Research Square

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Prognostic Value of Stress Hyperglycemia Ratio, Glycemic Gap, and Hemoglobin Glycation Index for Mortality in ICU Patients with Pneumonia: A Retrospective Cohort Study Based on the MIMIC-IV Database

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Research Article

Keywords: stress hyperglycemia ratio, glycemic gap, hemoglobin glycation index, pneumonia, intensive care unit, mortality, MIMIC-IV

Posted Date: September 24th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10754094/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Dysglycemia is associated with adverse outcomes in critically ill patients, but admission glucose alone cannot reliably distinguish stress hyperglycemia from chronic hyperglycemia. The stress hyperglycemia ratio (SHR), glycemic gap, and hemoglobin glycation index (HGI) are three metrics derived from admission glucose and HbA1c; however, no head-to-head comparison of their prognostic value has been performed in the same ICU pneumonia population.

Methods

This retrospective cohort study included 2,740 adult ICU patients with pneumonia from the MIMIC-IV database. SHR, glycemic gap, and HGI were calculated from admission glucose and HbA1c. Logistic and Cox proportional hazards regression models were used to evaluate associations with 28-day and 90-day mortality, respectively. Restricted cubic spline analysis, subgroup analysis, and five sensitivity analyses were performed to assess dose-response relationships and robustness.

Results

Among 2,740 ICU patients with pneumonia (28-day mortality: 492, 18.0%; 90-day mortality: 719, 26.2%), SHR was independently associated with both 28-day (OR 1.31, 95% CI 1.11–1.53, p = 0.001) and 90-day mortality (HR 1.20, 95% CI 1.10–1.32, p < 0.001) in the fully adjusted Model 3. Per-standard-deviation increments of the glycemic gap were significantly associated with mortality (HR 1.13, 95% CI 1.05–1.21, p = 0.001), but the continuous variable effect size was minimal (OR/HR = 1.00). HGI lost statistical significance after full adjustment (Model 3, 90-day: HR 0.95, 95% CI 0.90–1.01, p = 0.094). Restricted cubic spline analysis revealed a positive linear dose-response relationship between SHR and 90-day mortality (P for overall = 0.001; P for non-linearity = 0.442). Subgroup analysis showed that the SHR-mortality association was not significant in non-sepsis patients (HR 0.98, p = 0.943). Five sensitivity analyses consistently supported the robustness of SHR.

Conclusions

SHR is a more robust prognostic indicator than the glycemic gap or HGI for mortality risk in ICU patients with pneumonia. SHR may serve as a readily available, cost-free tool for clinical risk stratification in this population.

Background

Pneumonia is a leading reason for intensive care unit (ICU) admission and the most common infectious cause of death among critically ill patients [1]. Despite advances in anti-infective therapy and organ support, mortality among ICU patients with pneumonia remains high, with 30-day mortality rates ranging from 13% to 30% [1, 2]. Accurate risk stratification is essential for clinical decision-making and resource allocation [3].

Dysglycemia is highly prevalent in critically ill patients and encompasses both stress hyperglycemia and hypoglycemia, both of which have been associated with adverse outcomes [4, 5, 6]. However, admission glucose levels are substantially confounded by chronic glycemic status—patients with diabetes have elevated baseline glucose, whereas those without diabetes have lower baseline levels—making it difficult to distinguish stress hyperglycemia from chronic hyperglycemia using absolute glucose values alone [7]. Consequently, removing the background of chronic glycemia and accurately assessing the true degree of stress hyperglycemia has become a research priority.

To overcome this limitation, several standardized metrics based on admission glucose and hemoglobin A1c (HbA1c)-derived estimated average glucose (eAG) have been proposed [8]. The three most representative metrics are the stress hyperglycemia ratio (SHR), glycemic gap, and hemoglobin glycation index (HGI). SHR is defined as the ratio of admission glucose to eAG, reflecting the relative degree of stress hyperglycemia [9]. The glycemic gap is defined as the absolute difference between admission glucose and eAG, reflecting the absolute magnitude of stress hyperglycemia [10]. HGI is defined as the difference between measured HbA1c and predicted HbA1c, reflecting the deviation in an individual's hemoglobin glycation propensity [11].

Previous studies have investigated the prognostic value of these three metrics separately in critically ill patients. Chen et al. [12] and Jensen et al. [13] found that an elevated glycemic gap was associated with adverse outcomes and increased 90-day mortality risk in diabetic patients with community-acquired pneumonia. Roberts et al. [9] first proposed the SHR and demonstrated its superiority over absolute glucose values in identifying critically ill patients at risk. Hempe et al. [11] reported that HGI identifies subgroups that may benefit from or be harmed by intensive glucose-lowering therapy. More recently, multiple studies based on the MIMIC database have further validated the prognostic value of SHR in patients with sepsis [14], heart failure [15], and in general ICU populations [16]. Liu et al. [17] reported that SHR was positively correlated with systemic inflammation and exhibited a J-shaped association with adverse clinical outcomes in diabetic patients with pneumonia. Egi et al. [18] further confirmed the important interaction between chronic hyperglycemia and acute glycemic management on prognosis.

However, no study has simultaneously compared the prognostic value of SHR, glycemic gap, and HGI in the same ICU pneumonia population. Although all three metrics are calculated from admission glucose and HbA1c, they reflect fundamentally different physiological dimensions—SHR captures the relative stress degree [9], the glycemic gap captures the absolute stress magnitude [10], and HGI captures the chronic glycation propensity [11]—and these differences may lead to divergent performance in prognostic assessment. Identifying which metric offers the greatest prognostic value for ICU patients with pneumonia will help guide the selection of appropriate glycemic assessment tools in clinical practice.

Therefore, this study, based on the MIMIC-IV database, included ICU patients with pneumonia and aimed to: (1) evaluate the associations of SHR, glycemic gap, and HGI with 28-day and 90-day mortality; (2) compare the robustness of these associations across multiple models and sensitivity analyses; and (3) explore the dose-response relationship between SHR and mortality risk as well as potential effect modifiers.

Methods

Study design and data source

This retrospective cohort study used data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database [19]. MIMIC-IV is a large, publicly available critical care database containing data on ICU patients admitted to Beth Israel Deaconess Medical Center between 2008 and 2022, including demographic information, vital signs, laboratory tests, medication records, diagnostic codes, and clinical outcomes. Miao Chen and Haiyun Sun completed the Collaborative Institutional Training Initiative examination and obtained database access (certification numbers: 14332284 and 15274796). Because MIMIC-IV contains de-identified patient information, this study was exempt from ethics review and informed consent requirements. All reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Study population

Adult patients with pneumonia during their first ICU admission were identified from the MIMIC-IV database. Pneumonia was identified using International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes. Inclusion criteria were: (1) age ≥ 18 years; (2) first ICU admission. Exclusion criteria were: (1) ICU stay < 24 hours; (2) missing

admission glucose data; (3) missing HbA1c data. A total of 2,740 eligible patients were included. Figure 1 illustrates the patient selection flowchart.

Data collection

The following variables were extracted from the MIMIC-IV database using structured query language:

Demographic information

age, sex, race, insurance type;

Vital signs

heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, respiratory rate, temperature, oxygen saturation (minimum, maximum, and mean values within 24 hours of ICU admission);

Laboratory tests

glucose, HbA1c, complete blood count, liver and renal function, electrolytes, coagulation function, arterial blood gas analysis (minimum and maximum values within 24 hours of ICU admission);

Comorbidities

components of the Charlson comorbidity index [21] based on ICD codes, including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, diabetes, chronic kidney disease, and malignant neoplasms; clinical diagnoses such as hypertension, heart failure, and acute kidney injury were also recorded;

Disease severity scores

Acute Physiology Score III (APSIII), Simplified Acute Physiology Score II (SAPSII), Oxford Acute Severity of Illness Score (OASIS), and Sequential Organ Failure Assessment (SOFA) score [21, 22, 23].

All glucose and HbA1c values were the first measurements after ICU admission.

Exposure definitions

The three exposure metrics were calculated from admission glucose (mg/dL) and HbA1c (%):

Estimated average glucose (eAG):
eAG (mg/dL) = 28.7 × HbA1c (%) − 46.7 [8]

Stress hyperglycemia ratio (SHR):

SHR = glucose (mg/dL) / eAG [9]

SHR is a unitless ratio reflecting the degree of stress hyperglycemia relative to baseline glycemic levels; SHR > 1 indicates stress hyperglycemia.
Glycemic gap:
Glycemic gap (mg/dL) = glucose (mg/dL) − eAG [10]

The glycemic gap is the absolute difference between admission glucose and eAG, reflecting the absolute magnitude of stress hyperglycemia.

Hemoglobin glycation index (HGI):
HGI (%) = HbA1c (%) − predicted HbA1c (%) [11]

where predicted HbA1c (%) = 4.882 + 0.0098 × glucose (mg/dL), derived from a linear regression model of HbA1c on admission glucose in the study population (n = 2,740). HGI reflects an individual's hemoglobin glycation propensity relative to their glucose level.

Outcome definitions

Primary outcome

90-day all-cause mortality, defined as death from any cause within 90 days of ICU admission. Cox proportional hazards regression models were used for analysis.

Secondary outcome

28-day all-cause mortality, defined as death from any cause within 28 days of ICU admission. Logistic regression models were used for analysis.

Survival time was calculated from death dates recorded in the MIMIC database. For surviving patients, the last follow-up date was used as the censoring time.

Covariates and adjustment models

Covariates were selected based on literature review and clinical expertise. Four sequentially adjusted Cox proportional hazards and logistic regression models were constructed:

- **Model 0**: unadjusted (crude model)
- **Model 1**: adjusted for age and sex
- **Model 2**: Model 1 plus Charlson comorbidity index, diabetes, and chronic kidney disease
- **Model 3** (fully adjusted model): Model 2 plus sepsis (Sepsis-3 definition [22]), acute kidney injury (within 7 days), and age-squared (age^2)

In all regression models, SHR, glycemic gap, and HGI were entered as continuous variables, and per-standard-deviation increments were also reported.

Statistical analysis

Normally distributed continuous variables were presented as mean ± standard deviation ($\bar{x}$ ± SD) and compared using independent-sample t tests; non-normally distributed variables were presented as median (interquartile range) and compared using Mann-Whitney U tests. Categorical variables were presented as frequency (percentage) and compared using chi-square tests.

Logistic regression models were used to evaluate associations with 28-day mortality, with results expressed as odds ratios (OR) and 95% confidence intervals (CI). Cox proportional hazards regression models were used to evaluate associations with 90-day mortality, with results expressed as hazard ratios (HR) and 95% CI. The proportional hazards assumption was verified using Schoenfeld residual tests.

Restricted cubic spline (RCS) analysis [24] was used to explore the dose-response relationship between SHR or glycemic gap and 90-day mortality risk, with knots placed at the 5th, 35th, 65th, and 95th percentiles.

Kaplan-Meier survival curves were used to display 90-day cumulative survival stratified by SHR tertiles, with between-group comparisons using the log-rank test.

Subgroup analyses were stratified by sex (male/female), diabetes (yes/no), sepsis (yes/no), chronic kidney disease (yes/no), and acute kidney injury (yes/no). Interaction significance was assessed using likelihood ratio tests.

All statistical analyses were performed using Free Statistics software version V2.5.1 and R software (The R Foundation for Statistical Computing). Two-sided $p < 0.05$ was considered statistically significant.

Sensitivity analyses

To test the robustness of the primary results, the following five sensitivity analyses were performed:

- **S1**: replaced age-squared with a linear age term in Model 3 to assess the impact of age specification
- **S2**: excluded diabetes from the adjustment models to evaluate the independence of SHR
- **S3**: excluded patients with extreme SHR values below the 0.5th percentile or above the 99.5th percentile
- **S4**: additionally adjusted for SOFA score in the sepsis subgroup (n = 2,128)
- **S5**: Schoenfeld residual test to verify the proportional hazards assumption

Results

Baseline characteristics

Of the 2,740 ICU patients with pneumonia from the MIMIC-IV database, 492 (18.0%) died within 28 days and 719 (26.2%) died within 90 days. Table 1 presents baseline characteristics stratified by 90-day mortality status.

Table 1
Baseline Characteristics of the Study Population According to 90-Day Mortality

Variables		**90 Day Mortality**		
	Total (n = 2740)	**NO (n = 2021)**	**YES (n = 719)**	***p***
Age(years)	66.8 ± 14.8	65.0 ± 14.9	71.9 ± 13.3	< 0.001
BMI(Kg/m^2)	30.6 ± 8.1	31.2 ± 8.2	28.8 ± 7.6	< 0.001
APSIII	59.5 ± 25.8	56.0 ± 24.4	69.5 ± 26.8	< 0.001
Charlson Comorbidity Index	6.6 ± 2.9	6.1 ± 2.8	7.8 ± 2.8	< 0.001
HbA1c(%)	6.5 ± 1.8	6.6 ± 1.8	6.4 ± 1.6	0.065
Glucose(mg/dl)	169.6 ± 95.4	167.8 ± 93.3	174.7 ± 100.9	0.095
SHR(%)	1.2 ± 0.6	1.2 ± 0.6	1.3 ± 0.7	0.001
Glycemic_Gap(mg/dl)	15.0 (-12.6, 54.9)	12.1 (-14.2, 50.3)	22.4 (-8.4, 64.7)	< 0.001
HGI(%)	-0.3 (-0.8, 0.4)	-0.3 (-0.8, 0.4)	-0.4 (-0.9, 0.2)	0.003
Gender (%)				0.156
Female	1105 (40.3)	799 (39.5)	306 (42.6)	
Male	1635 (59.7)	1222 (60.5)	413 (57.4)	
Race (%)				0.006
Black	338 (12.3)	268 (13.3)	70 (9.7)	
Other	867 (31.6)	612 (30.3)	255 (35.5)	
White	1535 (56.0)	1141 (56.5)	394 (54.8)	
Sepsis (%)	2128 (77.7)	1521 (75.3)	607 (84.4)	< 0.001
CKD (%)	711 (25.9)	498 (24.6)	213 (29.6)	0.009
Diabetes (%)	1249 (45.6)	935 (46.3)	314 (43.7)	0.231
Heart Failure(%)	1067 (38.9)	739 (36.6)	328 (45.6)	< 0.001
Hypertension (%)	1987 (72.5)	1454 (71.9)	533 (74.1)	0.259
AKI (%)	2320 (84.7)	1677 (83)	643 (89.4)	< 0.001
LOS Hospital(day)	15.6 (9.0, 26.1)	15.8 (9.0, 27.2)	15.1 (8.6, 23.8)	0.008
LOS ICU(day)	5.4 (2.4, 12.1)	4.9 (2.2, 11.6)	7.0 (3.1, 13.0)	< 0.001

BMI:Body Mass Index, APSIII:Acute Physiology Score III, SHR:Stress Hyperglycemia Ratio, HGI:Hemoglobin Glycation Index, CKD:Chronic Kidney Disease, AKI:Acute Kidney Injury, LOS:Length Of Stay.

Compared with survivors, patients in the 90-day mortality group were older (71.9 ± 13.3 vs. 65.0 ± 14.9 years, $p < 0.001$), had lower BMI (28.8 ± 7.6 vs. 31.2 ± 8.2 kg/m², $p < 0.001$), and had higher disease severity scores (APSIII: 69.5 ± 26.8 vs. 56.0 ± 24.4; CCI: 7.8 ± 2.8 vs. 6.1 ± 2.8, both $p < 0.001$). The proportions of sepsis (84.4% vs. 75.3%), CKD (29.6% vs. 24.6%), heart failure (45.6% vs. 36.6%), and AKI (89.4% vs. 83.0%) were significantly higher in the mortality group than in the survivor group (all $p < 0.05$). There were no significant differences in sex ($p = 0.156$), diabetes ($p = 0.231$), or hypertension ($p = 0.259$) between the two groups.

Regarding glycemic metrics, SHR was significantly higher in the mortality group than in the survivor group (1.3 ± 0.7 vs. 1.2 ± 0.6, p = 0.001). The glycemic gap was also significantly elevated in non-survivors (22.4 (− 8.4, 64.7) vs. 12.1 (− 14.2, 50.3) mg/dL, p < 0.001), whereas HGI was lower in the mortality group (− 0.4 (− 0.9, 0.2) vs. −0.3 (− 0.8, 0.4) %, p = 0.003). Admission glucose (p = 0.095) and HbA1c (p = 0.065) did not differ significantly between groups.

Associations of SHR, glycemic gap, and HGI with 28-day and 90-day mortality

Table 2 summarizes the associations of the three glycemic metrics with 28-day mortality (logistic regression) and 90-day mortality (Cox regression).

Table 2
Univariable and Multivariable Associations of SHR, Glycemic Gap, and HGI with 28-Day and 90-Day Mortality

variables	**outcome**	**Model 0 OR/HR (95%CI)**	***p***	**Model 1 OR/HR (95%CI)**	***p***	**Model 2 OR/HR (95%CI)**	***p***	**Model 3 OR/HR (95%CI)**	***p***
SHR	28d (Logistic)	1.28(1.1–1.5)	0.001	1.22(1.12–1.32)	< 0.001	1.37(1.16–1.62)	< 0.001	1.31(1.11–1.53)	0.001
Per-SD	28d (Logistic)	1.16(1.06–1.28)	0.001	1.20(1.09–1.32)	< 0.001	1.21(1.10–1.34)	< 0.001	1.18(1.07–1.30)	0.001
SHR	90d (Cox)	1.18(1.08–1.29)	< 0.001	1.22(1.12–1.32)	< 0.001	1.23(1.13–1.34)	< 0.001	1.20(1.10–1.32)	< 0.001
Per-SD	90d (Cox)	1.11(1.05–1.17)	< 0.001	1.13(1.07–1.19)	< 0.001	1.13(1.08–1.19)	< 0.001	1.12(1.06–1.18)	< 0.001
GlycemicGap	28d (Logistic)	1.00(1.00–1.00)	0.001	1.00(1.00–1.00)	< 0.001	1.00(1.00–1.00)	< 0.001	1.00(1.00–1.00)	0.001
Per-SD	28d (Logistic)	1.16(1.06–1.27)	0.001	1.19(1.08–1.30)	< 0.001	1.21(1.10–1.34)	< 0.001	1.18(1.07–1.30)	0.001
GlycemicGap	90d (Cox)	1.00(1.00–1.00)	0.001	1.00(1.00–1.00)	< 0.001	1.00(1.00–1.00)	< 0.001	1.00(1.00–1.00)	0.001
Per-SD	90d (Cox)	1.11(1.04–1.18)	0.001	1.13(1.06–1.20)	< 0.001	1.15(1.07–1.22)	< 0.001	1.13(1.05–1.21)	0.001
HGI	28d (Logistic)	0.91(0.85–0.97)	0.004	0.91(0.85–0.98)	0.008	0.92(0.85–0.99)	0.028	0.94(0.87–1.01)	0.096
Per-SD	28d (Logistic)	0.86(0.77–0.95)	0.004	0.86(0.77–0.96)	0.008	0.87(0.77–0.98)	0.028	0.90(0.80–1.02)	0.096
HGI	90d (Cox)	0.92(0.88–0.97)	0.002	0.92(0.87–0.97)	0.003	0.94(0.88–0.99)	0.023	0.95(0.90–1.01)	0.094
Per-SD	90d (Cox)	0.88(0.81–0.95)	0.002	0.88(0.81–0.96)	0.003	0.9(0.82–0.99)	0.023	0.92(0.84–1.01)	0.094

Data are presented as OR (95% CI) for 28-day mortality (logistic regression) and HR (95% CI) for 90-day mortality (Cox regression). Model 0: unadjusted. Model 1: adjusted for age and sex. Model 2: additionally adjusted for Charlson comorbidity index, diabetes, and chronic kidney disease. Model 3: additionally adjusted for sepsis-3 and acuete kidney injury with quadratic age term.

SHR

SHR remained significantly and positively associated with both 28-day and 90-day mortality across all four models. In the fully adjusted Model 3, each one-unit increase in SHR was associated with a 31% increase in 28-day mortality risk (OR 1.31, 95% CI 1.11–1.53, $p = 0.001$) and a 20% increase in 90-day mortality risk (HR 1.20, 95% CI 1.10–1.32, $p < 0.001$). Per-standard-deviation increments of SHR were associated with an 18% (OR 1.18, 95% CI 1.07–1.30) and 12% (HR 1.12, 95% CI 1.06–1.18) increase in 28-day and 90-day mortality risk, respectively.

Glycemic gap

Per-standard-deviation increments of the glycemic gap were significantly associated with both 28-day mortality (Model 3 OR 1.18, 95% CI 1.07–1.30, $p = 0.001$) and 90-day mortality (Model 3 HR 1.13, 95% CI 1.05–1.21, $p = 0.001$). However, when analyzed as a continuous variable, the effect size was negligible (OR/HR = 1.00), suggesting that its clinical relevance is primarily driven by extreme values rather than unit increments.

HGI: In unadjusted and partially adjusted models, HGI was negatively associated with mortality (i.e., lower HGI was associated with higher mortality risk). However, this association lost statistical significance after full adjustment in Model 3 (28-day: OR 0.94, 95% CI 0.87–1.01, $p = 0.096$; 90-day: HR 0.95, 95% CI 0.90–1.01, $p = 0.094$), indicating that the prognostic effect of HGI was largely explained by disease severity and comorbidities.

Kaplan-Meier survival analysis

Figure 2 shows the 90-day Kaplan-Meier survival curves stratified by SHR tertiles (low < 0.97, medium 0.97–1.31, high > 1.31). The cumulative survival rate in the high SHR group was significantly lower than in the medium and low SHR groups (log-rank $p < 0.001$).

Subgroup analysis

Table 3 and Fig. 3 present the association between SHR and 90-day mortality across predefined subgroups. The effect of SHR was directionally consistent across all subgroups, with no significant interactions detected (sex interaction $p = 0.338$, diabetes $p = 0.503$, sepsis $p = 0.254$, CKD $p = 0.662$, AKI $p = 0.791$). Of note, SHR was not significantly associated with 90-day mortality in non-sepsis patients (HR 0.98, 95% CI 0.64–1.52, $p = 0.943$), whereas the association was significant in sepsis patients (HR 1.22, 95% CI 1.11–1.33, $p < 0.001$), suggesting that the prognostic value of SHR may be more prominent in patients with sepsis. However, the wide 95% confidence interval (0.64–1.52) in the non-sepsis subgroup indicates that a clinically meaningful effect cannot be ruled out. The non-sepsis subgroup had a relatively small sample size (n = 612), and this negative finding warrants validation in larger studies.

Table 3
Subgroup Analysis of the Association Between SHR and 90-Day Mortality

Subgroup	Total	event%	Followup Time	Crude HR 95CI	Crude *P* value	Adj HR 95CI	Adj *P* value	*P* for.interaction
Gender								
Female	1105	306 (27.7)	79859.9	1.23 (1.05 ~ 1.44)	0.009	1.32 (1.11 ~ 1.58)	0.002	0.338
Male	1635	413 (25.3)	119852.5	1.16 (1.04 ~ 1.3)	0.008	1.16 (1.03 ~ 1.3)	0.014	
Diabetes								
NO	1491	405 (27.2)	107737.3	1.2 (1.08 ~ 1.33)	< 0.001	1.23 (1.11 ~ 1.36)	< 0.001	0.503
YES	1249	314 (25.1)	91975.1	1.15 (0.99 ~ 1.34)	0.063	1.14 (0.97 ~ 1.35)	0.107	
Sepsis								
NO	612	112 (18.3)	48275.2	1 (0.67 ~ 1.5)	0.998	0.98 (0.64 ~ 1.52)	0.943	0.254
YES	2128	607 (28.5)	151437.2	1.17 (1.06 ~ 1.28)	0.001	1.22 (1.11 ~ 1.33)	< 0.001	
CKD								
NO	2029	506 (24.9)	149445.4	1.27 (1.09 ~ 1.47)	0.002	1.23 (1.05 ~ 1.44)	0.009	0.662
YES	711	213 (30)	50267	1.12 (0.99 ~ 1.27)	0.071	1.16 (1.03 ~ 1.3)	0.011	
AKI								
NO	420	76 (18.1)	33015.5	1.22 (0.83 ~ 1.79)	0.319	1.17 (0.79 ~ 1.73)	0.439	0.791
YES	2320	643 (27.7)	166696.9	1.17 (1.07 ~ 1.28)	0.001	1.2 (1.1 ~ 1.32)	< 0.001	

Adjusted for age, age², sex, CCI, sepsis-3, CKD, diabetes, and AKI, except the stratifying variable. P-interaction from likelihood ratio test comparing models with and without the interaction term.

Restricted cubic spline analysis

Figure 4 presents the restricted cubic spline analysis of SHR and 90-day mortality risk. SHR showed a positive linear association with mortality (P for overall = 0.001; P for non-linearity = 0.442). Figure 5 shows the RCS analysis for the glycemic gap, which similarly demonstrated a positive linear association (P for overall = 0.009; P for non-linearity = 0.499).

Sensitivity analyses

Five sensitivity analyses were performed to test the robustness of the findings (Additional files 1–5):

Additional file 1 (age specification): replacing age-squared with a linear age term resulted in negligible changes in the SHR HR (< 5% difference).

Additional file 2 (excluding diabetes): excluding diabetes from the adjustment models did not alter the strength of the SHR association.

Additional file 3 (excluding extreme SHR values): excluding patients with SHR below the 0.5th percentile or above the 99.5th percentile yielded stable and significant SHR effects.

Additional file 4 (additional SOFA adjustment): after additionally adjusting for the SOFA score in the sepsis subgroup (n = 2,128), the SHR HR remained consistent with the primary analysis.

Additional file 5 (proportional hazards assumption test): Schoenfeld residual tests confirmed that both SHR (p = 0.354) and the global model (p = 0.100) satisfied the proportional hazards assumption.

Discussion

Main findings

In this MIMIC-IV-based study, we systematically compared the associations of SHR, glycemic gap, and HGI with 28-day and 90-day mortality in 2,740 ICU patients with pneumonia. The main findings were: (1) SHR was consistently and positively associated with both 28-day and 90-day mortality across all four sequentially adjusted models, making it the most robust prognostic metric; (2) per-standard-deviation increments of the glycemic gap were significantly associated with mortality, but the continuous variable effect size was minimal; (3) HGI lost statistical significance after full adjustment for disease severity and comorbidities; and (4) SHR exhibited a positive linear dose-response relationship with mortality, and this association was not modified by diabetes status, sex, CKD, or AKI, but was not significant in non-sepsis patients.

Differences among SHR, glycemic gap, and HGI: from formula definition to clinical interpretation

The central finding of this study is the superiority of SHR over the glycemic gap and HGI in prognostic assessment; this difference can be explained by the formula definitions and physiological implications of the three metrics.

SHR (admission glucose / eAG) is a ratio that reflects the degree of stress hyperglycemia relative to the patient's baseline glycemic level. This ratio inherently adjusts for inter-individual differences in chronic glycemia: for the same admission glucose level (e.g., 200 mg/dL), a non-diabetic patient with HbA1c of 5.5% has an eAG of approximately 111 mg/dL and an SHR of approximately 1.80, whereas a diabetic patient with HbA1c of 8.0% has an eAG of approximately 183 mg/dL and an SHR of approximately 1.09. Although the absolute glucose values are similar, the relative stress degree is substantially higher in the non-diabetic patient, consistent with the clinical observation known as the "diabetic paradox" in which non-diabetic patients with stress hyperglycemia have worse outcomes [5, 7]. Marik et al. [25] also noted that stress hyperglycemia is fundamentally an adaptive survival response and that excessive glucose lowering may be harmful.

In contrast, the glycemic gap (admission glucose – eAG) is an absolute difference whose magnitude is highly correlated with the absolute glucose level. When admission glucose is high (as in patients with poorly controlled diabetes), the glycemic gap may be large even when the stress degree is minimal, thereby introducing confounding. This explains the paradoxical finding in our study that the glycemic gap as a continuous variable yielded OR/HR of 1.00 (despite significant per-SD increments)—the absolute scale of the metric masks its clinical meaning. Jensen et al. [13] observed a similar phenomenon in a prospective cohort of community-acquired pneumonia, in which only extreme quartiles of the glycemic gap were significantly associated with 90-day mortality, whereas the continuous variable showed no significant association.

HGI (measured HbA1c − predicted HbA1c) reflects the deviation in an individual's hemoglobin glycation propensity rather than acute stress status. A higher HGI indicates that HbA1c is higher than expected for a given glucose level. In our study, HGI showed a spurious protective effect in unadjusted models (OR/HR < 1, i.e., lower HGI associated with higher mortality risk), but this association lost significance after full adjustment (Model 3). This pattern suggests that lower HGI may merely be an epiphenomenon of disease severity—inflammatory response, anemia, and blood transfusion in critically ill patients can all lower HbA1c levels. However, Luethi et al. [26] demonstrated that ICU admission HbA1c reliably reflects pre-admission glycemic control; thus, low HGI more likely indicates disease severity rather than a true low glycation propensity. Hempe et al. [11] also noted in the ACCORD trial that the prognostic value of HGI depends on the intensity of glucose control and treatment context rather than being an intrinsic trait independent of clinical status. Furthermore, the HGI prediction formula used in our study was derived from the study population itself, and external validation in independent ICU pneumonia cohorts is warranted before its clinical application can be recommended.

Comparison with previous studies

The SHR effect size in our study (Model 3, 90-day HR 1.20, 95% CI 1.10–1.32) is consistent with recent MIMIC-based studies. Zhang et al. [16] reported a J-shaped association between SHR and all-cause mortality in a general ICU population, and Zhang et al. [14] found SHR to be independently associated with in-hospital mortality in sepsis patients (OR 2.08). Our study focused on ICU pneumonia specifically and provides the first head-to-head comparison of the three metrics within the same cohort, addressing a gap in the literature. Bai et al. [27] also confirmed that SHR was significantly associated with in-hospital mortality in patients with respiratory failure (HR 1.22), further supporting the prognostic value of SHR in critically ill patients. Liu et al. [17] reported a J-shaped association between SHR and adverse outcomes in diabetic patients with pneumonia, which differs from our RCS results, possibly reflecting differences in study population characteristics or adjustment strategies.

Two recent meta-analyses have provided high-level evidence regarding the prognostic value of SHR. Esdaile et al. [28] included 32 cardiovascular studies (80,010 patients) and found that high SHR was significantly associated with all-cause mortality risk (RR 1.67, 95% CI 1.46–1.91). Chen et al. [29] included 39 critical care studies (102,414 patients) and further confirmed SHR as a robust predictor of mortality in critically ill patients. Of note, although the effect size in our study is somewhat lower than the pooled effect sizes reported in these meta-analyses, this difference is expected given our more rigorous adjustment strategy (including age-squared and disease severity scores).

Notably, SHR was not significantly associated with mortality in the non-sepsis pneumonia subgroup (HR 0.98, 95% CI 0.64–1.52, p = 0.943). This finding parallels the positive results reported by Zhang et al. [14] in sepsis patients and may suggest that the prognostic value of SHR is more pronounced in sepsis-driven stress states. However, the wide confidence interval in the non-sepsis subgroup precludes definitive conclusions about the absence of a clinically meaningful association. Non-sepsis pneumonia patients have a relatively milder stress response with limited glycemic elevation, resulting in a narrower range of SHR variation and potentially insufficient statistical power. From a clinical perspective, these findings suggest that SHR may be best suited for risk stratification in sepsis-associated pneumonia; for non-sepsis pneumonia, further studies with adequate power are needed before firm recommendations can be made.

Interpretation of RCS findings

Restricted cubic spline analysis showed a positive linear association between SHR and 90-day mortality (P for overall = 0.001; P for non-linearity = 0.442), with mortality risk increasing steadily as SHR increased, without significant J-shaped or U-shaped trends. The RCS analysis for the glycemic gap similarly showed a positive linear relationship (P for overall = 0.009; P for non-linearity = 0.499). This linear pattern is consistent with the findings of Ge et al. [30] in critically ill patients with acute heart failure but differs from the J-shaped association reported by Zhang et al. [16], which may reflect differences in the pathophysiological characteristics of hyperglycemia in pneumonia patients compared with general ICU populations.

Clinical implications

Our study has the following clinical implications: (1) in glycemic assessment of ICU patients with pneumonia, SHR offers greater prognostic value than the glycemic gap or HGI and should be prioritized; (2) as a unitless ratio, SHR is unaffected by absolute glucose and HbA1c units, facilitating cross-population comparison and clinical implementation; and (3) for sepsis patients with pneumonia, elevated SHR should be considered a high-risk signal warranting more intensive monitoring and potential intervention. Moreover, SHR calculation requires only two routinely available laboratory tests (admission glucose and HbA1c), incurs no additional cost, and has excellent clinical operability.

Limitations

This study has several limitations. First, as a retrospective cohort study, residual confounding cannot be completely excluded, although we maximized control for known confounders through multi-model adjustment and multiple sensitivity analyses. Second, this study was based on the single-center MIMIC-IV database, and the generalizability of findings may be limited. Third, SHR, glycemic gap, and HGI were all calculated from the first glucose and HbA1c measurements after ICU admission and do not capture dynamic changes in glycemic metrics. Fourth, glucose data from the pre-ICU period were not included in the analysis. Fifth, the HGI prediction formula was derived from our study population and has not been externally validated. Sixth, the non-sepsis subgroup had a relatively small sample size (n = 612), and the negative finding for SHR in this subgroup may be limited by statistical power. Future multicenter prospective studies are needed to validate our findings and to explore whether SHR-guided glycemic management strategies can improve clinical outcomes in ICU patients with pneumonia.

Conclusions

In ICU patients with pneumonia, SHR is a more robust prognostic indicator of mortality risk than the glycemic gap and HGI. SHR is independently and positively associated with both 28-day and 90-day mortality, and this association remained stable across multiple sensitivity analyses. Sepsis status may modify the prognostic value of SHR. As a simple, cost-free, and readily available metric, SHR may serve as an effective tool for risk stratification in ICU patients with pneumonia.

Abbreviations

AKI
acute kidney injury
APSIII
Acute Physiology Score III
BMI
body mass index
CCI
Charlson comorbidity index
CI
confidence interval
CKD
chronic kidney disease
eAG
estimated average glucose
HbA1c
hemoglobin A1c
HGI
hemoglobin glycation index
HR
hazard ratio

ICD
International Classification of Diseases
ICU
intensive care unit
MIMIC-IV
Medical Information Mart for Intensive Care IV
OASIS
Oxford Acute Severity of Illness Score
OR
odds ratio
RCS
restricted cubic spline
SAPSII
Simplified Acute Physiology Score II
SHR
stress hyperglycemia ratio
SOFA
Sequential Organ Failure Assessment
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. The MIMIC-IV database was approved by the Institutional Review Board of the Massachusetts Institute of Technology (MIT). All patient information in the MIMIC-IV database is de-identified. Therefore, ethics approval and informed consent were waived for this study.

Clinical trial number

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The dataset(s) supporting the conclusions of this article are available in the MIMIC-IV repository, https://physionet.org/content/mimiciv/, https://doi.org/10.13026/kpb9-mt58 (version 3.1) [19, 20]. MIMIC-IV is a de-identified, publicly available critical care database; access requires credentialed approval from PhysioNet. The code used for statistical analysis is available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the 2024 Key Medical and Health Discipline of Shandong Province (Construction Unit) (No. Lu Wei Han [2024] No. 449).

Authors' contributions

MC: conceptualization, methodology, investigation, writing—original draft. HR: funding acquisition. HS: conceptualization, supervision, writing—review and editing, corresponding author. All authors read and approved the final manuscript.

Acknowledgements

The authors wish to thank the team of the Laboratory for Computational Physiology from the Massachusetts Institute of Technology (LCP-MIT) for keeping the MIMIC-IV databases available.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used generative AI tools (including large language model-based chat assistants) to assist with language polishing and minor structural editing of the manuscript text. AI tools were not used to generate, analyze, or interpret the study data, nor to draw scientific conclusions. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Figures

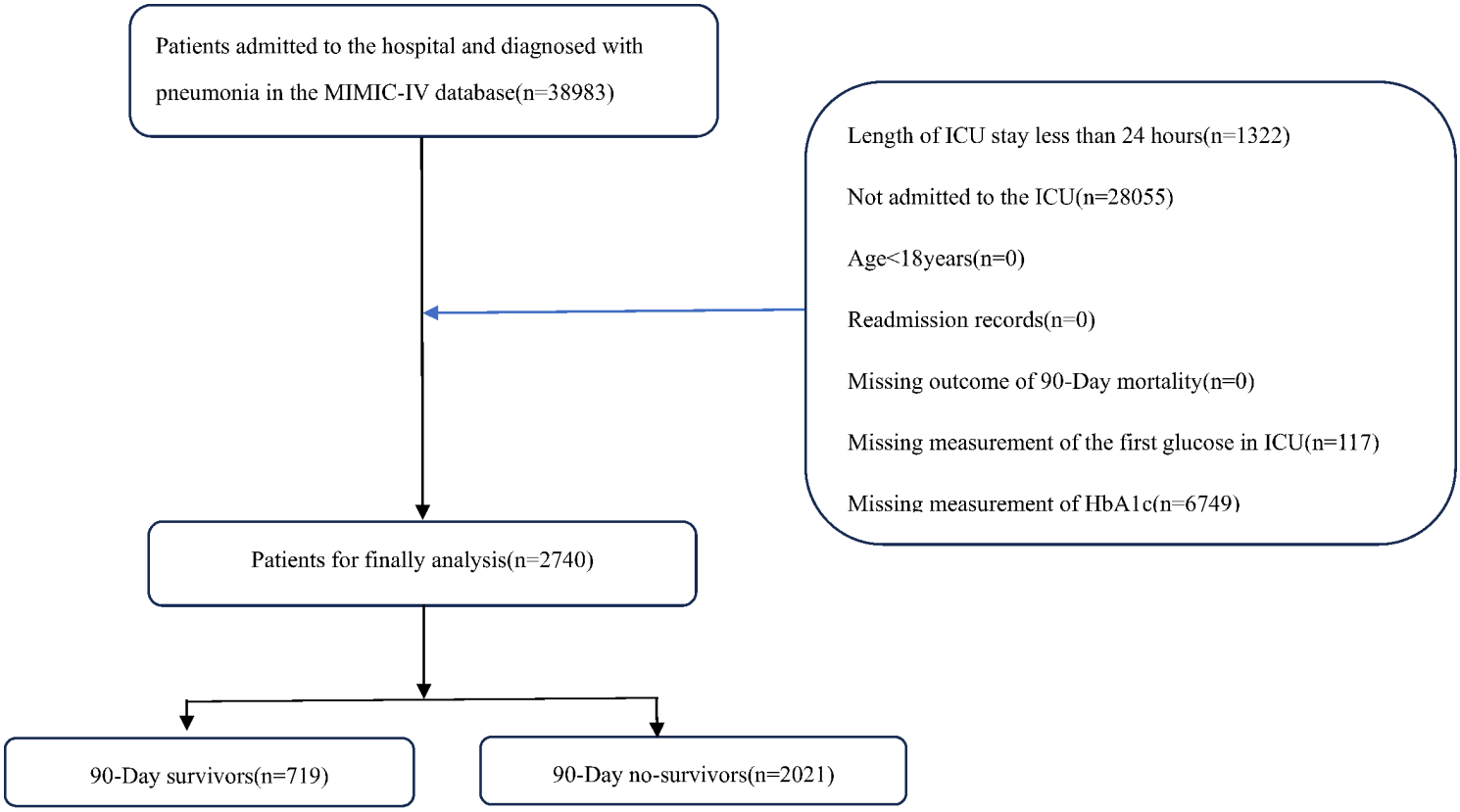

Figure 1. Flow chart of participant selection

Figure 1

See image above for figure legend.

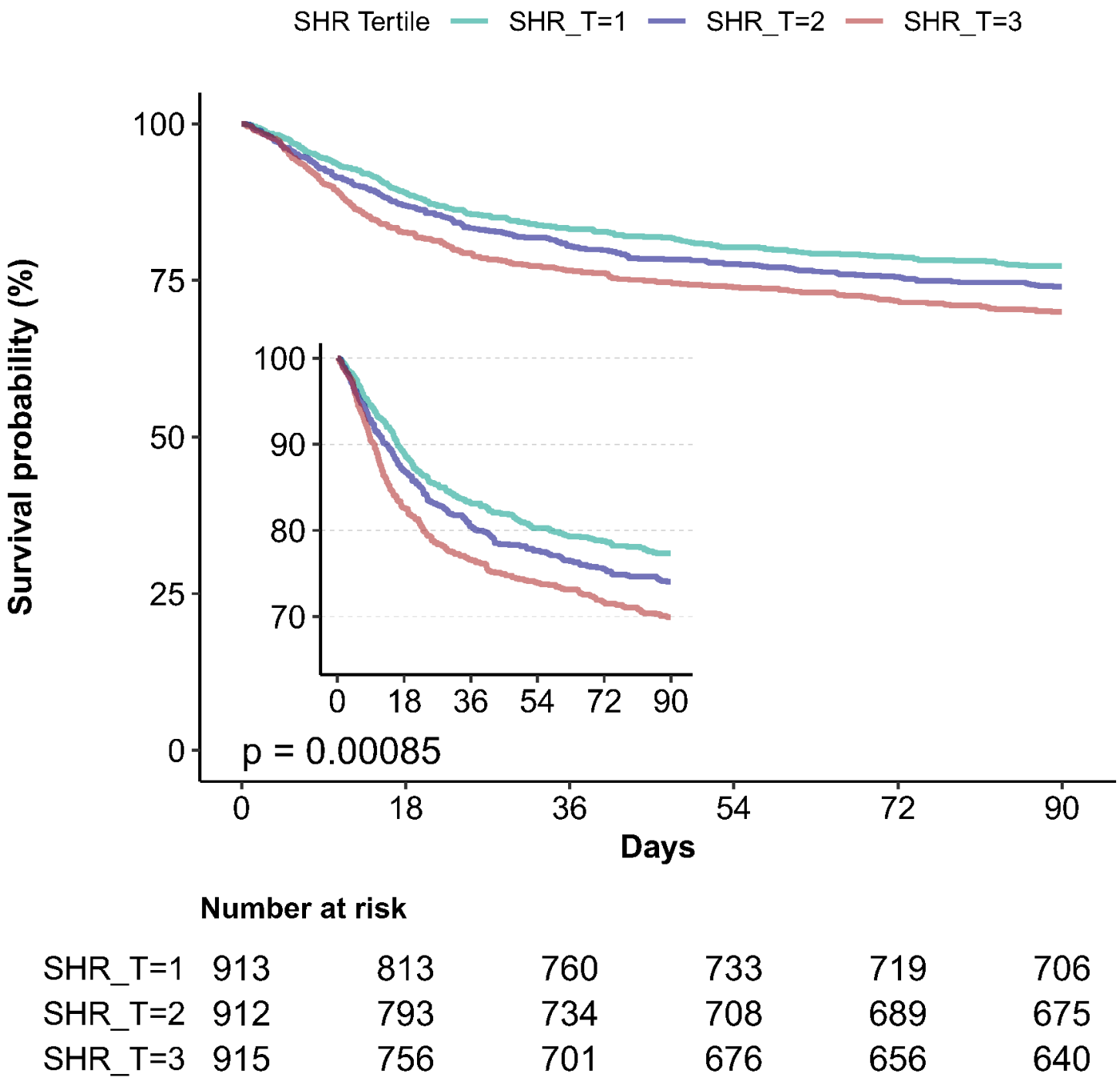

Figure 2

Kaplan-Meier curves of 90-day survival according to SHR tertiles (low < 0.97, medium 0.97–1.31, high > 1.31). The log-rank test was used for between-group comparisons.

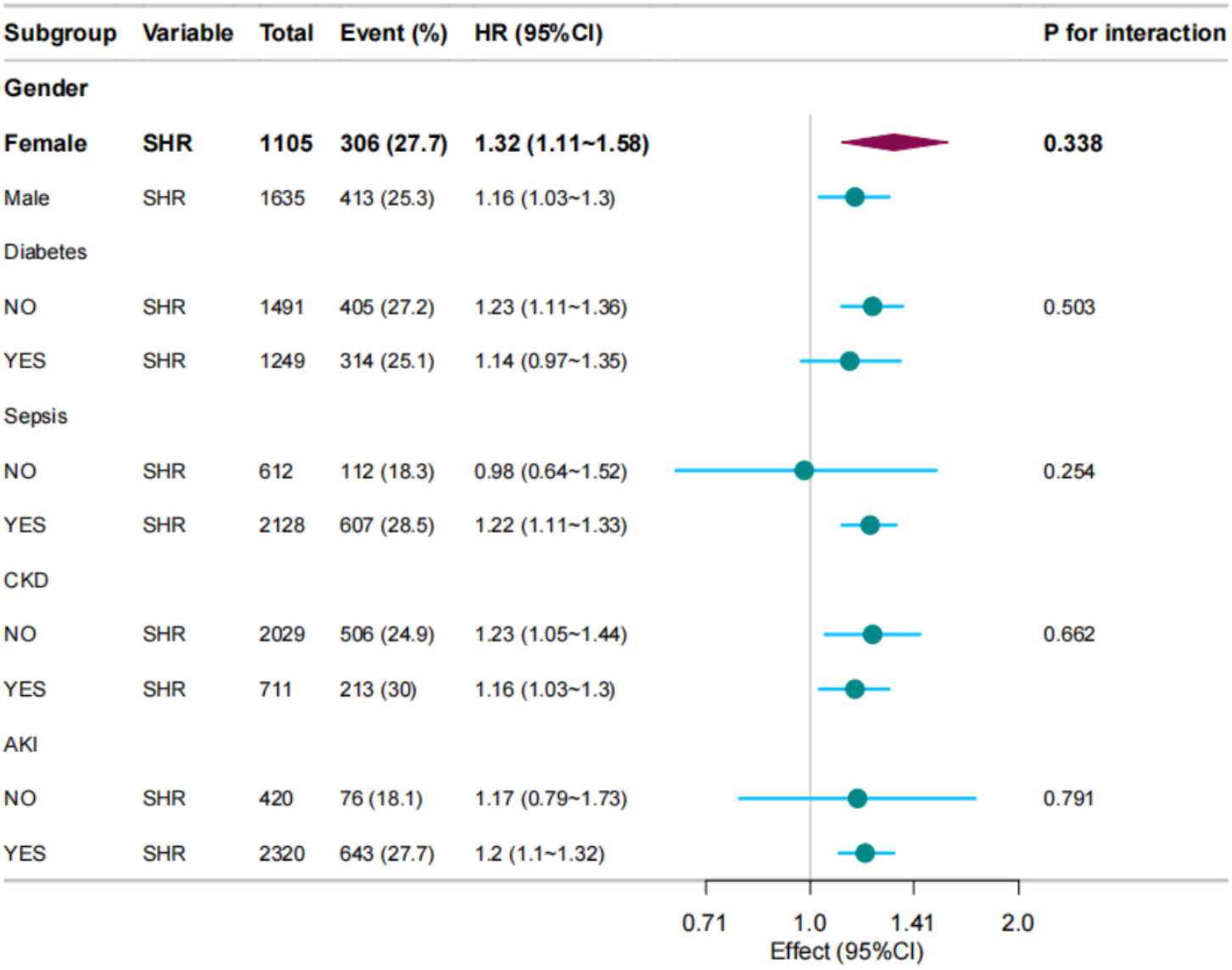

Figure 3

Stratified analysis of SHR and 90-day mortality across prespecified subgroups (sex, diabetes, sepsis, chronic kidney disease, and acute kidney injury). Squares represent hazard ratios; horizontal lines represent 95% confidence intervals. Interaction p values were calculated using likelihood ratio tests.

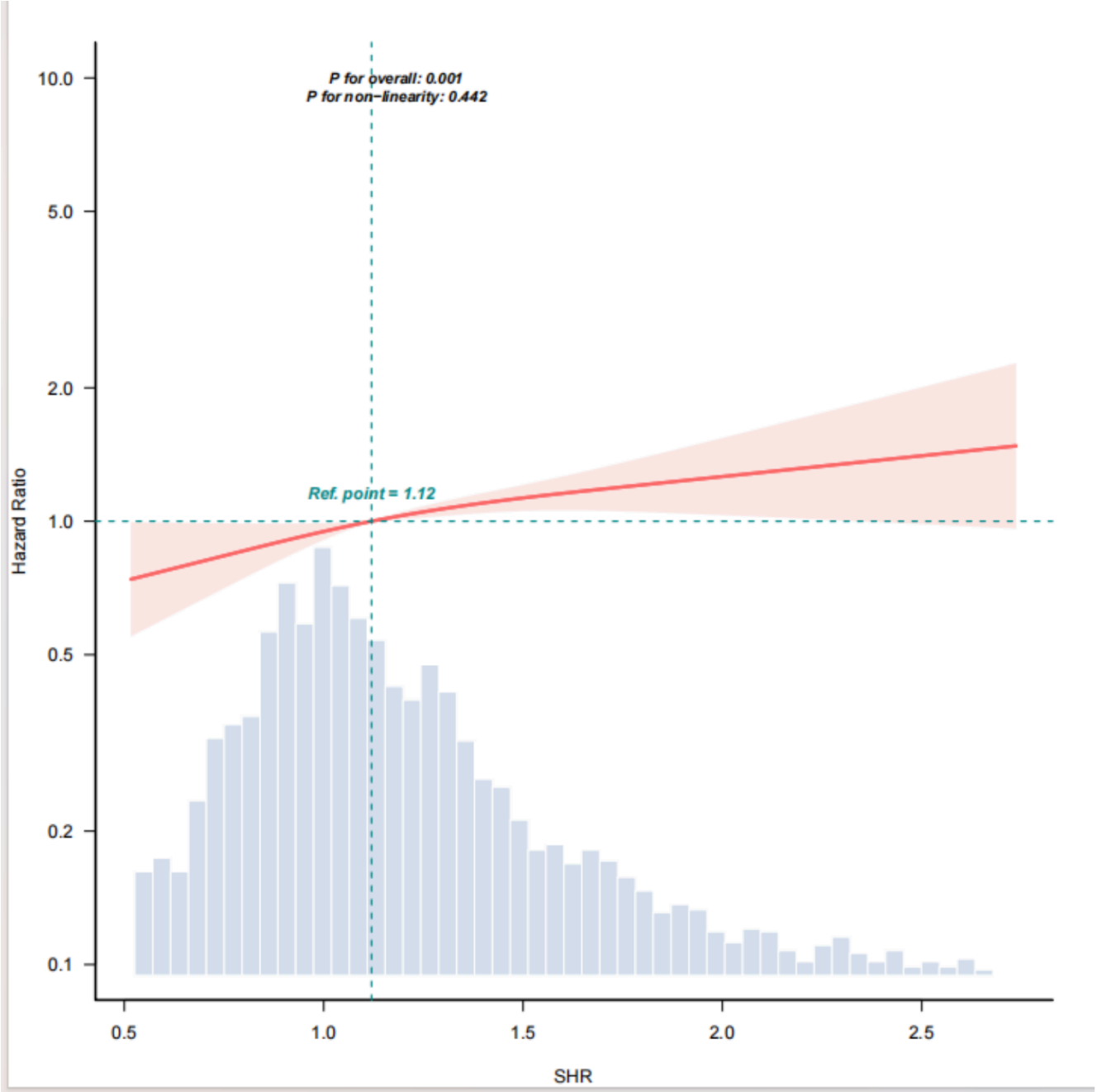

Figure 4

Restricted cubic spline analysis of the association between SHR and 90-day mortality. The solid line represents the adjusted hazard ratio; the shaded area represents the 95% confidence interval. Knots were placed at the 5th, 35th, 65th, and 95th percentiles.

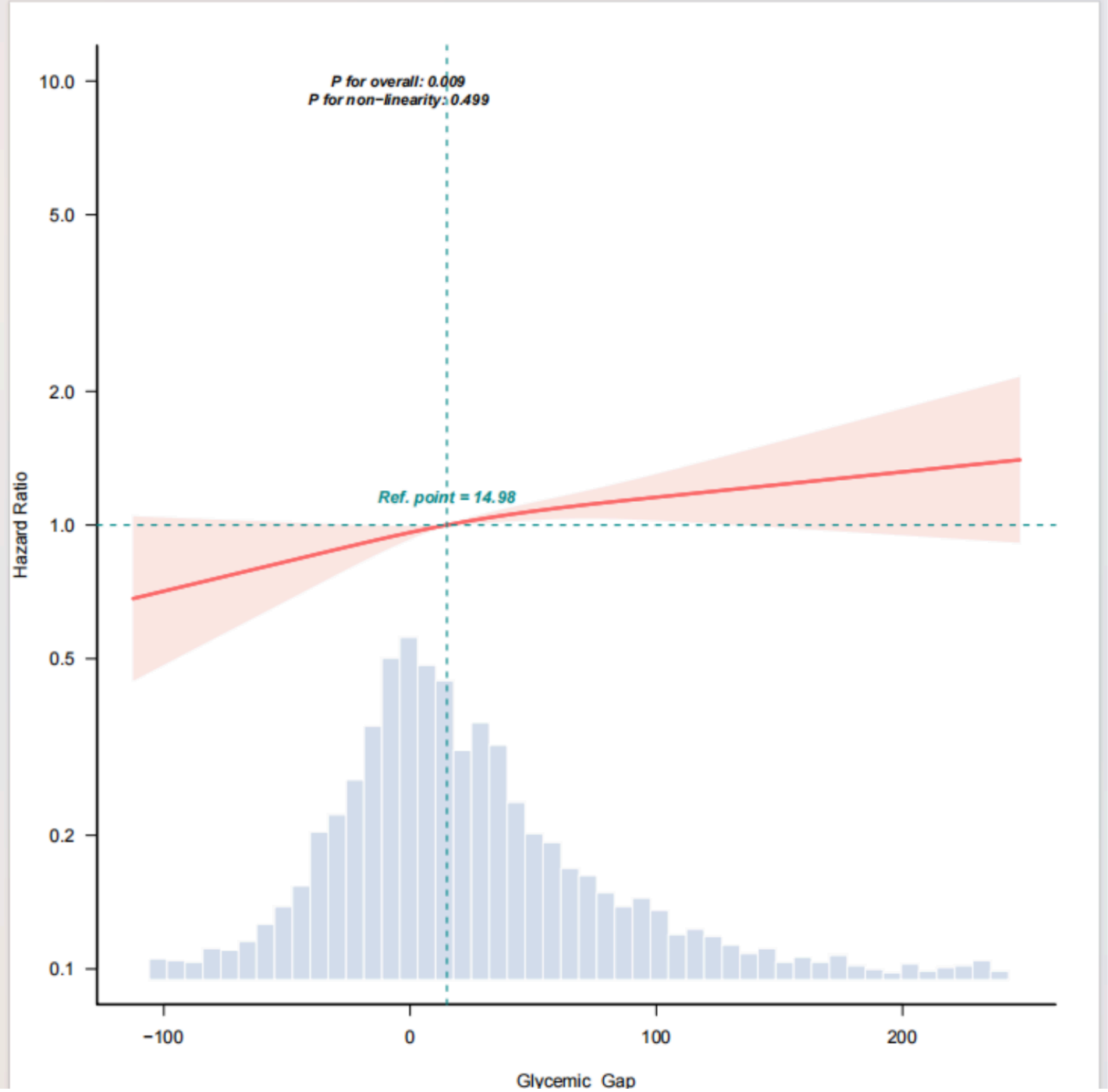

Figure 5

Restricted cubic spline analysis of the association between the glycemic gap and 90-day mortality. The solid line represents the adjusted hazard ratio; the shaded area represents the 95% confidence interval. Knots were placed at the 5th, 35th, 65th, and 95th percentiles.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1.SensitivityAnalysisComparingAgeSpecificationintheFullyAdjustedModel.doc

- Additionalfile2.SensitivityAnalysisExcludingDiabetesfromtheAdjustmentModel.doc
- Additionalfile3.SensitivityAnalysisExcludingExtremeSHRValues.doc
- Additionalfile4.SensitivityAnalysisWithAdditionalAdjustmentforSOFAScore.doc
- Additionalfile5.ProportionalHazardsAssumptionTest.doc