2015;94(36):e1525. doi:10.1097/MD.0000000000001525
12. Liao WI, Wang JC, Lin CS, et al. Elevated glycemic gap predicts acute respiratory failure and in-hospital mortality in acute heart failure patients with diabetes. *Sci Rep*. 2019;9(1):6279. doi:10.1038/s41598-019-42666-0
13. Mi D, Li Z, Gu H, et al. Stress hyperglycemia is associated with in-hospital mortality in patients with diabetes and acute ischemic stroke. *CNS Neurosci Ther.* 2022;28(3):372–381. doi:10.1111/cns.13764
14. Rau CS, Wu SC, Chen YC, et al. Stress-induced hyperglycemia in diabetes: A cross-sectional analysis to explore the definition based on the trauma registry data. *Int J Environ Res Public Health*. 2017;14(12):1527. doi:10.3390/ijerph14121527
15. Richards JE, Kauffmann RM, Obremskey WT, May AK. Stress-induced hyperglycemia as a risk factor for surgical-site infection in nondiabetic orthopedic trauma patients admitted to the intensive care unit. *J Orthop Trauma*. 2013;27(1):16–21. doi:10.1097/BOT.0b013e31825d60e5
16. Roberts GW, Quinn SJ, Valentine N, et al. Relative hyperglycemia, a marker of critical illness: Introducing the stress hyperglycemia ratio. *J Clin Endocrinol Metab*. 2015;100(12):4490–4497. doi:10.1210/jc.2015-2660
17. Tao J, Hu Z, Lou F, et al. Higher stress hyperglycemia ratio is associated with a higher risk of stroke-associated pneumonia. *Front Nutr.* 2022;9:784114. doi:10.3389/fnut.2022.784114
18. Yang CJ, Liao WI, Tang ZC, et al. Glycated hemoglobin A1c-based adjusted glycemic variables in patients with diabetes presenting with acute exacerbation of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1923–1932. doi:10.2147/COPD.S131232
19. Yang CJ, Liao WI, Wang JC, et al. Usefulness of glycated hemoglobin A1c-based adjusted glycemic variables in diabetic patients presenting with acute ischemic stroke. *Am J Emerg Med*. 2017;35(9):1240–1246. doi:10.1016/j.ajem.2017.03.049
20. Zhu B, Pan Y, Jing J, et al. Stress hyperglycemia and outcome of non-diabetic patients after acute ischemic stroke. *Front Neurol*. 2019;10:1003. doi:10.3389/fneur.2019.01003
21. Wang W, Chen W, Liu Y, et al. Blood glucose levels and mortality in patients with sepsis: Dose-response analysis of observational studies. *J Intensive Care Med*. 2021;36(2):182–190. doi:10.1177/0885066619889322
22. Alberti C, Brun-Buisson C, Burchardi H, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med*. 2002;28(2):108–121. doi:10.1007/s00134-001-1143-z
23. van Vught LA, Holman R, de Jonge E, de Keizer NF, van der Poll T. Diabetes is not associated with increased 90-day mortality risk in critically ill patients with sepsis. *Crit Care Med*. 2017;45(10):e1026–e1035. doi:10.1097/CCM.0000000000002590
24. Fabbri A, Marchesini G, Benazzi B, et al. Stress hyperglycemia and mortality in subjects with diabetes and sepsis. *Crit Care Explor.* 2020;2(7):e0152. doi:10.1097/CCE.0000000000000152
25. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303–1310. doi:10.1097/00003246-200107000-00002
26. Lee SH, Hsu TC, Lee MG, et al. Nationwide trend of sepsis: A comparison among octogenarians, elderly, and young adults. *Crit Care Med*. 2018;46(6):926–934. doi:10.1097/CCM.0000000000003085
27. Nasa P, Juneja D, Singh O. Severe sepsis and septic shock in the elderly: An overview. *World J Crit Care Med*. 2012;1(1):23–30. doi:10.5492/wjccm.v1.i1.23
28. van den Beld AW, Kaufman JM, Zillikens MC, Lamberts SWJ, Egan JM, van der Lely AJ. The physiology of endocrine systems with ageing. *Lancet Diabetes Endocrinol*. 2018;6(8):647–658. doi:10.1016/S2213-8587(18)30026-3
29. Nathan DM, Kuenen J, Borg R, et al. Translating the A1C assay into estimated average glucose values. *Diabetes Care*. 2008;31(8):1473–1478. doi:10.2337/dc08-0545
30. Johnson A, Bulgarelli L, Pollard T, Horng S, Celi LA, Mark R. MIMIC-IV (version 2.1). PhysioNet. 2022. Accessed January 20, 2022. doi:10.13026/rrgf-xw32
31. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801–810. doi:10.1001/jama.2016.0287
32. Clegg A, Hassan-Smith Z. Frailty and the endocrine system. *Lancet Diabetes Endocrinol.* 2018;6(9):743–752. doi:10.1016/S2213-8587(18)30110-4
33. Grande D, Terlizzese P, Gioia MI, et al. New frontiers in the therapeutic approach of patients with cardiovascular and endocrine diseases. *Endocr Metab Immune Disord Drug Targets*. 2019;19(5):605–621. doi:10.2174/1871530319666190101151542
34. Paragliola RM, Locantore P, Corsello SM, Salvatori R. Treating hypopituitarism in the over 65s: Review of clinical studies. *Clin Interv Aging*. 2023;18:423–439. doi:10.2147/CIA.S370782
35. Chang CM. Geriatric syndrome, conditions, or syndemics: a modifiable intermediary and vicious cycle between medical treatment and long-term care. *Int J Gerontol*. 2025;19(3):128–129. doi:10.6890/IJGE.202507_19(3).EC3