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Association between hemoglobin glycation index and poor prognosis in patients with AKI: a retrospective cohort analysis of the MIMIC-IV database

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ABSTRACT

Background: There have been no investigations on the relationship between hemoglobin glycation index **(**HGI) and poor prognosis in patients with acute kidney injury (AKI).

Methods: Patients were enrolled from the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database. The HGI was calculated using a linear regression model fitted to glycosylated hemoglobin and fasting plasma glucose (FPG). Kaplan–Meier survival analysis and Cox proportional hazards regression analysis were performed based on HGI quartiles to determine the independent association between HGI and mortality risk. A restricted cubic spline (RCS) was employed to assess the potential nonlinear relationship between HGI and mortality risk. A two-piecewise linear regression model was developed to identify the threshold effect. Additionally, a linear regression model was applied to evaluate the association between HGI and the length of hospital stays.

Results: A total of 3684 patients with AKI were included in this study. Among them, 486 patients died within 28 days, and 673 patients died within 90 days. Multivariate Cox regression analysis identified HGI as an independent risk factor for both 28-day mortality (hazard ratio [HR], 1.65 [95% CI 1.26 to 2.16], $p < 0.001$) and 90-day mortality (HR, 1.45 [95% CI 1.16 to 1.82], $p < 0.001$) in AKI. The RCS analysis revealed a significant L-shaped association between HGI and both 28-day (nonlinear $p < 0.001$) and 90-day mortality (nonlinear $p < 0.001$). For 28-day mortality, the inflection point was 1.09 (HR = 0.72, 95% CI: 0.65 to 0.805). For 90-day mortality, the inflection point was 1.14 (HR = 0.76, 95% CI: 0.69 to 0.84). Notably, the association between HGI and outcomes was more significant in nondiabetic patients ($p < 0.05$). Additionally, HGI was found to be significantly and inversely associated with the length of hospital stays.

Conclusion: In patients with AKI, a low HGI is an independent risk factor for 28-day and 90-day mortality, exhibiting an L-shaped association. HGI may serve as a potential predictor of mortality risk.

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1. Introduction

Acute kidney injury (AKI) is characterized by a sudden decline or loss of renal function due to a variety of causes and has an increasing prevalence worldwide [1–3]. Studies have reported that AKI affects up to 21.6% of hospitalized adult patients [4] and occurs in >50% of patients admitted to intensive care units (ICUs) [5]. It has been shown to be closely associated with increased in-hospital mortality, longer hospital stays, and many long-term complications, making it a significant global public health concern [6,7].

AKI is composed of multiple clinical conditions and has a poor prognosis, leading to an increased risk of chronic kidney disease (CKD), end-stage renal disease, and death [8]. Research has shown that the baseline estimated glomerular filtration rate, coronary heart disease, and diabetes mellitus (DM) are risk factors for a poor prognosis in patients with AKI [9,10]. The prognosis of AKI is affected by numerous factors,

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and the reliance on serum creatinine (Scr) and urine volume alone for predictions is limited by delayed Scr measurements and the inaccuracy of urine volume monitoring. Recently, several emerging biomarkers have been investigated for the early detection of AKI and prediction of a poor outcome, but the clinical application of these biomarkers remains restricted because of many confounding factors [11–13]. Consequently, identifying additional prognostic indicators is critical for improving risk stratification and management of AKI and reducing the mortality of patients with AKI.

Glycosylated hemoglobin (HbA1c) reflects average blood glucose levels over a 2- to 3-month period and serves as a critical metric for the long-term monitoring of blood glucose control in patients with DM. However, significant interindividual variability exists between HbA1c and mean fasting plasma glucose (FPG) due to factors independent of blood glucose levels, which limits its utility [14]. Hempe et al. proposed the hemoglobin glycation index (HGI), which is defined as the difference between observed and predicted HbA1c [15]. The variations in HbA1c driven by nonglycemic factors, such as genetic and environmental influences, are measured by this index [16]. Previous studies have demonstrated that variation in the HGI is a significant risk factor for multiple diseases and a valuable indicator of glycemic control in critically ill patients. A low HGI was significantly correlated with all-cause mortality in individuals with acute decompensated heart failure and critical coronary artery disease (CAD) [17,18]. The risk of all-cause mortality after percutaneous coronary intervention in patients with CAD was significantly greater in both the low- and high-HGI subgroups than in the moderate-HGI subgroup [19]. In the Chinese population, there is a 'U-shaped' correlation between the HGI and the 5-year risk of major adverse cardiovascular events [20]. A study investigating the association between the HGI and diabetic kidney disease (DKD) in Chinese patients with type 2 diabetes revealed that a high HGI is associated with an increased risk of DKD [21]. Another study suggested that a high HGI is a likely risk factor for CKD [22]. Glycemic control is particularly important for survival in patients with AKI in intensive care. However, research on the association between the HGI and poor prognosis in AKI patients is lacking. We hypothesized that the HGI was associated with a poor prognosis in AKI patients and undertook a retrospective cohort study to elucidate the link between the HGI and patient prognosis in AKI patients.

2. Methodology

2.1. Data sources

We gathered data for this investigation from the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database (https://mimic.mit.edu). This database stores ICUs inpatient health data from Beth Israel Deaconess Medical Center from 2008 to 2019 and de-identifies all private patient information. Therefore, it received ethical approval and informed consent waivers. Y.S., one of the writers, got authorization to view the dataset and extract pertinent data.

2.2. Study population

Adult patients with AKI who were first admitted to the ICUs were included. Patients missing weight, glucose, and HbA1c within 24 h of ICU admission were excluded. AKI via Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines Criteria is defined as an increase in Scr of ≥0.3 mg/dL (>26.5 μmol/L) within 48 h; or an increase in Scr to ≥1.5 times the basal value that is known or inferred to have occurred within 7 days; or sustained 6-h urine output <0.5 mL/kg/h [23].

2.3. Data acquisition

In this study, we retrospectively extracted patient demographic information (age, sex, height, weight), Sequential Organ Failure Assessment (SOFA) scores, comorbidities (CKD, heart failure, hypertension, DM), interventions (renal replacement therapy [RRT], diuretics, and vasoactive drugs), laboratory indices (red blood cell counts [RBC], white blood cell counts [WBC], hemoglobin, platelets, Scr, blood urea nitrogen [BUN], albumin, glucose, HbA1c, and potassium), and outcome events (28-day mortality, 90-day mortality, and length of hospital stays). All laboratory indicators were initial values within 24 h after admission to the ICU. Missing values were filled in by applying multiple interpolations. Variables with a missing value rate >20% were excluded.

2.4. Study subgroups and outcome endpoints

We established a linear regression model based on FPG and HbA1c in the research population and obtained the formula for predicted HbA1c as: predicted HbA1c = 0.011*FPG +4.639. HGI = HbA1c actual − HbA1c predicted. Four groups were formed from all of the patients based on their HGI quartiles, *Q*1 (≤ −0.69), *Q*2 (−0.69, −0.23), *Q*3 (−0.23, 0.38), and *Q*4 (>0.38).

The primary outcome endpoints were 28-day mortality and 90-day mortality. The secondary outcome endpoint was the length of hospitalization.

2.5. Statistical analysis

After the normality test, continuous variables in this study were reported as median (interquartile range) and compared across groups using Kruskal–Wallis H. Categorical variables were reported as *n* (%) and compared between groups using the chi-squared test or Fisher's exact test.

Cox regression modeling was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) to explore the association of HGI with 28-day and 90-day mortality. A multivariate Cox regression analysis was performed, adjusting for multiple confounding variables, including sex, age, BMI, hemoglobin, Scr, albumin, BUN, potassium, vasoactive drugs, diuretics, RRT, hypertension, heart failure, DM, and CKD. Confounding variables were chosen using clinical experience and stepwise regression. Kaplan–Meier survival analysis was utilized to evaluate 28-day and 90-day mortality based on

HGI stratification, and differences between groups were assessed by Log-Rank tests. We employed a restricted cubic spline (RCS) model to generate smooth curves, aiming to explore potential nonlinear dose–response relationships between HGI and 28-day as well as 90-day mortality. In this model, HGI was treated as a continuous variable with four knots. Nonlinearity was assessed using a likelihood ratio test, comparing a model containing only a linear term to one incorporating both linear and cubic spline terms. Based on the smoothing curve results, we further developed a two-piecewise linear regression model to identify the threshold effect, while adjusting for potential confounders [24]. The subgroup analyses were conducted by CKD, hypertension, BMI, DM, age, and gender. Interaction across subgroups was tested using the likelihood ratio test. Finally, linear regression models were used to analyze the relationship between HGI and the length of hospital stays.

STATA software (Version 16.0, StataCorp LLC, College Station, TX) and R software (Version 4.2.0) were used for data analysis and visualization. A two-tailed test revealed that statistical significance was defined as $p < 0.05$.

3. Results

3.1. Baseline characterization

On the basis of the inclusion and exclusion criteria (Figure 1), a total of 3684 AKI patients with a median age of 68.4 years were included in this study, of which 2156 (58.5%) were male. The patients were divided into four groups according to their HGI quartiles, and Table 1 displays their baseline characteristics. Compared with the high-HGI group, the low-HGI group had greater SOFA scores, WBC counts, and RRT application ratios but lower BMIs, RBC counts, hemoglobin levels, and platelet counts. In addition, the low-HGI group had higher 28-day and 90-day mortality rates and longer hospital stays.

3.2. Primary endpoints

During the follow-up period, 486 (13.2%) patients died within 28 days, and 673 (18.3%) patients died within 90 days. Kaplan–Meier curves (Figure 2) were generated to evaluate 28-day and 90-day mortality in each group. The results revealed that mortality was significantly greater in the group of patients with HGI ≤ −0.69 (log-rank $P < 0.0001$).

The multivariate Cox regression model (Table 2) demonstrated that the HGI was independently associated with 28-day mortality (HR, 0.84 [95% CI 0.78 to 0.91], $p < 0.001$) and 90-day mortality (HR, 0.87 [95% CI 0.81 to 0.93], $p < 0.001$) in patients with AKI, indicating a significant negative association. When the HGI was analyzed as a categorical variable, after full adjustment, the risk of 28-day mortality (HR, 1.65 [95% CI 1.26 to 2.16], $p < 0.001$) and 90-day mortality (HR, 1.45 [95% CI 1.16 to 1.82], $p < 0.001$) significantly increased in the low-HGI group (Q1). In addition, the RCS curve displays an L-shaped connection between the HGI and 28-day and 90-day mortality (nonlinear, $p < 0.001$) after all factors were corrected (Figure 3). In the threshold analysis, the HR of 28-day mortality was 0.72 (95% CI: 0.65 to 0.805, $p < 0.001$) in participants with HGI < 1.09 (Table 3). This means that for every one-unit increase in HGI, the risk of 28-day mortality was reduced by 28%. However, when the HGI was ≥1.09, the

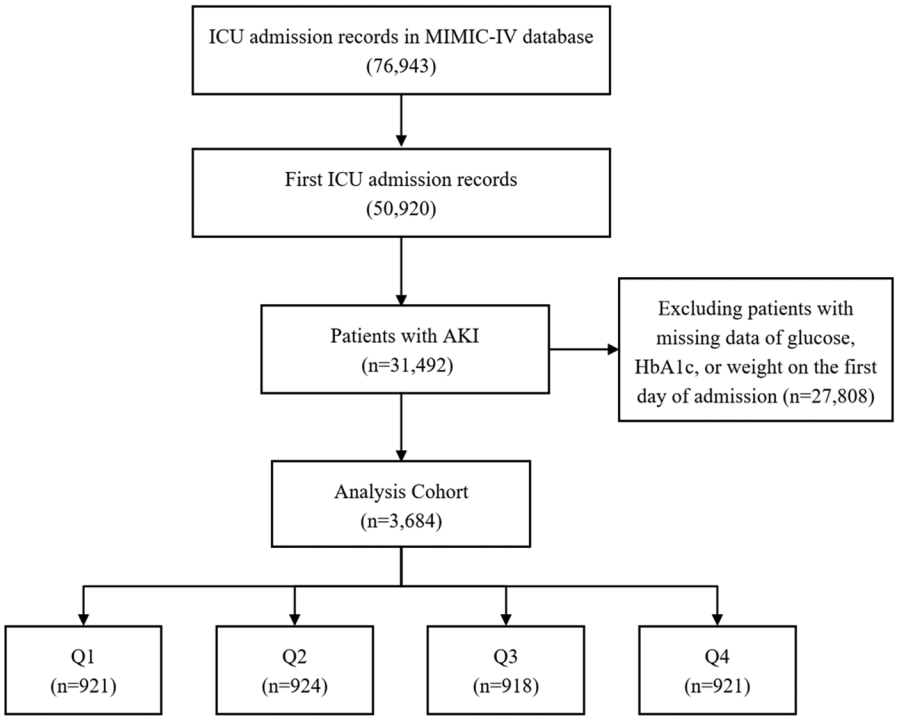

Figure 1. Flowchart of patient selection.

Table 1. Baseline characteristics according to HGI quartiles.

Variables	Overall $n=3684$	$Q1$ (≤−0.69) $n=921$	$Q2$ (−0.69, −0.23) $n=924$	$Q3$ (−0.23, 0.38) $n=918$	$Q4$ (>0.38) $n=921$	P-value
Age (years)	68.4 (56.8, 79.1)	66.6 (54.4, 77.2)	68.9 (55.8, 80.8)	72.1 (61.0, 81.5)	66.8 (56.7, 76.5)	<0.001
Male, *n* (%)	2156 (58.5)	549 (59.6)	536 (58.0)	519 (56.5)	552 (59.9)	0.424
BMI (kg/m^2)	28.7 (24.4, 34.0)	28.0 (24.1, 33.0)	28.0 (23.9, 33.0)	28.8 (24.4, 33.5)	30.3 (25.6, 36.1)	<0.001
SOFA	3.0 (2.0, 6.0)	5.0 (2.0, 8.0)	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	<0.001
Comorbidities, *n* (%)						
Heart failure	1174 (31.9)	307 (33.3)	245 (26.5)	296 (32.2)	326 (35.4)	<0.001
CKD	752 (20.4)	195 (21.2)	161 (17.4)	155 (16.9)	241 (26.2)	<0.001
Hypertension	1825 (49.5)	405 (44.0)	483 (52.3)	498 (54.3)	439 (47.7)	<0.001
Diabetes mellitus	894 (24.3)	155 (16.8)	111 (12.0)	177 (19.3)	451 (49.0)	<0.001
Interventions, *n* (%)						
RRT	256 (7.0)	105 (11.4)	52 (5.6)	48 (5.2)	51 (5.5)	<0.001
Diuretics	1189 (32.3)	312 (33.9)	251 (27.2)	306 (33.3)	320 (34.7)	0.002
Vasoactive drugs	730 (19.8)	279 (30.3)	150 (16.2)	137 (14.9)	164 (17.8)	<0.001
Laboratory tests						
RBC (m/μL)	4.0 (3.4, 4.5)	3.7 (3.2, 4.4)	4.0 (3.6, 4.5)	4.0 (3.5, 4.5)	4.0 (3.5, 4.5)	<0.001
WBC (K/μL)	10.7 (8.0, 14.3)	12.3 (8.7, 17.0)	10.8 (8.1, 14.1)	9.8 (7.5, 12.7)	10.3 (7.9, 13.6)	<0.001
Hemoglobin (g/dL)	11.9 (10.2, 13.4)	11.5 (9.6, 13.2)	12.3 (10.6, 13.6)	12.0 (10.4, 13.5)	11.7 (10.2, 13.2)	<0.001
Platelet (K/μL)	204.0 (159.0, 259.0)	191.0 (142.0, 254.0)	206.0 (165.0, 256.5)	203.5 (164.0, 256.0)	214.0 (167.0, 269.0)	<0.001
Scr (mg/dL)	1.0 (0.8, 1.4)	1.1 (0.8, 1.6)	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)	1.1 (0.8, 1.5)	<0.001
BUN (mg/dL)	19.0 (14.0, 29.0	20.0 (14.0, 32.0)	18.0 (13.0, 25.0)	18.0 (13.0, 27.0)	21.0 (14.0, 34.0)	<0.001
Albumin (g/dL)	3.3 (2.9, 3.7)	3.3 (2.8, 3.7)	3.4 (2.9, 3.7)	3.4 (2.9, 3.8)	3.3 (2.9, 3.7)	0.003
Glucose (mg/dL)	137.0 (109.0, 191.0)	167.0 (129.0, 235.0)	125.0 (106.0, 151.0)	115.0 (99.0, 145.0)	169.0 (123.0, 239.0)	<0.001
HbA1c (%)	5.9 (5.5, 6.8)	5.4 (5.0, 5.8)	5.6 (5.4, 5.9)	6.0 (5.8, 6.3)	8.2 (6.9, 10.1)	<0.001
Potassium (mmol/L)	4.1 (3.7, 4.5)	4.1 (3.7, 4.6)	4.1 (3.7, 4.4)	4.1 (3.7, 4.4)	4.1 (3.8, 4.5)	0.055
Events						
28-day mortality, *n* (%)	486 (13.2)	172 (18.7)	121 (13.1)	104 (11.3)	89 (9.7)	<0.001
90-day mortality, *n* (%)	673 (18.3)	223 (24.2)	163 (17.6)	151 (16.5)	136 (14.8)	<0.001
Hospital stays (days)	8.4 (5.0, 14.9)	9.3 (5.3, 16.8)	8.3 (5.1, 14.9)	7.8 (4.9, 13.8)	8.0 (4.8, 14.2)	<0.001

BMI: body mass index; SOFA: sequential organ failure assessment; CKD: chronic kidney disease; RRT: renal replacement therapy; RBC: red blood cell; WBC: white blood cell; Scr: serum creatinine; BUN: Blood urea nitrogen; HbA1c: glycosylated hemoglobin; HGI: high glycation index.

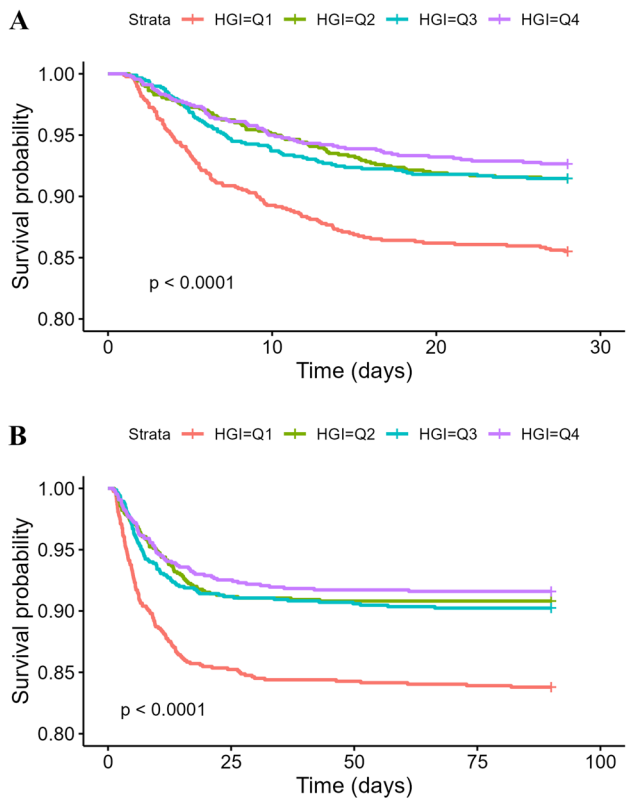

Figure 2. (A) Kaplan–Meier survival analysis curve for 28-day mortality in the overall study population. (B) Kaplan–Meier survival analysis curve for 90-day mortality in the overall study population. (HGI index quartile *Q*1: ≤−0.69; *Q*2: −0.69, −0.23; *Q*3: −0.23, 0.38; *Q*4: >0.38) Kaplan–Meier curves showing cumulative probability of all-cause mortality according to groups at 28 days and 90 days. The results showed that mortality was significantly higher in those with HGI ≤−0.69 (log-rank $P < 0.0001$).

relationship between HGI and 28-day mortality became non-significant (Table 3). This finding implies that as the HGI rises, the 28-day mortality no longer decreases with the HGI. Similarly, for participants with HGI < 1.14, the HR for 90-day mortality was 0.76 (95% CI: 0.69 to 0.84, $p<0.001$), indicating that a one-unit increase in the HGI corresponded to a 24% reduction in the risk of 90-day mortality. In contrast, when the HGI was ≥1.14, the association between the HGI and 90-day mortality was no longer evident (Table 3). This result implies that as the HGI increases, the 90-day mortality does not decrease.

To further elucidate the intricate relationship between the HGI and mortality in various AKI subgroups, we also performed subgroup analyses. As shown in Figure 4, a significant correlation was observed between the HGI and the risk of 28-day mortality in most subgroups, excluding patients with DM and CKD. Similarly, in the subgroup analysis using 90-day mortality as the study endpoint (Figure 5), a substantial association between the HGI and 90-day mortality was identified, except in patients with DM. Notably, the association between the HGI and outcomes was more significant in the nondiabetic subgroup, regardless of whether the outcome was 28-day mortality or 90-day mortality (P for interaction < 0.05).

3.3. Secondary endpoints

To further investigate the impact of the HGI on the length of hospital stays in patients with AKI, we performed multiple linear regression analysis. As shown in Table 4, the HGI was significantly negatively correlated with the length of hospital stays, both as continuous and categorical variables. In

Table 2. Cox proportional hazard ratios for 28-day and 90-day mortality.

Categories	Model 1 HR (95% CI)	*P*-value	Model 2 HR (95% CI)	*P*-value	Model 3 HR (95% CI)	*P*-value
28-day mortality						
HGI	0.79 (0.73, 0.85)	<0.001	0.79 (0.73, 0.85)	<0.001	0.84 (0.78, 0.91)	<0.001
HGI (category)						
*Q*1 (≤−0.69)	2.06 (1.60, 2.66)	<0.001	2.02 (1.56, 2.61)	<0.001	1.65 (1.26, 2.16)	<0.001
*Q*2 (−0.69, −0.23)	1.37 (1.94, 1.81)	0.023	1.25 (0.95, 1.65)	0.113	1.16 (0.87, 1.55)	0.315
*Q*3 (−0.23, 0.38)	1.19 (0.89, 1.58)	0.234	1.03 (0.77, 1.36)	0.859	0.95 (0.71, 1.29)	0.805
*Q*4 (>0.38)	Ref.		Ref.		Ref.	
P for trend		<0.001		<0.001		<0.001
90-day mortality						
HGI	0.82 (0.77, 0.87)	<0.001	0.82 (0.77, 0.88)	<0.001	0.87 (0.81, 0.93)	<0.001
HGI (category)						
*Q*1 (≤−0.69)	1.77 (1.43, 2.19)	<0.001	1.74 (1.41, 2.16)	<0.001	1.45 (1.16, 1.82)	<0.001
*Q*2 (−0.69, −0.23)	1.22 (0.97, 1.53)	0.091	1.11 (0.88, 1.39)	0.385	1.07 (0.84, 1.36)	0.596
*Q*3 (−0.23, 0.38)	1.13 (0.89, 1.43)	0.297	0.96 (0.76, 1.22)	0.765	0.93 (0.73, 1.18)	0.550
*Q*4 (>0.38)	Ref.		Ref.		Ref.	
P for trend		<0.001		<0.001		<0.001

Model 1 was unadjusted.
Model 2 was adjusted for sex, age, and BMI.
Model 3 was adjusted for sex, age, BMI, hemoglobin, Scr, albumin, BUN, potassium, vasoactive drugs, diuretics, RRT, hypertension, heart failure, diabetes mellitus, and CKD.
BMI: body mass index; Scr: serum creatinine; BUN: Blood urea nitrogen; RRT: renal replacement therapy; CKD: chronic kidney disease; HGI: hyper glycation index; HR: hazard ratio.

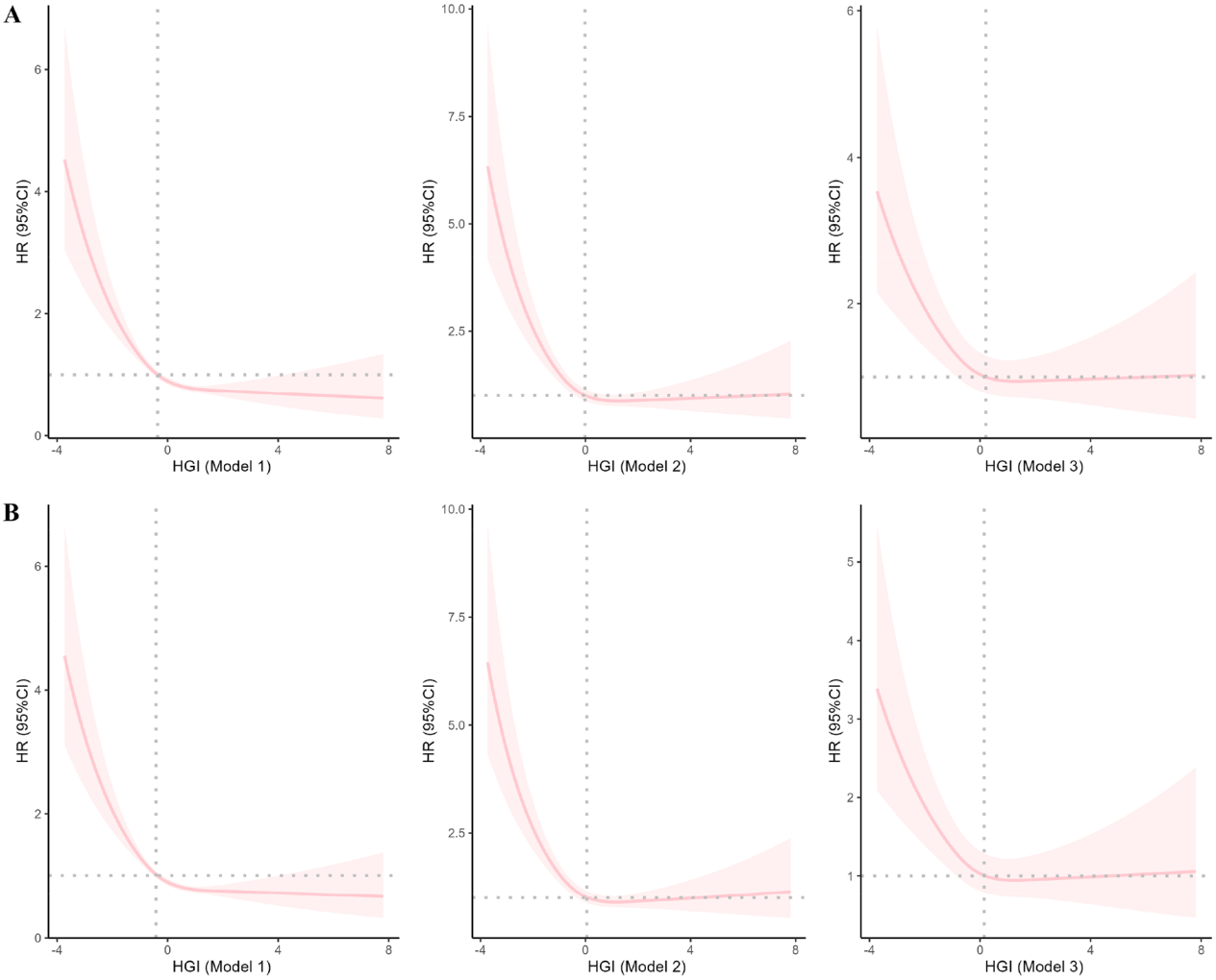

Figure 3. (A) RCS curve of HGI with 28-day mortality. (B) RCS curve of HGI with 90-day mortality (nonlinear, $p < 0.001$). Model 1 was unadjusted; model 2 was adjusted for sex, age, and BMI; model 3 was adjusted for sex, age, BMI, hemoglobin, Scr, albumin, BUN, potassium, vasoactive drugs, diuretics, RRT, hypertension, heart failure, DM, and CKD. (BMI: body mass index; Scr: serum creatinine; BUN: Blood urea nitrogen; RRT: renal replacement therapy; CKD: chronic kidney disease).

Table 3. Threshold effect analysis of the relationship of HGI with 28-day and 90-day mortality.

Outcome	Adjusted model	
28-day mortality	**HR (95% CI)**	***P*-value**
<1.09	0.72 (0.65, 0.805)	<0.001
≥1.09	1.11 (0.89, 1.37)	0.359
Likelihood ratio test		0.001
90-day mortality	**HR (95% CI)**	***P*-value**
<1.14	0.76 (0.69, 0.84)	<0.001
≥1.14	1.14 (0.87, 1.48)	0.36
Likelihood ratio test		0.001

OR: odds ratio; CI: confidence interval; HGI: high glycation index; HR: hazard ratio. Adjusted for Model 3.

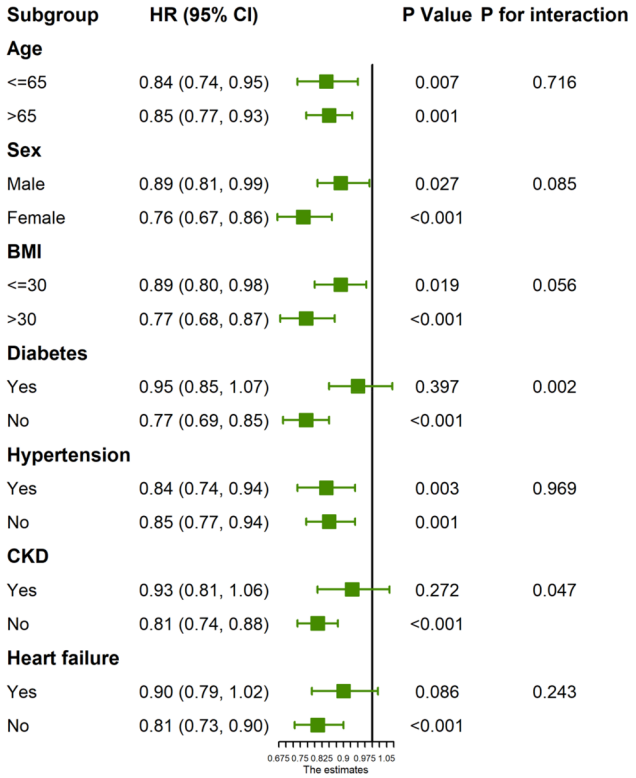

Figure 4. Forest plots for 28-day mortality. Subgroups are stratified by [age, sex, BMI, diabetes, hypertension, CKD, and heart failure]. The hazard ratio (HR) and 95% confidence interval (CI) are shown for each subgroup.

unadjusted model 1, higher HGI levels at admission were significantly associated with shorter hospital stays (β = −0.39, 95% CI: −0.66 to −0.12, $p = 0.004$). This negative correlation persisted after partial adjustment (β = −0.43, 95% CI: −0.70 to −0.16, $p = 0.002$) and full adjustment (β = −0.46, 95% CI: −0.73 to −0.19, $p = 0.001$). When the HGI value was analyzed as a categorical variable, the association remained significant in the fully adjusted model. Specifically, compared with the highest HGI quartile (*Q*4, HGI > 0.38), the lowest quartile (*Q*1, HGI ≤ −0.69) was associated with a significantly longer hospital stay (β = 1.71, 95% CI: 0.52 to 2.89, $p = 0.005$).

4. Discussion

In this retrospective analysis, we first demonstrated a connection between the HGI and 28-day and 90-day mortality in patients with AKI. The findings revealed that higher HGI

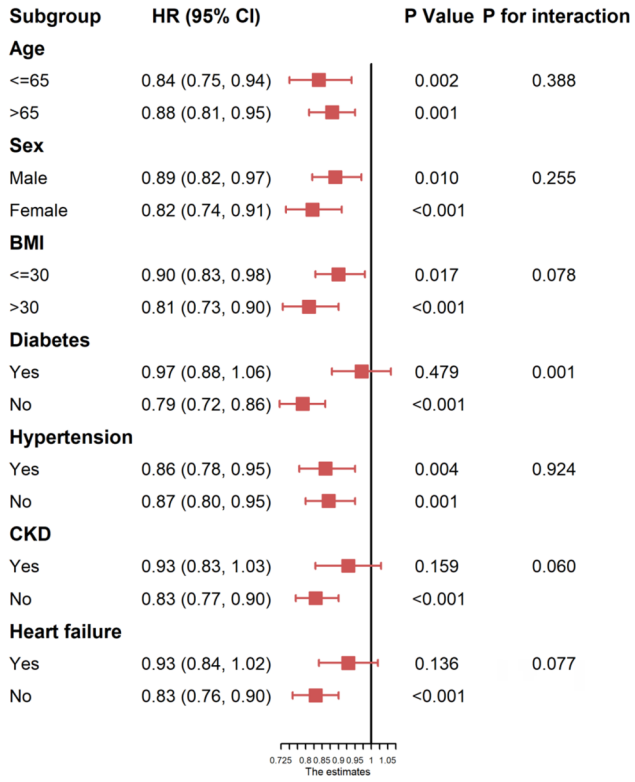

Figure 5. Forest plots for 90-day mortality. Subgroups are stratified by [age, sex, BMI, diabetes, hypertension, CKD, and heart failure]. The hazard ratio (HR) and 95% confidence interval (CI) are shown for each subgroup.

levels were associated with reduced mortality and shorter hospital stays among AKI patients. This connection remained even after various confounders were accounted for. Additionally, the RCS curves revealed a nonlinear association between the HGI and 28-day and 90-day mortality in patients with AKI, and the relationship between the HGI and clinical outcomes was more significant in nondiabetic patients ($p < 0.05$).

The development of AKI is closely related to blood glucose levels. Previous studies have shown that patients with type 2 DM have a greater risk of developing AKI than nondiabetic patients do [25,26]. Although the precise mechanisms underlying this increased risk remain unclear, hyperglycemia-induced renal damage may involve injury to renal tubular epithelial cells, vascular endothelial cells, and podocytes. These effects are likely mediated by the release of inflammatory factors and increased oxidative stress in the context of chronic hyperglycemia [27]. ICU patients often experience a rapid rise in blood glucose over a short period of time during severe illnesses, namely, stress hyperglycemia [28]. Unlike persistently elevated blood glucose, rapid glucose fluctuations are more likely to provoke oxidative stress, generating excessive superoxide that reacts with nitric oxide to form metabolic derivatives such as peroxynitrite, leading to endothelial damage [29,30]. Additionally, hyperglycemia may induce osmotic diuresis, leading to dehydration and causing neutrophil dysfunction, which significantly increases the risk of infection [31]. All these factors may exacerbate the risk of death in AKI patients. Stress hyperglycemia and the ratio of stress

Table 4. Multiple linear regression of the association between HGI and hospital stays.

Categories	Model 1 β (95% CI)	*P*-value	Model 2 β (95% CI)	*P*-value	Model 3 β (95% CI)	*P*-value
HGI	−0.39 (−0.66, −0.12)	0.004	−0.43 (−0.70, −0.16)	0.002	−0.46 (−0.73, −0.19)	0.001
HGI (category)						
*Q*1 (≤ −0.69)	2.07 (0.90, 3.23)	<0.001	2.02 (0.85, 3.19)	0.001	1.71 (0.52, 2.89)	0.005
*Q*2 (−0.69, −0.23)	1.04 (−0.12, 2.20)	0.080	1.14 (−0.03, 2.30)	0.057	2.03 (0.84, 3.21)	0.001
*Q*3 (−0.23, 0.38)	0.09 (−1.08, 1.25)	0.884	0.34 (−0.83, 1.51)	0.563	1.02 (−0.15, 2.19)	0.087
*Q*4 (>0.38)	Ref.		Ref.		Ref.	
P for trend		<0.001		<0.001		0.008

Model 1 was unadjusted.
Model 2 was adjusted for sex, age, and BMI.
Model 3 was adjusted for sex, age, BMI, hemoglobin, Scr, albumin, BUN, potassium, vasoactive drugs, diuretics, RRT, hypertension, heart failure, diabetes mellitus, and CKD.
BMI: body mass index; Scr: serum creatinine; BUN: Blood urea nitrogen; RRT: renal replacement therapy; CKD: chronic kidney disease; HGI: high glycation index.

hyperglycemia have been found to be risk factors for increased mortality in AKI patients, and this correlation is significant in nondiabetic patients [32,33].

In our fitted HbA1c curve, the predicted HbA1c value is expressed as follows: HbA1c predicted = 0.011*FPG +4.639. The disparity between the actual and predicted values of HbA1c is defined as the HGI. When stress hyperglycemia occurs, FPG increases, predicted HbA1c increases, the HGI decreases, and the pathophysiological changes associated with stress hyperglycemia exacerbate the poor prognosis of AKI and increase the mortality rate. Therefore, the occurrence of stress hyperglycemia may explain the relationship between a low HGI and a high risk of mortality in AKI patients. In addition, under conditions of similar blood glucose levels, a high HGI indicates that the observed HbA1c level is higher than the predicted HbA1c level, whereas patients with low HGI have lower observed HbA1c levels. Physicians may believe that high-HGI patients have poor glycemic control and intensify their glycemic management, which may be one of the reasons for the decreased risk of death in high-HGI patients among AKI patients. In our subgroup analysis, the significant negative association between the HGI and the risk of death in AKI patients was significant in nondiabetic patients. This finding may be attributed to stricter glycemic monitoring and management typically provided to diabetic patients, thereby attenuating the predictive value of the HGI for mortality in this subgroup. A secondary analysis of the Action in Diabetes and Vascular Disease (ADVANCE) trial revealed that a high HGI predicted a lower risk of death in diabetic patients receiving intensive glycemic therapy [34]. However, intensive blood glucose therapy was shown to improve the mortality outcomes of diabetic patients with low to moderate HGI in a secondary analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [35]. This discrepancy may be related to differences in the experimental protocols of the two trials, which need to be further explored. Nonetheless, both findings reflect the impact of glycemic control on mortality risk and emphasize the role of the HGI in diabetic and nondiabetic patients. The HGI, which reflects a combination of long-term (HbA1c) and short-term (FPG) blood glucose levels, provides a comprehensive metric for assessing glycemic status. This index offers valuable insights for clinicians in optimizing blood glucose management and improving patient outcomes.

Furthermore, in patients with AKI, we discovered an L-shaped association between the HGI and 28-day and 90-day mortality. This nonlinear relationship suggests that the HGI does not significantly affect 28-day or 90-day mortality when it is increased to a certain level. One possible explanation for this result is that for AKI patients, the increase in HGI caused by the reduction in stress hyperglycemia can reduce the risk of death. However, when the HGI exceeds a certain level, the substantial discrepancy between the observed and predicted HbA1c values may reflect a heightened likelihood of hypoglycemia. Therefore, the positive effect of HGI on mortality gradually weakens. As mentioned earlier, stress hyperglycemia can lead to a decrease in the HGI and cause a series of injuries to the body, which may explain prolonged hospital stays. Furthermore, intensive glycemic control in patients with high HGIs may explain the reduced length of hospital stays.

The findings of the present study, together with those of previous studies, suggest that in clinical practice, monitoring not only the long-term and short-term glucose levels of diabetic patients but also the HGI of nondiabetic patients is critical. Early identification of individuals at high risk of all-cause AKI death may be facilitated by HGI evaluation to strengthen the management of patients' HGI and control it within a certain range. For individuals with a low HGI, implementing appropriate strategies to enhance glycemic control may contribute to better prognoses and reduced mortality in AKI patients.

However, this study had several limitations. Although confounders were accounted for, the use of insulin or other hypoglycemic drugs was not considered. Previous research has shown that intensive glucose therapy may have an impact on the risk of death in patients, which may have biased the results. Additionally, other unmeasured confounders may have affected the findings. This research used a limited sample size and was a single-center retrospective cohort study, and the patients included were limited to critically ill patients in the USA. Extrapolation to a wider population requires further research for validation, such as multicenter, large-sample retrospective cohort studies, prospective studies, and laboratory studies.

5. Conclusion

This was a large retrospective cohort study. We innovatively revealed an L-shaped correlation between the HGI and 28-day and 90-day mortality in AKI patients, with an inflection point of approximately 1.09/1.14. We also revealed the relationship between the HGI and the length of hospital stays in patients with AKI. Based on our results and those of previous studies, we innovatively propose that the HGI can be used as a predictor of mortality risk and length of hospitalization in AKI patients. In clinical practice, the use of HbA1c to judge the blood glucose control of patients is not limited. In patients with AKI, a lower HGI was associated with a greater risk of 28-day and 90-day mortality, but this relationship weakened when it exceeded a threshold value.

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Author contributions

Jing Liu: conceptualization, data curation, writing—original draft. Yue Shi: data curation, investigation, visualization. Hangyu Duan: formal analysis, software. Xiujie Shi: writing—review and editing. Yu Zhang: writing—review and editing, supervision, funding acquisition. Mingming Zhao: writing—review and editing, funding acquisition.

Ethics approval and consent to participate

The Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center Institutional Review Boards gave their approval to the project.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

Data will be made available from the corresponding author on reasonable request.

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