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Association Between Hemoglobin Glycation Index and Delirium Risk in Sepsis Patients in the Intensive Care Unit

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Background: Sepsis-associated encephalopathy is a prevalent complication in the sepsis population, especially in patients in the intensive care unit (ICU). The relationship between the hemoglobin glycation index (HGI) and delirium in sepsis patients in the ICU is not yet clearly established.

Aims: To investigate the relationship between HGI and delirium risk in sepsis patients admitted to the ICU.

Study Design: Retrospective cohort study.

Methods: The data were extracted from the Medical Information Mart for Intensive Care IV 3.1 for the sepsis population in the ICU. The primary outcome was delirium occurrence in the ICU, whereas the secondary outcome was 30-day all-cause mortality (ACM) after ICU admission. The patients were stratified into tertiles according to HGI levels: T1 (HGI < -0.612), T2 ($-0.612 \leq$ HGI < 0.008), and T3 (HGI ≥ 0.008). The link of HGI to clinical outcomes in ICU patients was examined through logistic regression (LR), Cox proportional hazard models, and restricted cubic spline (RCS) and threshold effect analyses. The robustness of our findings was rated through subgroup analyses and interaction tests.

Results: In total, 3,744 patients were encompassed in the final analysis. The LR model showed that delirium risk in the T1 group was 67.7% higher than that in the T2 group [odds ratio (OR) = 1.677, 95% confidence interval (CI): 1.414, 1.992], while that in the T3 group was 24.8% higher than that in the T2 group (OR = 1.248, 95% CI: 1.048, 1.487). The Cox proportional hazard model indicated a 36.2% higher risk of 30-day ACM in T1 compared to T2 (hazard ratio = 1.362; 95% CI: 1.041-1.782). The RCS curve demonstrated an approximately U-shaped relation of HGI to delirium risk. The threshold effect analysis revealed an inflection point at HGI = -0.34. When HGI ≤ -0.34, each one-unit increase in HGI lowered the delirium risk by 36.2% (95% CI: 0.527-0.768).

Conclusion: This study suggested an independent association between HGI and both delirium risk and short-term prognosis in particularly in patients admitted to the ICU. HGI may be used as a prognostic risk stratification biomarker.

INTRODUCTION

Sepsis-associated encephalopathy (SAE) is a prevalent complication in sepsis patients, especially those admitted to the intensive care unit (ICU). The clinical manifestations of SAE are diverse, and delirium is its most prominent presentation.[1] SAE is related to increased ICU and hospital mortality rates and may result in long-term cognitive and functional impairments.[2] SAE pathophysiology is complex and multifactorial, involving disturbances in neurotransmitter function, inflammatory and ischemic brain injury, microglial activation, and dysfunction of the blood-brain barrier (BBB).[3] During sepsis, systemically released endotoxins and pro-inflammatory cytokines activate the microglia and the cerebral endothelial cells. This activation leads to the downregulation of tight junction proteins and an enhanced leukocyte recruitment, thereby exacerbating neuroinflammation and BBB disruption.[2] Its current diagnosis is mainly based on clinical presentation and neuropathological evaluation, while the treatment strategies largely focus on controlling the underlying sepsis. Therefore, further investigation into underlying SAE mechanisms is essential in developing novel therapeutic strategies.[4]

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Glycated hemoglobin (HbA1c), reflecting the average blood glucose during the prior 3 months, is one of the most widely utilized glycemic control biomarkers.[5] However, acute hyperglycemia is a recognized independent risk factor for SAE because it may aggravate neuroinflammation and delirium by promoting microglial glycolysis and inflammatory responses.[6] The hemoglobin glycation index (HGI) is a metric that quantifies interindividual disparities in HbA1c. By correcting for baseline chronic glycemia, HGI can specifically capture the dynamic interplay between acute stress and chronic metabolic imbalance.[7] An elevated HGI is independently related to a greater likelihood of diabetic complications, cardiovascular events, and death in the critically ill population.[8] The potential mechanisms involve heightened oxidative stress, endothelial dysfunction, and amplified inflammatory responses.[9] Nevertheless, the role of HGI in sepsis-associated delirium (SAD) remains unclear. This study aims to elucidate HGI's relation to delirium risk in ICU patients, thereby offering new insights into the management of sepsis patients.

MATERIALS AND METHODS

Data source

Data were obtained from Medical Information Mart for Intensive Care IV (MIMIC-IV) 3.1, a comprehensive clinical database containing records of over 65,000 individuals in the ICU and 200,000 emergency department cases from Beth Israel Deaconess Medical Center (BIDMC), affiliated with Harvard Medical School in America. It includes detailed demographics, medical records, laboratory results, pharmacologic treatments, and survival outcomes and is among the most widely used databases in emergency and critical care medicine.[10] Database access was granted to the researcher, Miao Shi, after successful completion of the online course and certification examination titled "Protecting Human Research Participants" of the U.S. National Institutes of Health (Record ID: 61915573). MIMIC-IV was de-identified and received ethical approval from the Massachusetts Institute of Technology and BIDMC, obviating the need for written informed consent.

Study population

This study included 27,882 sepsis patients first entering the ICU. The exclusion criteria were as follows: (1) ICU length of stay < 24 h or survival time < 24 h; (2) missing fasting blood glucose (FBG) or HbA1c values; (3) absence of a delirium diagnosis; and (4) comorbid Alzheimer's disease, psychiatric disorders, or dementia. Sepsis was diagnosed as per the Third International Consensus Definitions for Sepsis and Septic Shock.[11] Ultimately, 3,744 patients met the inclusion criteria. These patients were stratified into three groups based on HGI tertiles (Figure 1).

Data extraction

Data were extracted from the MIMIC-IV 3.1 database using PostgreSQL software. Baseline variables included sex, age, and ethnicity. Vital signs measured were heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), and oxygen saturation. Laboratory parameters included blood glucose, HbA1c, white blood cell (WBC), hemoglobin, red blood cell (RBC), platelet count (PC), albumin, alanine aminotransferase, aspartate aminotransferase, serum creatinine (SCr), blood urea nitrogen (BUN), ferritin, D-dimer, international normalized ratio (INR), serum potassium (SP), serum sodium (SS), triglycerides, and serum calcium (SC). Comorbidities recorded were Alzheimer's disease, dementia, schizophrenia, diabetes, hypertension, atrial fibrillation (AF), anemia, end-stage renal disease (ESRD), and coronary heart disease (CHD). Medication records were extracted for imipenem/cilastatin, moxifloxacin, aspirin, dexamethasone, methylprednisolone, dexmedetomidine, furosemide, metoprolol, omeprazole, and norepinephrine. Records of specialized treatments such as continuous renal replacement therapy (CRRT) and mechanical ventilation (MV) were also gathered. Severity scores extracted were the sequential organ failure assessment (SOFA), Glasgow Coma Scale (GCS), acute physiology score III (APS III), Oxford Acute Severity of Illness Score (OASIS), and simplified acute physiology score II (SAPS II). Clinical outcomes evaluated were delirium occurrence and 30-day survival status of ICU patients. All continuous variables were collected based on the first measurement in the first 24 h after ICU admission. Variables showing missing data rates above 20% were excluded. For the remaining variables (≤ 20%), missing values were imputed using random forest (Supplementary Table 1).[12]

HGI is real, and forecast HbA1c difference is derived from FBG.[13] A linear regression model was developed based on the entire study cohort to predict HbA1c from the FBG using the following equation: Predicted HbA1c = FBG × 0.008 + 5.260. HGI was the difference between the actual and predicted HbA1c.

Clinical outcomes

The primary outcome was delirium occurrence during the patient's ICU stay. The secondary outcome was 30-day all-cause mortality (ACM) after ICU admission. Delirium was screened at least twice daily at the bedside by the ICU nursing personnel using the Confusion Assessment Method for the ICU (CAM-ICU). Two nurses who received unified training independently assessed delirium at different shifts. The assessment domains were the presence of acute onset, attention disorder, confusion, and changes in the level of consciousness. Each patient was assessed once in the morning shift (approximately 7-9 am) and the evening shift (approximately 7-9 pm) every day.[14,15] The consciousness level was rated via the Richmond agitation-sedation scale (RASS).[16] CAM-ICU assessments were performed only for patients with a RASS score ≥ -3. A delirium diagnosis was confirmed only if both assessors reached a consistent conclusion. In cases of disagreement, a third party reviewed the findings to make a final determination.

Statistical analysis

Patients were divided into three groups (T1, T2, and T3) by HGI. The normality of continuous variables was examined using the Shapiro-Wilk test. None were normally distributed; therefore, they were shown in medians with interquartile ranges. Intergroup comparisons were performed using the Kruskal-Wallis test. Categorical ones were

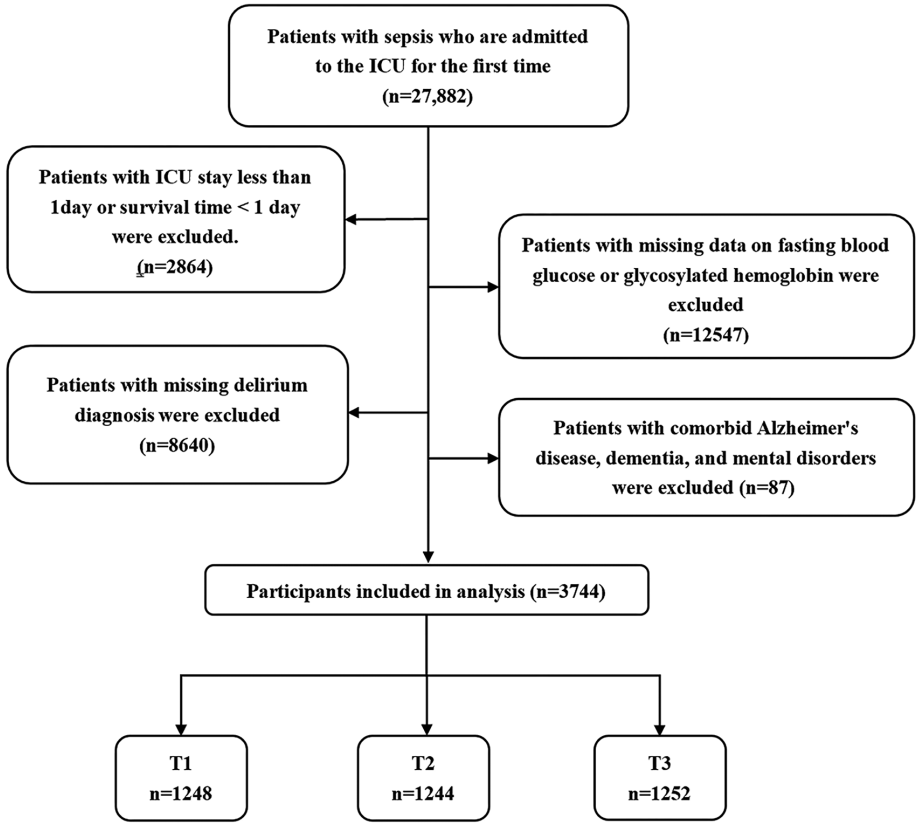

FIG. 1. Flowchart of the study design.
ICU, intensive care unit.

reported in frequencies and percentages, with group comparisons conducted using the Pearson chi-squared test. Multicollinearity among all covariates included in the models was assessed. The variables with a variance inflation factor ≥ 5 were excluded.

The relation of HGI to delirium risk was investigated using multivariable logistic regression (LR) models. We minimized the influence of potential confounders by constructing three models with incremental adjustments. Model 1 was unadjusted, whereas Model 2 was adjusted for age, sex, and race. Model 3 was further adjusted for vital signs (SBP, DBP, heart rate, RR, and oxygen saturation), medications (dexamethasone, dexmedetomidine, and omeprazole), comorbidities (diabetes, hypertension, AF, anemia, ESRD, and CHD), special treatments (CRRT and MV), laboratory indices (SC, SCr, BUN, hemoglobin, INR, PC, SP, SS, and WBC), and severity scores (SOFA, GCS, APS III, OASIS, and SAPS II).

The relation of HGI to 30-day ACM was further investigated using Cox proportional hazard models with the same three tiers of adjustment. Model 1 was crude, whereas Model 2 involved age, sex, and race adjustments. Model 3 was additionally adjusted for vital signs, comorbidities, medications, special treatments, and laboratory parameters. The intermediate tertile of HGI (T2) was used as the reference group in Models 2 and 3.

A possible non-linear relation of HGI to delirium occurrence was explored through restricted cubic spline (RCS) regression. A recursive algorithm was applied to identify inflection points in the HGI-delirium relationship. We further investigated this for our result robustness association by constructing two-piecewise LR models on either side of the identified inflection point. Moreover, subgroup analyses by age, sex, AF, CHD, diabetes, and hypertension were conducted evaluation, accompanied by interaction tests.

Our statistical analyses were enabled by R 4.4.1. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

A total of 3,744 patients were included. Their median age was 69 years, and 58% were male. Of the total, 1,163 patients developed delirium during hospitalization, while 367 died. The patients were divided into T1 (HGI < -0.612), T2 (-0.612 ≤ HGI < 0.008), and T3 (HGI ≥ 0.008). Table 1 presents their baseline characteristics. Compared to T2, individuals in the low-HGI group (T1) tended to be younger and were female, with a greater occurrence of anemia and ESRD but a lower AF, CHD, and diabetes prevalence. T1 also exhibited higher heart rate, RR, FBG, BUN, APS III, and SOFA, as well as a greater

TABLE 1. Baseline Characteristics of Patients Stratified by HGI Tertiles.

Characteristic	Overall	T1 (HGI < -0.612)	T2 (-0.612 ≤ HGI < 0.008)	T3 (HGI ≥ 0.008)	*p* value
Demographics					
Number	3.744	1.248	1.244	1.252	
Age	69 (59,78)	66 (56,77)	71 (61,80)	69 (61,77)	< 0.001
Gender					< 0.001
Female	1.579 (42%)	565 (45%)	474 (38%)	540 (43%)	
Male	2.165 (58%)	683 (55%)	770 (62%)	712 (57%)	
Race					< 0.001
Black	436 (12%)	85 (6.8%)	137 (11%)	214 (17%)	
White	2.527 (67%)	887 (71%)	852 (68%)	788 (63%)	
Others	781 (21%)	276 (22%)	255 (20%)	250 (20%)	
Vital signs					
SBP (mmHg)	119 (104,138)	117 (103,137)	118 (103,135)	122 (106,141)	< 0.001
DBP (mmHg)	66 (56,79)	66 (56,80)	65 (56,77)	67 (56,80)	0.155
Heart rate (beats/min)	87 (76,102)	89 (77,103)	84 (75,99)	88 (77,103)	< 0.001
RR (beats/min)	18 (15,23)	19 (15,23)	18 (14,23)	19 (15,23)	0.008
SpO_2 (%)	98 (95,100)	98 (95,100)	98 (95,100)	98 (95,100)	0.002
Laboratory parameters					
SC (mg/dL)	8.30 (7.80,8.80)	8.30 (7.80,8.80)	8.30 (7.80,8.80)	8.40 (7.90,8.90)	0.008
SCr (mg/dL)	1.10 (0.80,1.70)	1.00 (0.70,1.70)	1.00 (0.70,1.40)	1.20 (0.90,1.90)	< 0.001
FBG (mg/dL)	118 (96,161)	121 (98,158)	104 (92,127)	140 (103,199)	< 0.001
HbA1c (%)	5.90 (5.50,6.80)	5.30 (5.00,5.60)	5.80 (5.60,6.00)	7.40 (6.60,8.80)	< 0.001
Hemoglobin (g/dL)	10.20 (8.70,11.80)	10.00 (8.50,11.70)	10.40 (8.90,11.90)	10.20 (8.80,11.70)	0.004
INR	1.30 (1.20,1.60)	1.30 (1.20,1.60)	1.30 (1.20,1.50)	1.30 (1.20,1.50)	0.013
PC (k/uL)	175 (123,245)	162 (113,240)	167 (124,236)	192 (139,257)	< 0.001
SP(mEq/L)	4.10 (3.80,4.60)	4.10 (3.70,4.50)	4.10 (3.80,4.50)	4.20 (3.80,4.70)	< 0.001
RBC (m/uL)	3.43 (2.93,3.97)	3.29 (2.81,3.85)	3.51 (2.97,4.01)	3.50 (3.03,4.06)	< 0.001
SS (mEq/L)	138 (135,141)	138 (135,141)	138 (136,141)	138 (135,141)	< 0.001
Urea nitrogen (mg/dL)	22 (14,35)	21 (14,35)	19 (14,30)	25 (17,42)	< 0.001
WBC (k/uL)	12 (8,16)	11 (8,16)	11 (8,15)	12 (8,16)	0.044
Comorbidities					
Delirium					< 0.001
No	2.581 (69%)	787 (63%)	922 (74%)	872 (70%)	
Yes	1.163 (31%)	461 (37%)	322 (26%)	380 (30%)	
Anemia					0.046
No	1.177 (31%)	380 (30%)	424 (34%)	373 (30%)	
Yes	2.567 (69%)	868 (70%)	820 (66%)	879 (70%)	
AF					< 0.001
No	2.296 (61%)	808 (65%)	686 (55%)	802 (64%)	
Yes	1.448 (39%)	440 (35%)	558 (45%)	450 (36%)	
CHD					< 0.001
No	1.810 (48%)	724 (58%)	594 (48%)	492 (39%)	
Yes	1.934 (52%)	524 (42%)	650 (52%)	760 (61%)	
Diabetes					< 0.001
No	1.955 (52%)	913 (73%)	858 (69%)	184 (15%)	
Yes	1.789 (48%)	335 (27%)	386 (31%)	1.068 (85%)	

TABLE 1. Continued.

Characteristic	Overall	T1 (HGI < -0.612)	T2 (-0.612 ≤ HGI < 0.008)	T3 (HGI ≥ 0.008)	*p* value
Renal dysfunction					< 0.001
No	3.431 (92%)	1.130 (91%)	1.172 (94%)	1.129 (90%)	
Yes	313 (8.4%)	118 (9.5%)	72 (5.8%)	123 (9.8%)	
Hypertension					< 0.001
No	1.199 (32%)	537 (43%)	362 (29%)	300 (24%)	
Yes	2.545 (68%)	711 (57%)	882 (71%)	952 (76%)	
Treatment					
Aspirin					< 0.001
No	1.085 (29%)	468 (38%)	316 (25%)	301 (24%)	
Yes	2.659 (71%)	780 (63%)	928 (75%)	951 (76%)	
Dexamethasone					0.425
No	3.344 (89%)	1.123 (90%)	1.114 (90%)	1.107 (88%)	
Yes	400 (11%)	125 (10%)	130 (10%)	145 (12%)	
Dexmedetomidine					0.007
No	3.024 (81%)	982 (79%)	1.039 (84%)	1.003 (80%)	
Yes	720 (19%)	266 (21%)	205 (16%)	249 (20%)	
Omeprazole					0.045
No	2.322 (62%)	804 (64%)	772 (62%)	746 (60%)	
Yes	1.422 (38%)	444 (36%)	472 (38%)	506 (40%)	
CRRT					0.005
No	3.516 (94%)	1.153 (92%)	1.188 (95%)	1.175 (94%)	
Yes	228 (6.1%)	95 (7.6%)	56 (4.5%)	77 (6.2%)	
Invasive MV					< 0.001
No	2.467 (66%)	819 (66%)	776 (62%)	872 (70%)	
Yes	1.277 (34%)	429 (34%)	468 (38%)	380 (30%)	
Non-invasive MV					0.007
No	3.611 (96%)	1.215 (97%)	1.205 (97%)	1.191 (95%)	
Yes	133 (3.6%)	33 (2.6%)	39 (3.1%)	61 (4.9%)	
Clinical severity scores					
APS III	44 (33,57)	45 (33,57)	42 (31,57)	46 (35,58)	< 0.001
GCS	15 (15,15)	15 (15,15)	15 (14,15)	15 (15,15)	0.037
OASIS	31 (26,36)	31 (26,37)	31 (25,36)	31 (26,36)	0.614
SAPS II	36 (29,45)	36 (29,45)	37 (29,45)	36 (29,45)	0.978
SOFA	5 (3,7)	5 (3,7)	4 (3,7)	4 (3,7)	< 0.001
Clinical outcomes					
LOS ICU (day)	2.37 (1.54,4.10)	2.63 (1.65,4.73)	2.30 (1.45,3.93)	2.28 (1.56,3.86)	< 0.001
30 days status					0.059
Alive	3.377 (90.2%)	1.142 (91.8%)	1.123 (90%)	1.112 (89%)	
Dead	367 (9.8%)	102 (8.2%)	129 (10%)	136 (11%)	
Time-30 days (day)	30.0 (30.0,30.0)	30.0 (30.0,30.0)	30.0 (30.0,30.0)	30.0 (30.0,30.0)	0.075

Continuous variables are shown in medians with interquartile ranges (IQRs), and intergroup comparisons were conducted using the Kruskal-Wallis test. Categorical variables are shown in frequencies and percentages, with intergroup comparisons performed using the Pearson chi-square test.
LOS, length of stay; Time-30 days, 30-day survival time; INR, international normalized ratio; CHD, coronary heart disease; CRRT, continuous renal replacement therapy; MV, mechanical ventilation; SOFA, sequential organ failure assessment score; APS III, acute physiology score III, a component of APACHE III; SAPS II, simplified acute physiology score II; OASIS, Oxford Acute Severity of Illness score; GCS, glasgow coma scale; ICU, intensive care unit; HGI, hemoglobin glycation index.

proportion of patients requiring CRRT. Compared with T2 and T3, T1 displayed lower FBG, RBC, hemoglobin, and PC levels and required MV less frequently but had a longer ICU LOS.

Association between HGI and clinical outcomes

According to the baseline data, the delirium occurrence was notably lower in T2 (-0.612 ≤ HGI < 0.008) than in T1 and T3 (26% vs. 37% vs. 30%, $p < 0.001$). Based on this finding, our study utilized T2 as the reference, and we constructed LR models to elucidate the relation of HGI to delirium (Table 2). The model stability was assessed using events per variable (EPV). The EPVs for delirium (1,163 patients, 35 variables, EPV = 33.2) and death (367 patients, 30 variables, EPV = 12.2) were both above the recommended threshold of EPV ≥ 10, indicating a good model fit. In Model 1, the delirium risk in the T1 group was 67.7% higher than that in the T2 group [odds ratio (OR) = 1.677, 95% confidence interval (CI): 1.414, 1.992]. This risk in the T3 group was 24.8% higher than that in the T2 group (OR = 1.248, 95% CI: 1.048, 1.487). After the age, sex, and race adjustments, the delirium risk in T1 increased by 76.8% in comparison to T2 (95% CI: 1.486-2.107; $p < 0.001$) and by 23.6% in T3 (95% CI: 1.036-1.476; $p = 0.019$) in Model 2. Even after further adjustments in Model 3, the delirium risk in T1 remained significantly higher than in T2, depicting a 58.7% increase (95% CI: 1.304-1.933; $p < 0.001$).

The relation of HGI to 30-day ACM was examined via a Cox proportional hazard model (Table 3). In Model 1, T1 had a 34.1% higher risk of 30-day ACM compared with T2 [hazard ratio (HR) = 1.341; 95% CI: 1.038-1.734; $p = 0.025$]. Model 2 yielded similar results with a 53.9% increased risk (HR = 1.539; 95% CI: 1.188-1.993; $p = 0.001$). In Model 3, T1 exhibited a 36.2% higher risk of 30-day ACM in contrast to T2 (HR = 1.362; 95% CI: 1.041-1.782; $p = 0.024$).

Non-linear relation of HGI to clinical outcomes

The possible non-linear relation of HGI to clinical outcomes was explored using the RCS analysis. Figure 2 shows a non-linear relation between HGI and the delirium risk (p for non-linearity < 0.001), demonstrating an approximately "U-shaped" association. We further investigated this non-linearity by conducting a threshold effect analysis (Table 4). Using the standard LR and two-piecewise LR models (log-likelihood ratio test: $p < 0.001$), the inflection point of HGI for the delirium occurrence was identified as -0.34. When HGI ≤ -0.34, each one-unit elevation in HGI lowered the delirium risk by 36.2% (95% CI: 0.527-0.768).

Subgroup analyses and interaction testing

We further investigated the associations between independent and outcome variables by performing subgroup analyses and interaction tests by age, sex, AF, CHD, diabetes, and hypertension. Figure 3 illustrates that the association between the low HGI (T1) and delirium remained consistent across most subgroups, except in those aged < 65 and in patients with CHD, diabetes, or without hypertension. The interaction testing indicated no significant interaction effects of HGI with age, sex, AF, or CHD ($p \geq 0.05$). Nevertheless, the differences in the delirium occurrence were significant in both the hypertension and diabetes subgroups ($p < 0.05$).

DISCUSSION

This study explores the non-linear relation of HGI to the incidence of delirium and ACM among sepsis patients by utilizing the MIMIC-IV data. Our findings revealed an approximately U-shaped relationship between HGI and the delirium incidence in septic patients in the ICU. This result indicates that maintaining an optimal HGI level may lower the SAD likelihood in the ICU. A marked relation of low HGI to elevated 30-day ACM was also observed. The low-HGI cohort

TABLE 2. LR Analysis of the Association Between HGI and ICU Delirium Risk in Sepsis Patients.

Characteristic	Model 1		Model 2		Model 3	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
HGI (continuous)	0.972 (0.926, 1.018)	0.232	0.968 (0.922, 1.016)	0.194	0.956 (0.900, 1.014)	0.135
Group						
T2	-		-		-	
T3	1.248 (1.048, 1.487)	0.013	1.236 (1.036, 1.476)	0.019	1.014 (0.815, 1.263)	0.899
T1	1.677 (1.414, 1.992)	< 0.001	1.768 (1.486, 2.107)	< 0.001	1.587 (1.304, 1.933)	< 0.001

Model 1 represents the unadjusted model; Model 2 adjusts for age, sex, and race; Model 3 further adjusts based on Model 2 for vital signs (SBP, DBP, heart rate, RR, oxygen saturation), comorbidities (diabetes, hypertension, AF, anemia, ESRD, CHD), medication use (dexamethasone, dexmedetomidine, omeprazole), special treatments (CRRT, MV), laboratory parameters (SC, SCr, BUN, hemoglobin, INR, PC, SP, SS, WBC), and clinical scores (SOFA, GCS, APS III, OASIS, SAPS II).

INR, international normalized ratio; CHD, coronary heart disease; CRRT, continuous renal replacement therapy; MV, mechanical ventilation; SOFA, sequential organ failure assessment score; APS III, acute physiology score III, a component of APACHE III; SAPS II, simplified acute physiology score II; OASIS, Oxford Acute Severity of Illness score; GCS, glasgow coma scale; OR: odds ratio; CI: confidence interval; PC, platelet count; SP, serum potassium; SS, serum sodium; WBC, white blood cell; AF, atrial fibrillation; ESRD, anemia, end-stage renal disease; SCr, serum creatinine; BUN, blood urea nitrogen; SC, serum calcium; ICU, intensive care unit, HGI, hemoglobin glycation index.

In model 1, the risk of delirium in the T1 group was 67.7% higher than in the T2 group, and the risk in the T3 group was 24.8% higher than in the T2 group. In model 2, the risk of delirium in the T1 group was 76.8% higher than in the T2 group, and the risk in the T3 group was 23.6% higher than in the T2 group. In model 3, the risk of delirium in the T1 group was 58.7% higher than in the T2 group.

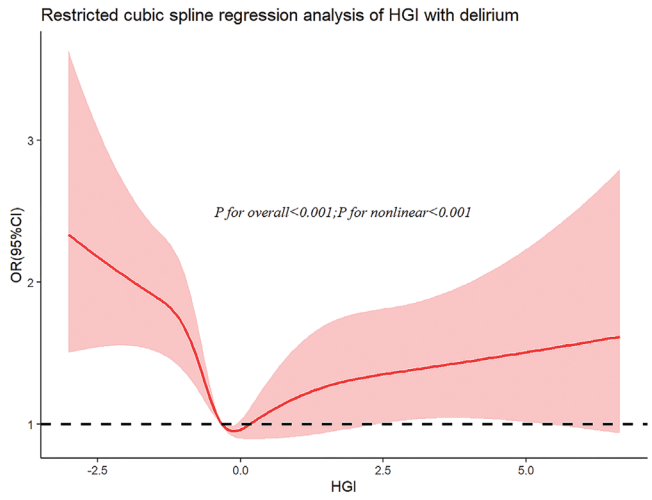

FIG. 2. Non-linear relationship between HGI and ICU delirium risk in sepsis patients.

RCS curve. The red line represents OR, and the pink shaded area represents the 95% CI. HGI, hemoglobin glycation index; ICU, intensive care unit; RCS, restricted cubic spline; OR, odds ratio; CI, confidence interval.

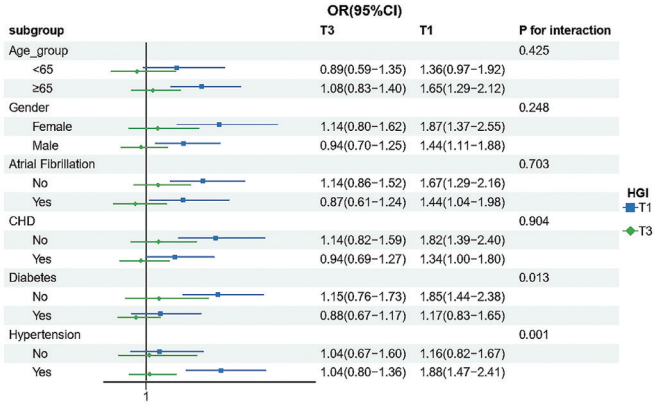

FIG. 3. Forest plot of stratified analysis of the association between HGI and ICU delirium risk across different subgroups.

CHD, coronary heart disease; HGI, hemoglobin glycation index; ICU, intensive care unit; OR, odds ratio; CI, confidence interval.

had a greater likelihood of death within 30 days, highlighting the potential utility of HGI in mitigating the delirium risk in the ICU and ameliorating clinical outcomes in sepsis patients.

HbA1c is derived via a non-enzymatic glycation of hemoglobin by circulating glucose. It represents the average glucose concentration in the blood during the prior 2-3 months due to the approximately 120-day erythrocyte lifespan.[17] However, HbA1c levels can be influenced by various physiological and pathological factors. The correlation between HbA1c and fasting plasma glucose significantly varies in individuals with elevated glucose levels.[18] For instance, iron-deficiency anemia can possibly cause falsely low HbA1c values, whereas iron supplementation elevates HbA1c levels.[19] HGI quantifies the discrepancy between the observed and predicted HbA1c values, emerging as a robust glycemic control indicator. Multiple studies reported its close association with the disease prognosis. Shangguan et al.[20] identified a U-shaped relation of HGI to cardiovascular and ACM in patients with hypertension, which underscored the importance of maintaining appropriate HGI levels in this population. Similarly, Zhao et al.[21] reported a U-shaped relation of HGI to ACM in individuals with non-alcoholic fatty liver disease, suggesting that HGI may serve as a useful marker for mortality risk stratification. Furthermore, HGI is a significant predictor of rapid renal function decline in diabetic patients.[22] These findings collectively indicate that monitoring and managing HGI may assist in more accurate prognostication and improve long-term health outcomes.

SAD is a common and serious sepsis complication, particularly in critically ill patients. Its pathophysiological mechanisms are multifactorial and include neuroinflammation, neurotransmitter imbalance, and cerebral hypoperfusion.[23,24] Delirium occurrence has been closely linked to long-term cognitive impairment. Even after a successful sepsis resolution, many patients experience persistent cognitive deficits, which may progress to dementia and significantly affect one's quality of life and increase the caregiver burden.[24,25] Abnormal glucose metabolism has been extensively implicated in SAD pathogenesis and prognosis. In hyperglycemic states, metabolic reprogramming of microglia may exacerbate neuroinflammation, thereby intensifying the SAE manifestations.[26] Acute hyperglycemia is considered an independent delirium risk factor correlated with poor outcomes in sepsis patients. The activation of microglia, which is a key factor in SAD pathogenesis, may be further amplified by glycemic fluctuations modulating microglial activity.[27] Yao et al.[6] found that hyperglycemia promotes microglial glycolysis through upregulation of the ChREBP/HIF-1α signaling pathway, thereby intensifying neuroinflammation and delirium. Additionally, dysregulated glycemia during sepsis in diabetic patients is related to an increased delirium incidence in the ICU.[28] Diabetes may be associated with neurodegeneration by inducing alterations in vascular structure and function, glucose metabolism, and insulin signaling and by affecting amyloid-β and tau metabolism.[29] Kushimoto et al.[30] observed a notable link of hypoglycemia to delirium in the septic population, especially among those without a diabetes history. Hypoglycemia may impair cerebral autoregulation, consequently leading to reduced cerebral perfusion and a heightened delirium risk.[31] Hypoglycemia is also linked to increased mortality in sepsis patients. A significantly higher 28-day death rate was reported among people presenting with hypoglycemia upon hospital admission.[32] Glycemic variability (GV) is likewise linked to death in sepsis patients, particularly in non-diabetic people, where hyperglycemia and high GV significantly elevate the mortality risk in patients in the ICU.[33] Lu et al.[33] demonstrated that maintaining the blood glucose levels between 120 and 140 mg/dL in patients without diabetes is related to the lowest mortality and incidence of hypoglycemia. Hence, appropriate glycemic control strategies are necessary for ameliorating clinical outcomes, attenuating neuroinflammation, and lowering the delirium risk among individuals with sepsis.[34]

TABLE 3. Cox Proportional Hazards Model Analysis of the Association Between HGI and ACM in ICU Sepsis Patient.

Characteristic	Model 1		Model 2		Model 3	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
HGI (continuous)	0.951 (0.890, 1.015)	0.132	0.945 (0.872, 1.024)	0.165	0.956 (0.900, 1.014)	0.051
Group						
T2	-		-		-	
T3	1.262 (0.973, 1.636)	0.079	1.350 (1.040, 1.754)	0.024	1.189 (0.892, 1.585)	0.239
T1	1.341 (1.038, 1.734)	0.025	1.539 (1.188, 1.993)	0.001	1.362 (1.041, 1.782)	0.024

Model 1 is crude; Model 2 adjusts for age, sex, and race; Model 3 further adjusts based on Model 2 for vital signs (SBP, DBP, heart rate, RR, oxygen saturation), comorbidities (diabetes, hypertension, AF, anemia, ESRD, CHD), medication use (dexamethasone, dexmedetomidine, omeprazole), special treatments (CRRT, MV), and laboratory parameters (SC, SCr, BUN, hemoglobin, INR, PC, SP, SS, WBC).
INR, international normalized ratio; CHD, coronary heart disease; CRRT, continuous renal replacement therapy; MV, mechanical ventilation; OR: odds ratio; CI: confidence interval; HR, hazard ratio; PC, platelet count; SP, serum potassium; SS, serum sodium; WBC, white blood cell; AF, atrial fibrillation; ESRD, anemia, end-stage renal disease; SCr, serum creatinine; BUN, blood urea nitrogen; SC, serum calcium; ICU, intensive care unit, HGI, hemoglobin glycation index; ACM, all-cause mortality.
In model 1, the risk of death in the T1 group was 34.1% higher than that in the T2 group. In model 2, the risk of death in the T1 group was 53.9% higher than that in the T2 group. In model 3, the risk of death in the T1 group was 36.2% higher than that in the T2 group.

TABLE 4. Threshold Effect Analysis of HGI on the ICU Delirium Risk in Sepsis Patients.

Delirium	OR (95% CI), *p* valve
Fitted by standard LR	0.956 (0.900, 1.014), 0.135
Fitted by a two-segment LR model	
Inflection point	- 0.34
HGI ≤ -0.34	0.638 (0.527, 0.768), < 0.001
HGI > -0.34	1.070 (0.992, 1.154), 0.078
Likelihood ratio p -value	< 0.001

HGI, Hemoglobin glycation index; The threshold inflection point of HGI for ICU delirium risk in septic patients is -0.34. When HGI ≤ -0.34, the incidence of delirium decreased by 36.2% with each unit increase in HGI.
ICU, intensive care unit; OR, odds ratio; LR, logistic regression; CI, confidence interval.

This study suggested a U-shaped association between HGI and delirium risk in patients in the ICU. The underlying mechanism may be related to metabolic homeostasis. On the one hand, a high HGI reflecting underlying insulin resistance and chronic inflammation may increase delirium risk by impairing the BBB and exacerbating neuroinflammation.[35,36] On the other hand, a low HGI may be a marker of malnutrition, sarcopenia, or frailty, all of which are established delirium risk factors.[37,38] In these states, the availability of substrates for non-enzymatic glycosylation (e.g., amino acids) is reduced, which may lead to relatively low HbA1c levels. This consequently contributes to a lower HGI. Furthermore, the underlying catabolic state and chronic inflammation directly increase the delirium risk.[39] Certain conditions shortening the lifespan of RBCs, including renal insufficiency, hemoglobinopathies, or occult hemolysis, can result in abnormally low HbA1c levels relative to blood glucose, which reduces HGI levels. These comorbidities are often associated with systemic inflammation and oxidative stress, which are central to the delirium pathophysiology.[40] Therefore, the U-shaped relationship may collectively reveal that an imbalance in physiological homeostasis is a core delirium contributor. Both high (metabolic disturbances) and low HGI (depletion of physiological reserves) predispose the brain to dysfunction, suggesting that HGI may serve as a warning marker for delirium risk.

In our subgroup analysis, the link of HGI to delirium risk in ICU patients remained significant across all subgroups, except for patients aged < 65, those with CHD, diabetic individuals, and those without hypertension. Furthermore, interaction effects were detected between HGI and both hypertension and diabetes. Younger patients may possess more robust glycemic regulatory mechanisms, which mitigate the direct impact of HGI fluctuations on cerebral function.[41] Patients with CHD often exhibit chronic insulin resistance[42] that may compensate for altered glycemic states by upregulating cerebral glucose transporters or enhancing ketone body utilization.[43] This, thus, buffers the effects of HGI variation on cerebral energy metabolism. According to a meta-analysis performed by Komici et al.,[44] delirium incidence is approximately 29% in diabetic patients, and the risk is significantly higher in comparison to that in patients without diabetes. This elevated risk may be attributable to the frequent coexistence of cardiovascular and cerebrovascular diseases in patients with diabetes and the chronic hyperglycemia-induced oxidative stress that may impair the cognitive function.[45] The inherently high baseline risk of delirium in this population may reduce the HGI sensitivity as a predictive marker, which may explain why no significant association exists between HGI and delirium in diabetic patients. Hypertension impairs multiple mechanisms of the cerebral blood flow regulation, including neurovascular coupling and microvascular integrity.[46,47] In patients without hypertension, a relatively preserved vascular function may confer a better autoregulatory capacity, thereby attenuating the effect of HGI. Consistently, no significant link of HGI to the delirium risk was observed in patients without hypertension, suggesting that to predict the delirium risk among sepsis patients, the interplay between HGI and comorbid conditions like hypertension and diabetes must be comprehensively considered.

Our findings demonstrate that HGI dynamically integrates information on metabolic dysregulation, stress response, and organ dysfunction and may hold potential value in reducing the incidence of new-onset delirium and mortality in sepsis patients. Clinically, HGI can help identify high-risk patients, optimize therapeutic strategies, and advance personalized medicine. Nevertheless, our study has limitations. First, this work was based on single-center, retrospective data from the MIMIC-IV database in the United States; therefore, the study population only reflected the care provided by a single medical center. Racial differences (e.g., hemoglobin metabolic characteristics in African Americans) may affect the HGI's biological significance. Therefore, future studies in multiple countries and diverse populations are needed to externally validate these results. Second, this study is retrospective. Although delirium is diagnosed based on the CAM-ICU criteria, we were unable to obtain data on the inter-rater reliability (e.g., Kappa values) and cannot ensure the standardization of this tool across all assessments, potentially introducing information bias. Third, the HGI calculation in this work may be biased because HbA1c and FBG were collected only as a single data point upon admission instead of as dynamic levels during hospitalization. HGI values used in our analysis were also derived from the study cohort itself and may not apply to other populations. The external validation in independent cohorts is necessary in the future. Fourth, although we used a robust method, called multiple imputation, in handling the missing data, this method is based on the assumption that data are randomly missing. We cannot completely rule out the possibility that the data are missing non-randomly, which, if present, can potentially bias the results. Fifth, this study is retrospective; therefore, it inherently limits the inference of causal relationships. Although we performed a multivariable adjustment and a subgroup analysis, many confounding factors were excluded from the analysis because of database limitations (e.g., patient's previous cognitive status, sedative dose, and ICU staffing ratio). Further prospective studies are needed to verify the obtained finding.

In conclusion, our study suggests a near U-shaped relation of HGI to the delirium risk in the sepsis population in the ICU. Low HGI levels are associated with an increased risk of 30-day ACM. Therefore, HGI may serve as a potentially valuable biomarker in reducing the new-onset delirium risk and mortality among sepsis patients in the ICU.

Ethics Committee Approval: MIMIC-IV was de-identified and gained ethical approval from the Massachusetts Institute of Technology (MIT) and BIDMC, obviating the need for written informed consent.

Informed Consent: All patients provided written informed consent.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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