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ORIGINAL RESEARCH

The Joint Effect of Stress Hyperglycemia Ratio and Inflammatory Burden Exacerbates Mortality Risk and Prolongs ICU Stay in Sepsis: A Combined Analysis

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Background: Previous studies have shown that stress-induced increases in blood sugar and inflammation are closely associated with the mortality risk in sepsis patients. The stress hyperglycemia ratio (SHR) and the aggregate index of systemic inflammation (AISI) are commonly used as key indicators to assess stress-induced blood glucose levels and inflammatory load. However, the relationship between these two factors and adverse outcomes in sepsis patients remains unclear.

Methods: This study adopted a retrospective cohort study design, selecting 1509 patients with sepsis from a self-registered cohort and the MIMIC-IV database. Cox regression analyzed associations between SHR, AISI, their interaction, and mortality. Cumulative risk curves evaluated mortality across groups, and the C-index assessed predictive performance of the combined metric. We also compared hospitalization and ICU stay durations among groups.

Results: The Cox regression analysis showed that both elevated SHR and AISI were strongly associated with an increased risk of death in sepsis patients, and their combination further amplified this risk. Specifically, the high SHR and high AISI groups had significantly higher mortality compared to the low SHR and low AISI groups. Additionally, the combined effect of SHR and AISI achieved a C-index of 0.7 for overall mortality, demonstrating a stronger predictive ability. The ICU stay duration was also significantly longer in the high SHR and high AISI groups.

Conclusion: The combined effects of SHR and AISI are strongly correlated with increased mortality and prolonged ICU stays in sepsis patients. Early control of stress glucose levels and inflammation may not only reduce death risk but also shorten ICU stays, aiding precision medicine and potentially reducing economic burden.

Keywords: stress hyperglycemia ratio, aggregate index of systemic inflammation, intensive care unit, sepsis, mortality risk

Introduction

Sepsis is a severe and life-threatening disease that poses a significant threat to human health.[1–3] Its incidence and mortality rates are particularly high in intensive care units.[4] In 2017, an estimated 48.9 million people worldwide were diagnosed with sepsis, and 11 million of them died from the disease.[4] In recent years, research on sepsis has increasingly focused on inflammatory responses and immune system dysfunction.[5,6] Studies on inflammatory responses have shown that sepsis patients experience uncontrolled inflammatory reactions and an imbalance between anti-inflammatory and pro-inflammatory responses, leading to multi-organ dysfunction.[6–8] This imbalance may explain the high mortality rate among sepsis patients. Similarly, research on immune dysfunction in sepsis patients has found that these individuals experience excessive activation of lymphocytes in the early stages, followed by functional inhibition, both of which are associated with poor prognosis.[9–12] Furthermore, due to these uncontrolled responses, sepsis patients often enter a state of physiological stress, resulting in increased secretion of stress-related hormones such as adrenaline and glucagon. These hormones exacerbate blood sugar fluctuations, further increasing the risk of death.[13–15] Therefore, immune imbalance, inflammatory response activation, and stress-induced blood sugar fluctuations collectively contribute to the high mortality risk in sepsis patients.

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Currently, the main indicators used for the early identification of sepsis severity are the Sequential Organ Failure Assessment (SOFA) score and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score.[16–18] These scores primarily evaluate patients' condition using laboratory test results. However, they do not account for other crucial factors that influence sepsis severity, such as immune-inflammatory status and stress-related glucose levels.

Stress hyperglycemia ratio (SHR), as a primary indicator of blood glucose levels under stress conditions, takes into account both the patient's previous blood glucose control status and the impact of stress on blood glucose. This allows for a more accurate assessment of the patient's blood glucose levels under stress.[19,20] Previous studies have consistently shown that elevated SHR levels are closely associated with various diseases and increased mortality risks, including cardiovascular diseases.[21–23] In clinical practice, relying solely on indicators such as white blood cells, C-reactive protein, or procalcitonin to assess inflammatory conditions has limitations. These markers cannot fully reflect the immune and inflammatory status of the body. Therefore, recent research has shifted focus to developing novel inflammatory indicators based on blood cell counts, such as the systemic inflammatory response index (SIRI), systemic immune-inflammatory index (SII), neutrophil-to-lymphocyte ratio (NLR), and aggregate index of systemic inflammation (AISI).[24–26] However, indicators such as NLR, SIRI and SII may have certain limitations, as they only incorporate individual or a limited number of blood cell types, making it difficult to fully reflect the body's overall stress status and inflammatory level. In contrast, AISI integrates a more comprehensive panel of blood cell parameters, demonstrating stronger systematic and integrative characteristics. It not only reflects the systemic inflammatory condition of the body but also incorporates data from multiple immune pathways, thereby providing a more holistic assessment of inflammatory status.[24,27,28] Recent studies also suggest that both SHR and AISI are linked to cardiovascular diseases and postoperative infections, highlighting the significant role of their combination in the onset and progression of diseases.[28–30] However, despite the fact that patients with sepsis often present with elevated stress and inflammatory responses upon admission, the combined impact of SHR (representing stress-induced blood glucose) and AISI (reflecting immune-inflammatory conditions) on the mortality risk in sepsis patients remains unexplored.

This study aimed to investigate the combined effect of glucose stress, as indicated by the SHR, and inflammatory burden, as represented by the AISI, on the mortality risk of sepsis patients at the time of admission. Our goal was to identify concise and reliable predictive indicators for sepsis, enabling early identification of high-risk patients. This early identification would facilitate timely intervention, improving treatment outcomes and reducing the occurrence of adverse outcomes and mortality risk.

Material and Methods

Study Population

This study included patients diagnosed with sepsis based on International Classification of Diseases (ICD) (9th and 10th editions) in the MIMIC-IV database, as well as those admitted to the Intensive Care Unit (ICU) of Xinxiang Central Hospital between January 2023 and August 2025, with a confirmed diagnosis of sepsis. These patients formed the study population. The exclusion criteria were: 1) age under 18 years; 2) ICU stay of less than 24 hours within the first 24 hours after admission; 3) missing key covariate data (glycated hemoglobin, platelets, neutrophils, monocytes, and lymphocytes) within the first 24 hours after ICU admission. After applying these exclusion criteria, a total of 1509 patients were included in the study (Figure 1).

This research was approved by the Ethics Committee of Xinxiang Central Hospital (No. XCH20221204010). All procedures adhered to the principles outlined in the Helsinki Declaration, and written informed consent was obtained from all patients or their families. This study was conducted based on data from the MIMIC database. As a public and open-access resource, the MIMIC database is accessible to researchers worldwide for secondary analysis.

Data Collection

The general information, laboratory tests, disease history, and medication usage of the participants were collected from electronic medical records and medical insurance data. Relevant data from the MIMIC-IV database were extracted using Structured Query Language through PostgreSQL (version 13.7.1) and Navicat Premium (version 16). The data were categorized into three main aspects: (1) demographic characteristics, including age, gender, body mass index (BMI),

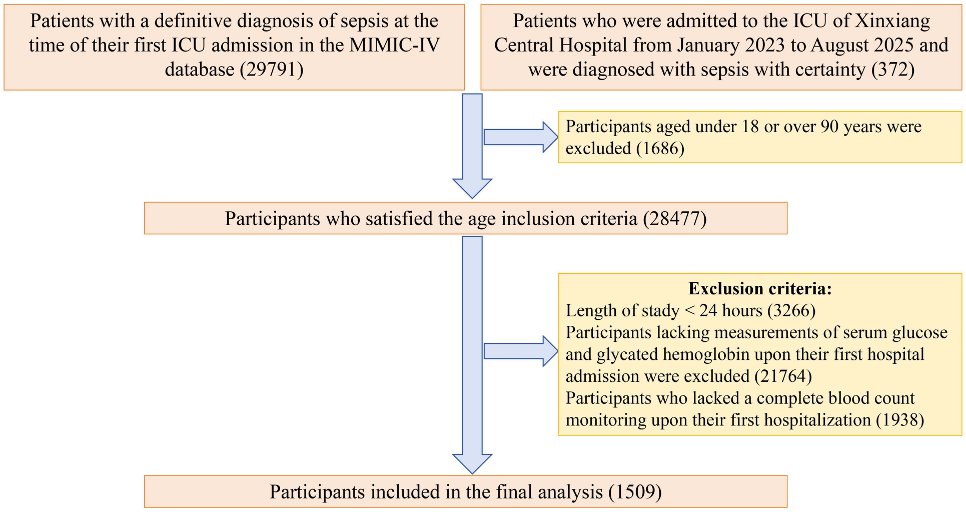

Figure 1 Flowchart for selection of study populations.

systolic blood pressure (SBP), and diastolic blood pressure (DBP); (2) laboratory parameters, including white blood cell count (WBC), platelet count, neutrophil count, lymphocyte count, monocyte count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, creatinine, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), B-type natriuretic peptide (BNP), blood glucose, glycated hemoglobin (HbA1c), Sequential Organ Failure Assessment (SOFA), and Acute Physiology and Chronic Health Evaluation II (APACHE II); (3) medical history, including previous diseases such as chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), heart failure, hypertension, and diabetes. All indicators were collected within 24 hours of the patient's admission to the intensive care unit. Detailed descriptions of the patient's previous and current diseases can be found in the supplementary materials (Supplementary Materials).

Calculations of SHR and AISI

Based on the results of relevant blood and biochemical tests, SHR and AISI are calculated. The specific calculation method is as follows:

SHR = fasting blood glucose (FBG) (mg/dl)/ [28.7 x HbA1c (%)– 46.7].[21,31]

AISI = (neutrophil count × platelet count × monocyte count)/lymphocyte count, with all cell counts expressed in units of 10^9/L.[24,32]

Clinical Outcomes

The outcomes of this study include the overall mortality and its subtypes (hospital mortality and 28-day mortality), as well as the length of hospital stay (including both the length of stay in the ICU and the total hospital stay for sepsis patients).

Statistical Analysis

Based on clinical outcomes, the patients in the study were divided into two groups: the survival group and the death group. Continuous variables were expressed as either the mean ± standard deviation (SD) or the median (interquartile range), depending on their distribution, while categorical variables were presented as frequencies and percentages. Patients were further classified into three groups based on the tertiles of SHR and AISI. We used COX regression analysis and adjusted for multiple models to examine the relationships between SHR, AISI, and various mortality risks.

Next, we investigated the dose-response relationship between SHR and AISI and the risk of sepsis-related death using restricted cubic spline (RCS) curves. A two-stage comparative analysis was then performed based on the identified inflection points. Additionally, a new comprehensive prediction index was constructed using the inflection points from the RCS analysis

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of SHR and AISI. We employed COX analysis to explore the relationship between this new index and both overall and subtype mortality risks in sepsis patients. Cumulative risk curves were drawn to assess the death risk across different groups.

Furthermore, C-statistic analysis was conducted to compare the predictive power of the combination of SHR and AISI with that of a single indicator. A comparative analysis of the length of stay in the intensive care unit and total hospital stay was also performed among the different groups. Lastly, extensive subgroup analyses were conducted to verify the stability of our results. The specific details of the statistical analysis are presented in detail in the Supplementary Materials.

The bilateral p-values were less than 0.05, indicating statistical significance. All statistical analyses in this paper were conducted using R software (version 4.4.3).

Table 1 Baseline Characteristics of the Study Population

Characteristic	**Overall**	**Survival Group**	**Death Group**	**P Value**
N	**1509**	**1151**	**358**	
Gender (%)				0.016
Female	650 (43.07%)	476 (41.36%)	174 (48.60%)	
Male	859 (56.93%)	675 (58.64%)	184 (51.40%)	
Age (years)	66.78±15.27	65.53±14.87	70.79±15.85	<0.001
BMI (kg/m^2)	29.11±8.52	29.48±8.82	27.94±7.37	0.003
SBP (mmHg)	121.94±18.69	122.17±17.92	121.20±20.97	0.391
DBP (mmHg)	64.94±11.72	65.24±11.72	63.97±11.70	0.074
Laboratory tests				
WBC (10^9/L)	12.63±9.28	12.12±7.56	14.26±13.28	<0.001
Platelet count (10^9/L)	218.03±97.56	219.72±97.12	212.58±98.92	0.227
Neutrophil count (10^9/L)	11.39±6.14	11.17±6.07	12.09±6.30	0.013
Monocyte count (10^9/L)	0.90±0.58	0.91±0.59	0.88±0.55	0.424
Lymphocyte count (10^9/L)	2.33±12.99	2.03±9.62	3.28±20.34	0.11
ALT (U/L)	99.02±566.64	96.29±616.90	107.80±360.94	0.737
AST (U/L)	174.08±1135.89	144.88±971.23	267.99±1549.18	0.073
Albumin (g/dL)	3.30±0.60	3.34±0.57	3.19±0.64	<0.001
Creatinine (mg/dL)	1.60±1.66	1.57±1.72	1.69±1.45	0.242
HDL (mg/dL)	45.09±17.76	44.86±17.57	45.80±18.35	0.381
LDL (mg/dL)	88.15±46.87	90.27±49.02	81.33±38.45	0.002
TG (mmol/L)	146.48±166.04	148.98±172.88	138.42±141.78	0.293
BNP (pg/mL)	7354.61±11,488.48	6818.09±11,066.98	9079.58±12,612.22	0.001
Blood glucose (mg/dL)	159.40±60.44	157.34±59.47	166.02±63.07	0.018
HbA1c (%)	6.69±2.03	6.78±2.13	6.40±1.65	0.002
SOFA score	5.22±3.12	4.87±2.81	6.35±3.75	<0.001
APACHE II score	47.62±19.88	44.59±17.52	57.38±23.57	<0.001
SHR	1.15±0.37	1.11±0.33	1.26±0.48	<0.001
AISI	3009.74±5605.97	2910.53±5466.29	3328.69±6030.20	0.218
Medical history				
Hypertension (%)	577 (38.24%)	417 (36.23%)	160 (44.69%)	0.004
Diabetes (%)	312 (20.68%)	231 (20.07%)	81 (22.63%)	0.297
COPD (%)	120 (7.95%)	89 (7.73%)	31 (8.66%)	0.571
Heart Failure (%)	298 (19.75%)	204 (17.72%)	94 (26.26%)	<0.001
ARDS (%)	1317 (87.28%)	1017 (88.36%)	300 (83.80%)	0.024
CKD (%)	191 (12.66%)	131 (11.38%)	60 (16.76%)	0.008

Notes: Data are presented as mean ± standard deviation, median (interquartile range), or as numbers, and percentages.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell count; ALT, alanine transaminase; AST, aspartate transaminase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; BNP, B-type Natriuretic Peptide; HbA1c, glycosylated hemoglobin; SHR, stress hyperglycemia ratio; AISI, aggregate index of systemic inflammation; COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; CKD, chronic kidney disease.

Results

Basic Characteristics of Participants

This study included a total of 1509 patients diagnosed with sepsis at Xinxiang Central Hospital and the MIMI-IV database. Based on their outcomes, the patients were divided into two groups: the survival group and the death group. Compared to the survival group, patients in the death group were older, had a higher proportion of females, and had a lower BMI. Regarding test results, the death group exhibited relatively higher WBC, neutrophil count, BNP, and blood glucose levels, while the levels of HbA1c, albumin, and LDL were lower. Additionally, the death group had higher SOFA and APACHE II scores. In terms of medical history, they were more likely to have hypertension, heart failure, ARDS, and CKD. No significant statistical differences were found between the two groups for other covariates (Table 1).

Relationship Between SHR and the Risk of Death Related to Sepsis

To explore the relationship between SHR and the mortality risk of patients with sepsis, a COX regression analysis was conducted. The results indicated that higher SHR levels were strongly associated with increased risks of overall mortality, in-hospital mortality, and 28-day mortality in sepsis patients. Specifically, in the fully adjusted model 4, for every one-unit increase in SHR, the overall mortality risk, in-hospital mortality risk, and 28-day mortality risk increased by 2.222 times [hazard ratio (HR): 2.222, 95% confidence interval (CI): 1.790–2.759], 2.140 times (HR: 2.140, 95% CI: 1.668–2.746), and 2.188 times (HR: 2.188, 95% CI: 1.765–2.712), respectively. Following this, SHR was divided into three groups based on tertiles. The results revealed that, compared with the first group, the overall mortality risk in the second and third groups increased by 30% and 97.7%, respectively; the in-hospital mortality risk increased by 15.9% and 89.5%, respectively; and the 28-day mortality risk increased by 34.8% and 94.4%, respectively. The trend test also yielded statistically significant results (Table 2).

Table 2 Relationship Between SHR and Sepsis-Related Mortality and Its Subtype Risks

Exposure	Model 1	Model 2	Model 3	Model 4
	HR (95% CI) P	HR (95% CI) P	HR (95% CI) P	HR (95% CI) P
Overall mortality				
SHR (per 1unit increase)	2.331 [1.888, 2.878] <0.001	2.397 [1.940, 2.960] <0.001	2.195 [1.778, 2.712] <0.001	2.222 [1.790, 2.759] <0.001
Tertiles of SHR				
Tertile 1	Reference	Reference	Reference	Reference
Tertile 2	1.299 [0.980, 1.721] 0.069	1.240 [0.933, 1.646] 0.138	1.301 [0.977, 1.731] 0.071	1.300 [0.977, 1.730] 0.072
Tertile 3	2.073 [1.594, 2.695] <0.001	2.046 [1.571, 2.664] <0.001	2.001 [1.533, 2.612] <0.001	1.977 [1.512, 2.583] <0.001
P for trend	<0.001	<0.001	<0.001	<0.001
In-hospital mortality				
SHR (per 1unit increase)	2.325 [1.849, 2.923] <0.001	2.310 [1.821, 2.930] <0.001	2.106 [1.657, 2.676] <0.001	2.140 [1.668, 2.746] <0.001
Tertiles of SHR				
Tertile 1	Reference	Reference	Reference	Reference
Tertile 2	1.230 [0.879, 1.721] 0.227	1.182 [0.844, 1.656] 0.330	1.176 [0.838, 1.651] 0.348	1.159 [0.824, 1.630] 0.395
Tertile 3	2.121 [1.556, 2.890] <0.001	2.024 [1.483, 2.761] <0.001	1.948 [1.423, 2.667] <0.001	1.895 [1.382, 2.599] <0.001
P for trend	<0.001	<0.001	<0.001	<0.001
28-day mortality				
SHR (per 1unit increase)	2.353 [1.912, 2.896] <0.001	2.396 [1.944, 2.953] <0.001	2.196 [1.778, 2.712] <0.001	2.188 [1.765, 2.712] <0.001
Tertiles of SHR				
Tertile 1	Reference	Reference	Reference	Reference
Tertile 2	1.355 [1.024, 1.794] 0.034	1.324 [0.999, 1.753] 0.050	1.355 [1.021, 1.798] 0.035	1.348 [1.016, 1.789] 0.038
Tertile 3	2.085 [1.604, 2.711] <0.001	2.051 [1.576, 2.670] <0.001	1.976 [1.515, 2.578] <0.001	1.944 [1.489, 2.539] <0.001
P for trend	<0.001	<0.001	<0.001	<0.001

Notes: Model 1: no covariates were adjusted. Model 2: age, sex, BMI, SBP, and DBP were adjusted. Model 3: Model 2 plus adjustment for ALT, AST, Albumin, Creatinine, HDL-C, LDL-C, TG, and BNP. Model 4: Model 3 plus adjustment for Hypertension, Diabetes, COPD, Heart Failure, ARDS, and CKD.
Abbreviations: SHR, stress hyperglycemia ratio; HR, hazard ratio; CI, confidence interval.

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To further explore the dose-response relationship between SHR and the overall mortality risk, in-hospital mortality risk, and 28-day mortality risk in sepsis patients, we plotted the RCS curve. The results revealed a clear linear correlation (Figure 2). Furthermore, the threshold benefit analysis showed that when SHR exceeded 1.08, 1.08, and 1.09 for overall mortality risk, in-hospital mortality risk, and 28-day mortality risk, respectively, these risks began to increase significantly (Figure 2). Based on the inflection points of the RCS curve, we then performed a two-stage comparative analysis. The results indicated that, compared to those with SHR levels below the inflection point, patients with SHR levels exceeding the inflection point had significantly higher overall mortality risk, in-hospital mortality risk, and 28-day mortality risk (Table 3). These findings suggest that as SHR increases in sepsis patients, their mortality-related risks also rise. This may also imply that controlling stress blood glucose levels at the time of admission could be beneficial in reducing the occurrence of mortality risks.

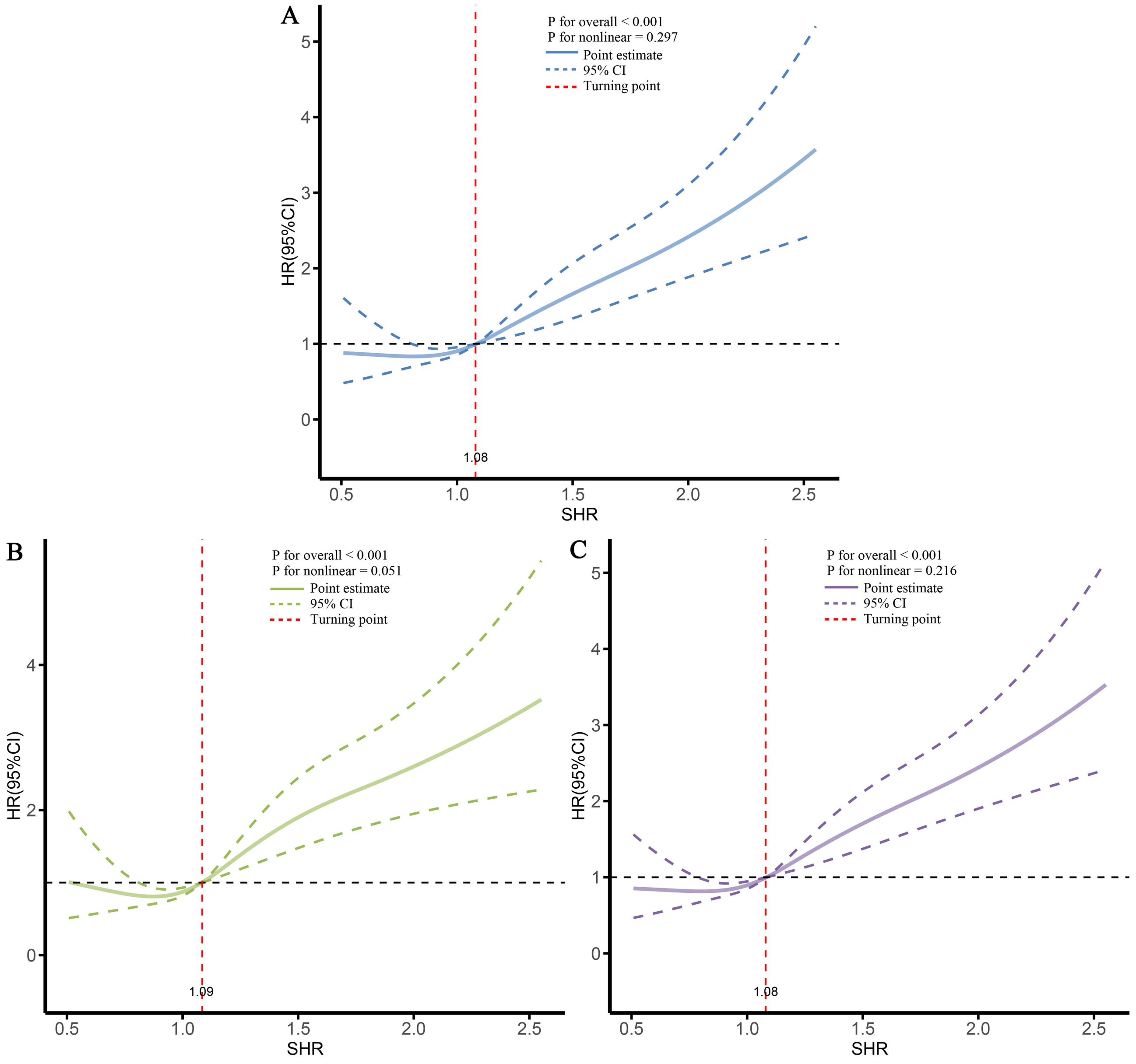

Figure 2 Dose-response relationship between SHR and the risk of death related to sepsis. (**A**) Overall mortality; (**B**) In-hospital mortality; (**C**) 28-day mortality.

Table 3 Two-Stage Comparative Analysis of the Relationship Between SHR and Mortality and Its Subtype Risks Based on the RCS Turning Points

Exposure	Model 1 HR (95% CI) P	Model 2 HR (95% CI) P	Model 3 HR (95% CI) P	Model 4 HR (95% CI) P
Overall mortality				
Turning point	1.08	1.08	1.08	1.08
<= 1.08	Reference	Reference	Reference	Reference
> 1.08	1.779 [1.432, 2.209] <0.001	1.747 [1.404, 2.173] <0.001	1.701 [1.365, 2.119] <0.001	1.693 [1.358, 2.111] <0.001
In-hospital mortality				
Turning point	1.09	1.09	1.09	1.09
<= 1.09	Reference	Reference	Reference	Reference
> 1.09	1.897 [1.475, 2.439] <0.001	1.802 [1.398, 2.322] <0.001	1.742 [1.350, 2.249] <0.001	1.723 [1.333, 2.227] <0.001
28-day mortality				
Turning point	1.08	1.08	1.08	1.08
<= 1.08	Reference	Reference	Reference	Reference
> 1.08	1.895 [1.528, 2.350] <0.001	1.866 [1.502, 2.316] <0.001	1.789 [1.438, 2.226] <0.001	1.777 [1.427, 2.213] <0.001

Notes: Model 1: no covariates were adjusted. Model 2: age, sex, BMI, SBP, and DBP were adjusted. Model 3: Model 2 plus adjustment for ALT, AST, Albumin, Creatinine, HDL-C, LDL-C, TG, and BNP. Model 4: Model 3 plus adjustment for Hypertension, Diabetes, COPD, Heart Failure, ARDS, and CKD.
Abbreviations: SHR, stress hyperglycemia ratio; RCS, restricted cubic spline; HR, hazard ratio; CI, confidence interval.

Table 4 Relationship Between AISI and Sepsis-Related Mortality and Its Subtype Risks

Exposure	Model 1	Model 2	Model 3	Model 4
	HR (95% CI) P	HR (95% CI) P	HR (95% CI) P	HR (95% CI) P
Overall mortality				
AISI (per 1SD)	1.062 [1.009, 1.211] 0.017	1.057 [1.007, 1.110] 0.025	1.055 [1.003, 1.110] 0.039	1.059 [1.006, 1.115] 0.029
Tertiles of AISI				
Tertile 1	Reference	Reference	Reference	Reference
Tertile 2	0.976 [0.719, 1.221] 0.630	0.966 [0.741, 1.258] 0.795	0.962 [0.736, 1.256] 0.775	0.949 [0.725, 1.240] 0.700
Tertile 3	1.334 [1.027, 1.726] 0.012	1.330 [1.025, 1.722] 0.023	1.327 [1.021, 1.719] 0.033	1.322 [1.019, 1.715] 0.035
P for trend	0.018	0.026	0.032	0.035
In-hospital mortality				
AISI (per 1SD)	1.086 [1.027, 1.147] 0.003	1.081 [1.023, 1.142] 0.005	1.078 [1.024, 1.135] 0.004	1.063 [1.012, 1.117] 0.015
Tertiles of AISI				
Tertile 1	Reference	Reference	Reference	Reference
Tertile 2	0.935 [0.679, 1.287] 0.679	0.898 [0.650, 1.239] 0.512	0.883 [0.639, 1.220] 0.452	0.879 [0.639, 1.209] 0.429
Tertile 3	1.556 [1.159, 2.089] 0.003	1.502 [1.114, 2.025] 0.007	1.502 [1.114, 2.025] 0.008	1.479 [1.105, 1.979] 0.009
P for trend	0.002	0.004	0.005	0.005
28-day mortality				
AISI (per 1SD)	1.057 [1.005, 1.113] 0.026	1.055 [1.004, 1.110] 0.031	1.054 [1.003, 1.109] 0.035	1.054 [1.002, 1.109] 0.040
Tertiles of AISI				
Tertile 1	Reference	Reference	Reference	Reference
Tertile 2	1.051 [0.808, 1.367] 0.707	1.049 [0.807, 1.364] 0.722	1.046 [0.803, 1.361] 0.741	1.035 [0.794, 1.348] 0.802
Tertile 3	1.331 [1.035, 1.716] 0.020	1.327 [1.030, 1.714] 0.029	1.325 [1.028, 1.713] 0.031	1.322 [1.022, 1.711] 0.034
P for trend	0.019	0.025	0.028	0.033

Notes: Model 1: no covariates were adjusted. Model 2: age, sex, BMI, SBP, and DBP were adjusted. Model 3: Model 2 plus adjustment for ALT, AST, Albumin, Creatinine, HDL-C, LDL-C, TG, and BNP. Model 4: Model 3 plus adjustment for Hypertension, Diabetes, COPD, Heart Failure, ARDS, and CKD.
Abbreviations: AISI, aggregate index of systemic inflammation; SD, Standard deviation; HR, hazard ratio; CI, confidence interval.

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Relationship Between AISI and the Risk of Death Related to Sepsis

Similarly, COX regression analysis was employed to investigate the relationship between the inflammatory load, represented by AISI, and the risk of sepsis-related mortality. The results demonstrated that for every 1 SD increase in AISI, the overall mortality risk, in-hospital mortality risk, and 28-day mortality risk increased by 1.059 times, 1.063 times, and 1.054 times, respectively (Table 4). When AISI was treated as a categorical variable, compared to the T1 group, the highest level in the T3 group showed a 32.2% increase in all-cause mortality risk, with the in-hospital mortality risk and 28-day mortality risk rising by 47.9% and 32.2%, respectively (Table 4). Further analysis through RCS revealed that when AISI exceeded 1403, both the overall mortality risk, in-hospital mortality risk, and 28-day mortality risk progressively increased (Figure 3). Additionally, the risk in the group with AISI levels greater than 1403 was significantly higher than in the group where AISI was less than or equal to 1403 (Table 5). These findings indicate that as the inflammatory load represented by AISI increases, the mortality risk also rises. This highlights the importance of early control of inflammation in sepsis patients, as reducing inflammatory responses could significantly improve the prognosis of these patients.

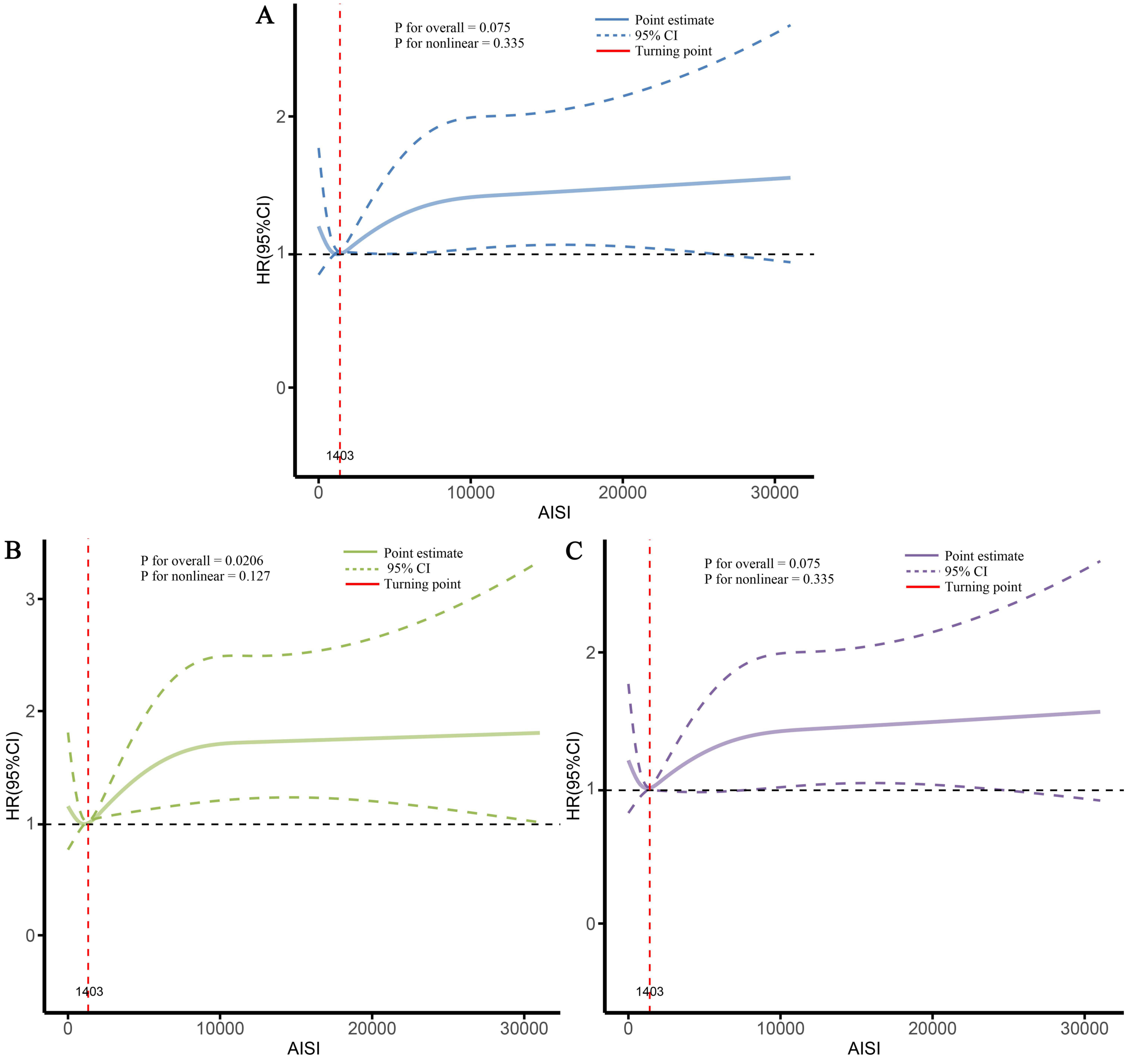

Figure 3 Dose-response relationship between AISI and the risk of death related to sepsis. (**A**) Overall mortality; (**B**) In-hospital mortality; (**C**) 28-day mortality.

Combined Effect of SHR and AISI on the Risk of Sepsis-Related Mortality

To further investigate the combined effect of SHR and AISI on the adverse prognosis of sepsis, we classified patients into four groups based on the inflection point of the RCS curve: Group 1 (SHR ≤ 1.08 and AISI ≤ 1403), Group 2 (SHR ≤ 1.08 and AISI > 1403), Group 3 (SHR > 1.08 and AISI ≤ 1403), and Group 4 (SHR > 1.08 and AISI > 1403). First, regarding the incidence of death-related events, Group 4 exhibited the highest mortality rates across all categories (including overall mortality, in-hospital mortality, and 28-day mortality), with a significantly higher rate than the other three groups (Figure 4). Similarly, when comparing Group 4 (high stress-induced blood glucose and high inflammatory load) with Group 1 (low stress-induced blood glucose and low inflammatory load), the former had significantly higher risks for overall mortality, in-hospital mortality, and 28-day mortality—1.881 times, 2.151 times, and 2.046 times higher, respectively (Table 6). At the same time, the cumulative mortality risk curves for the four groups revealed that Group 4 consistently had the highest cumulative risk across all three sepsis-related death outcomes (Figure 5). Furthermore, when we performed a separate analysis using our own cohort data as an external validation set, similar results were obtained, confirming that Group 4 still exhibited the highest mortality risk (Table S1). Finally, to assess the predictive value of the combined effect of SHR and AISI on sepsis-related mortality, we performed a C-index analysis. The results demonstrated that the C-index for the combined SHR and AISI model was significantly higher than those for SHR alone or AISI alone, indicating that the combined effect of SHR and AISI provides a stronger predictive capability for overall mortality, in-hospital mortality, and 28-day mortality risk in sepsis patients (Table 7).

Compares the Length of Hospital Stay in the ICU and the Length of Hospital Stay Overall for Sepsis Patients in Different Groups SHR Combined with AISI Classification

Table 8 compares the length of hospital stay, including both ICU and total hospitalization duration, across different groups. The results indicate that the ICU stay was significantly longer in Groups 2, 3, and 4 compared to Group 1, with Group 4 exhibiting the longest median ICU stay of 4.79 days. In contrast, no statistically significant differences were observed among the groups in total hospitalization time (Table 8). This pattern was further supported by a small violin plot, which visually reinforced the prolonged ICU stay in Group 4 (Figure 6).

These findings suggest that among sepsis patients, elevated stress glucose and inflammatory markers at admission are associated with greater disease severity and an extended ICU stay. This highlights the clinical importance of early management of stress hyperglycemia and inflammatory responses in sepsis patients, which may not only shorten ICU

Table 5 Two-Stage Comparative Analysis of the Relationship Between AISI and Mortality and Its Subtype Risks Based on the RCS Turning Points

Exposure	Model 1	Model 2	Model 3	Model 4
	HR (95% CI) P	HR (95% CI) P	HR (95% CI) P	HR (95% CI) P
Overall mortality				
Turning point	1403	1403	1403	1403
<= 1403	Reference	Reference	Reference	Reference
> 1403	1.263 [1.194, 1.533] <0.001	1.299 [1.197, 1.579] <0.001	1.276 [1.195, 1.552] <0.001	1.277 [1.195, 1.555] <0.001
In-hospital mortality				
Turning point	1403	1403	1403	1403
<= 1403	Reference	Reference	Reference	Reference
> 1403	1.402 [1.098, 1.789] 0.007	1.425 [1.114, 1.822] 0.005	1.385 [1.082, 1.773] 0.010	1.385 [1.081, 1.773] 0.010
28-day mortality				
Turning point	1403	1403	1403	1403
<= 1403	Reference	Reference	Reference	Reference
> 1403	1.237 [1.005, 1.522] 0.045	1.266 [1.027, 1.560] 0.027	1.234 [1.001, 1.523] 0.049	1.241 [1.005, 1.532] 0.044

Notes: Model 1: no covariates were adjusted. Model 2: age, sex, BMI, SBP, and DBP were adjusted. Model 3: Model 2 plus adjustment for ALT, AST, Albumin, Creatinine, HDL-C, LDL-C, TG, and BNP. Model 4: Model 3 plus adjustment for Hypertension, Diabetes, COPD, Heart Failure, ARDS, and CKD.
Abbreviations: AISI, aggregate index of systemic inflammation; RCS, restricted cubic spline; HR, hazard ratio; CI, confidence interval.

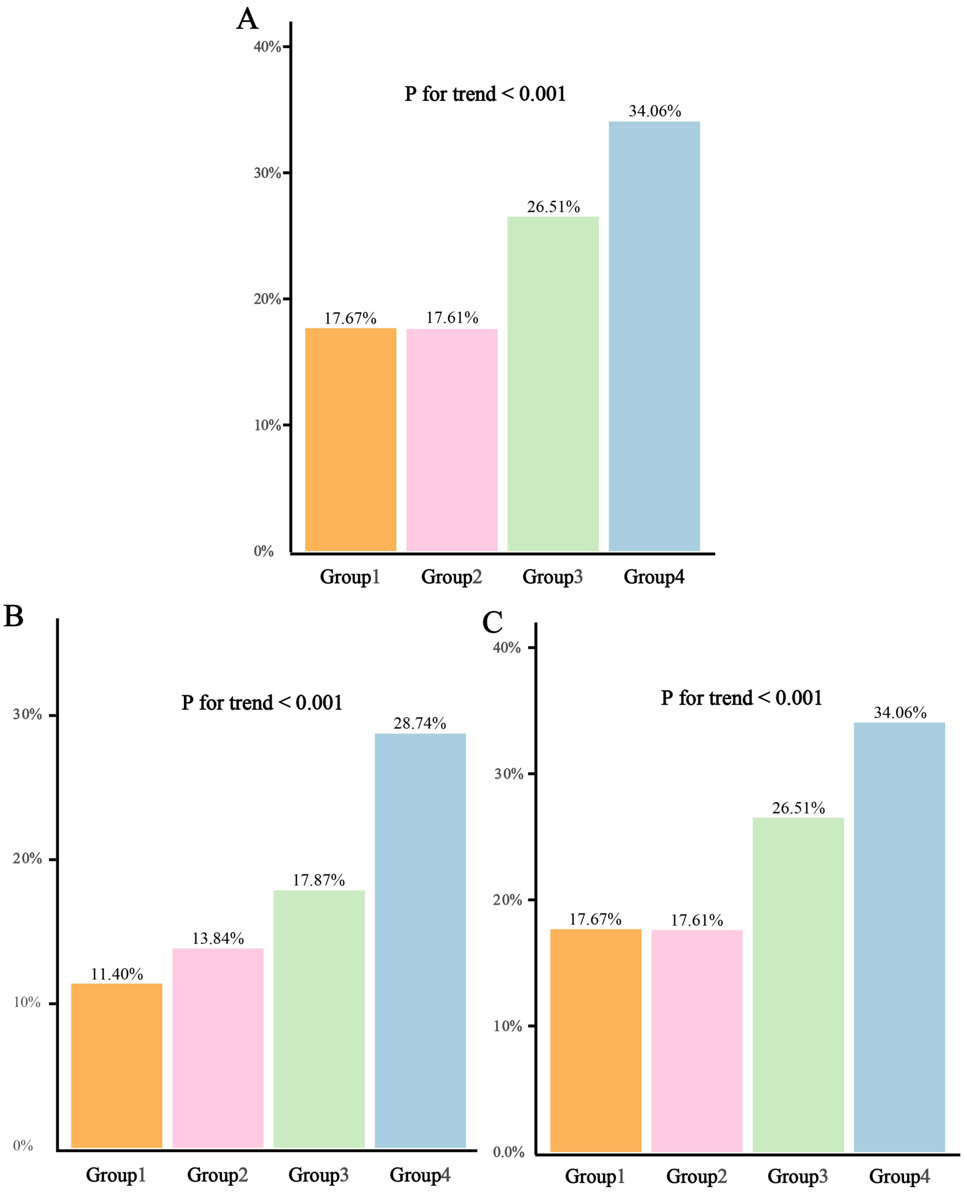

Figure 4 The incidence of sepsis-related mortality risk among different groups based on the combined classification of SHR and AISI. (**A**) Overall mortality; (**B**) In-hospital mortality; (**C**) 28-day mortality.

length of stay and alleviate the financial burden of care but also potentially reduce mortality risk. Such implications hold substantial clinical and public health significance.

Subgroup Analysis

To verify the stability of the combined effect of SHR and AISI on sepsis-related mortality risk, we performed subgroup analyses based on patient gender, age, and comorbidities including hypertension, diabetes, heart failure, and acute respiratory distress syndrome. A forest plot was generated to visualize the subgroup analysis results (Figure 7). The outcomes across all subgroups remained consistent with the overall findings, indicating robust associations. Specifically, groups with elevated SHR and AISI levels showed significantly higher risks of mortality. These stable results reinforce the conclusion that early management of stress hyperglycemia and reduction of inflammation in sepsis patients are crucial for lowering mortality risk.

Table 6 Effect of SHR Combined with AISI on Mortality and Subtype Risk in Patients with Sepsis

Exposure	**Model 1**	**Model 2**	**Model 3**	**Model 4**
	HR (95% CI) P	**HR (95% CI) P**	**HR (95% CI) P**	**HR (95% CI) P**
Overall mortality				
Group 1	Reference	Reference	Reference	Reference
Group 2	1.067 [0.755, 1.510] 0.712	1.049 [0.739, 1.487] 0.790	1.030 [0.726, 1.462] 0.866	1.025 [0.721, 1.458] 0.883
Group 3	1.629 [1.200, 2.211] 0.002	1.593 [1.172, 2.165] 0.003	1.570 [1.158, 2.128] 0.004	1.557 [1.144, 2.121] 0.005
Group 4	1.971 [1.484, 2.617] <0.001	1.945 [1.468, 2.576] <0.001	1.890 [1.422, 2.511] <0.001	1.881 [1.413, 2.505] <0.001
In-hospital mortality				
Group 1	Reference	Reference	Reference	Reference
Group 2	1.148 [0.761, 1.732] 0.511	1.129 [0.750, 1.697] 0.561	1.208 [0.802, 1.820] 0.366	1.179 [0.782, 1.779] 0.432
Group 3	1.546 [1.062, 2.249] 0.0023	1.546 [1.061, 2.251] 0.023	1.503 [1.030, 2.192] 0.035	1.435 [0.981, 2.101] 0.063
Group 4	2.364 [1.694, 3.299] <0.001	2.305 [1.647, 3.224] <0.001	2.194 [1.565, 3.075] <0.001	2.151 [1.532, 3.021]] <0.001
28-day mortality				
Group 1	Reference	Reference	Reference	Reference
Group 2	1.063 [0.752, 1.503] 0.729	1.041 [0.735, 1.475] 0.819	1.036 [0.731, 1.468] 0.843	1.002 [0.710, 1.415] 0.991
Group 3	1.654 [1.220, 2.242] 0.001	1.624 [1.199, 2.201] 0.002	1.592 [1.173, 2.161] 0.003	1.561 [1.149, 2.122] 0.004
Group 4	2.174 [1.641, 2.879] <0.001	2.161 [1.635, 2.857] <0.001	2.049 [1.544, 2.718] <0.001	2.046 [1.540, 2.717] <0.001

Notes: Group 1: SHR<=1.08 and AISI<=1403. Group 2: SHR<=1.08 and AISI>1403. Group 3: SHR>1.08 and AISI<=1403. Group 4: SHR>1.08 and AISI>1403. Model 1: no covariates were adjusted. Model 2: age, sex, BMI, SBP, and DBP were adjusted. Model 3: Model 2 plus adjustment for ALT, AST, Albumin, Creatinine, HDL-C, LDL-C, TG, and BNP. Model 4: Model 3 plus adjustment for Hypertension, Diabetes, COPD, Heart Failure, ARDS, and CKD.

Abbreviations: SHR, stress hyperglycemia ratio; AISI, aggregate index of systemic inflammation; HR, hazard ratio; CI, confidence interval.

Discussion

In our study, we found that both SHR and AISI were strongly associated with the overall mortality risk, in-hospital mortality risk, and 28-day mortality risk in patients with sepsis. By combining these two indicators based on the RCS threshold, we observed a synergistic effect between them. The results indicated that this combined effect significantly exacerbated the occurrence of related mortality risks in sepsis patients. Compared to single-indicator assessments, the combination demonstrated higher predictive value for adverse outcomes. Moreover, this relationship remained consistent across various clinical subgroups, further supporting our findings. Additionally, from both clinical and economic perspectives, we found that a high SHR combined with a high AISI was significantly associated with prolonged ICU stays. This further emphasizes that in clinical practice, the combination of SHR and AISI can be used to identify sepsis patients at higher risk for adverse outcomes. Such identification can help implement precision medicine strategies, enabling early control of blood glucose levels and reduction of inflammatory burden, which can subsequently shorten ICU stays and lower medical costs. This approach also holds significant economic value.

The SHR indicator incorporates glycated hemoglobin, which reflects the patient's glycemic status over the past 2–3 months.[21,22] By standardizing the patient's glycemic indicators, it fully accounts for the impact of stress on blood sugar levels, helping clinicians assess how stress influences glycemic control.[22,33] Previous studies have shown that a high SHR is associated with an increased risk of cardiovascular and cerebrovascular events, sepsis, acute pancreatitis, and tumors.[33–38] Specifically, the relationship between SHR and 28-day all-cause mortality in sepsis patients has been characterized as "U-shaped". This suggests a significant positive correlation between higher SHR levels and increased 28-day all-cause mortality.[31,39] Compared to those with low SHR, patients with high SHR are at a higher risk of both in-hospital death and 28-day mortality.[31] Additionally, high SHR has been identified as a risk factor for cardiovascular diseases.[40–42] A study examining early risks in intensive care unit patients with cardiovascular diseases found that those with high SHR faced a higher risk of in-hospital and 1-year mortality, as well as a significantly increased risk of acute kidney injury.[40,42] Furthermore, the RCS curve revealed that SHR follows a "U-shaped" relationship with mortality risk, with a turning point at 1.355.[42]

AISI is an emerging, comprehensive biomarker for systemic inflammation. It reflects the balance between pro-inflammatory and anti-inflammatory cells in the blood, as well as the three key pathways involved in the systemic

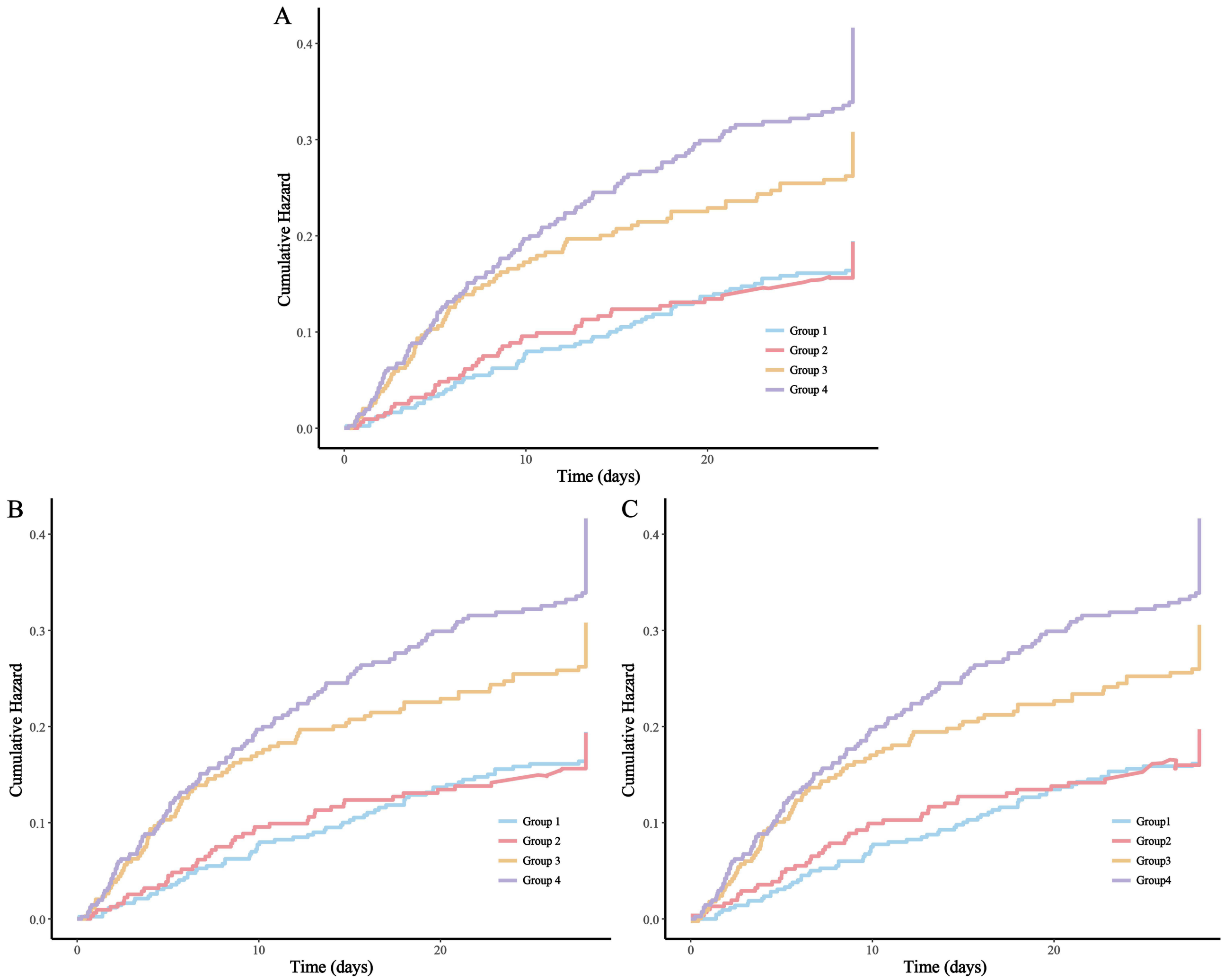

Figure 5 Cumulative mortality risk curves between different groups based on the combined classification of SHR and AISI. (**A**) Overall mortality; (**B**) In-hospital mortality; (**C**) 28-day mortality.

inflammatory response: innate immunity, adaptive immunity, and coagulation.[43,44] In this way, AISI provides a more holistic representation of the complexity and interconnectedness of systemic inflammation.[45] Several studies have found that AISI is associated with adverse outcomes in infectious diseases, tumors, metabolic-related fatty liver, and cardiovascular diseases.[38,46–48] Specifically, research on metabolic-related fatty liver and inflammatory markers has shown that

Table 7 Performance of SHR Combined with AISI in Predicting Mortality and Subtype Risk in Sepsis

Inflammatory Markers	C-Index
Overall mortality	
Model 4	0.647
+SHR	0.676
+AISI	0.656
+SHR+AISI	0.701

(*Continued*)

Table 7 (Continued).

Inflammatory Markers	C-Index
In-hospital mortality	
Model 4	0.642
+SHR	0.677
+AISI	0.654
+SHR+AISI	0.695
28-day mortality	
Model 4	0.646
+SHR	0.673
+AISI	0.652
+SHR+AISI	0.684

Notes: Model 4: Age, Sex, BMI, SBP, DBP, ALT, AST, Albumin, Creatinine, HDL-C, LDL-C, TG, BNP, Hypertension, Diabetes, COPD, Heart Failure, ARDS, and CKD were adjusted.
Abbreviations: SHR, stress hyperglycemia ratio; AISI, aggregate index of systemic inflammation.

Table 8 Comparison of the Length of Stay in the ICU and the Total Hospital Stay Among the Four Groups of Sepsis Patients in the SHR Combined with AISI

Characteristic	Group 1	Group 2	Group 3	Group 4	P value
ICU Length of Stay	3.86 (1.85–7.82)	3.93 (2.02–8.18)	3.96 (2.06–7.76)	4.79 (2.44–9.48)	0.007
Length of Stay	9.46 (5.46–15.93)	9.78 (5.10–17.44)	9.15 (5.51–15.85)	9.77 (5.77–17.67)	0.565

Note: Data are presented as median (interquartile range).
Abbreviations: SHR, stress hyperglycemia ratio; AISI, aggregate index of systemic inflammation.

for every one-unit increase in AISI, the risk of metabolic fatty liver rises by 74%.[27] Additionally, a study on non-traumatic subarachnoid hemorrhage identified a cutoff value of 1362.45 for AISI; patients with values exceeding this threshold had a 1.67-fold increase in 90-day mortality.[45] Furthermore, a study on systemic inflammatory markers and spinocerebellar ataxia revealed that increased AISI levels were associated with a higher risk of Parkinson's disease and movement disorders.[49]

Previous studies have consistently confirmed that both SHR and AISI are associated with the risk of various diseases, including sepsis.[31,50,51] Therefore, we further explored the synergistic effect between the two by combining them. The results revealed that high stress glucose levels (represented by high SHR) and high inflammatory load (represented by high AISI) significantly increased the risk of mortality in sepsis patients. This highlights the importance of reducing stress conditions and inflammatory states. In our subgroup analysis, we observed an interesting finding: there was an interaction based on age, with younger patients (under 65 years) showing a greater impact. Specifically, SHR and AISI had a more pronounced effect on the mortality risk in younger sepsis patients. The possible explanation for this is that elderly patients often by multiple chronic conditions and age-related physiological decline, which may confound or attenuate the isolated impact of acute stress and inflammation on mortality. In contrast, younger patients, typically without such extensive comorbidities, might exhibit a more direct and potent pathophysiological response. Their immune and inflammatory systems may be more readily activated under stress, and once the threshold is crossed, this could potentially lead to a more rapid progression towards a dysregulated immune response ("storm"), accelerating adverse

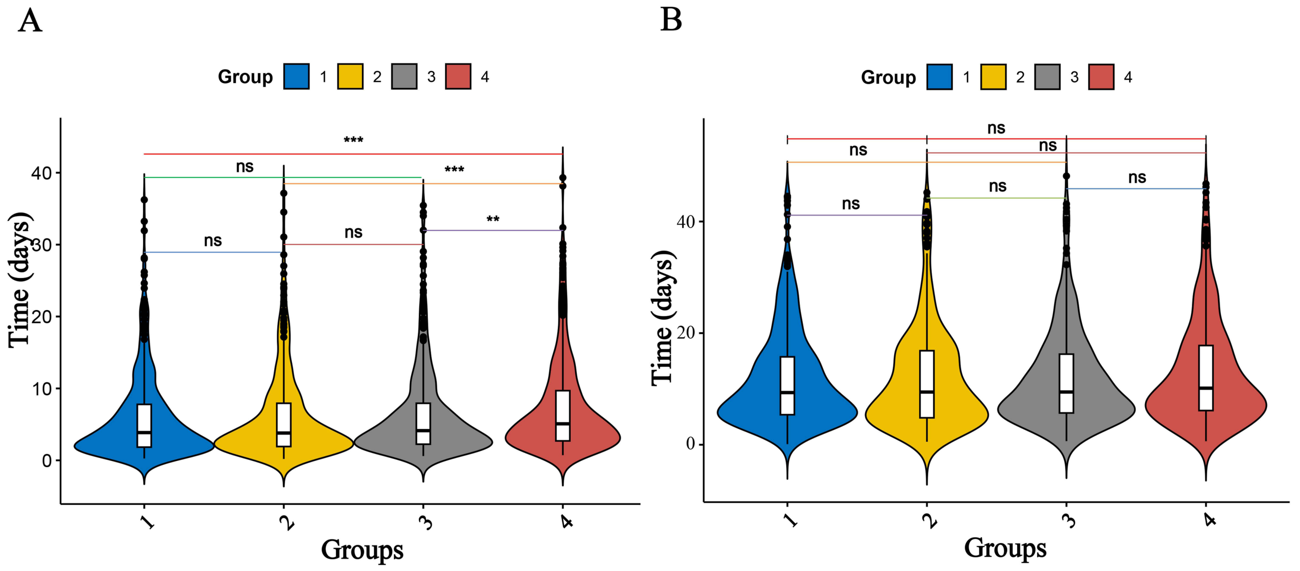

Figure 6 Comparison of ICU stay duration and total hospitalization time between different groups based on the combined classification of SHR and AISI. (**A**) ICU Length of Stay; (**B**), Length of Stay.
Note: ** P < 0.01; *** P < 0.001.
Abbreviation: ns, no significant.

outcomes.[52,53] This suggests that relatively younger patients with sepsis should place greater emphasis on controlling early inflammation and stress glucose levels to reduce the risk of future mortality.

The strength of this study lies in its use of the extensive MIMIC-IV database alongside its own cohort data, integrating new indicators, SHR and AISI, to explore their relationship with various mortality risks in sepsis patients. This approach not only tested the predictive performance of this combined model for adverse sepsis outcomes but also examined its association with the length of stay in the intensive care unit. This has significant public health and economic implications, as the findings may contribute to the implementation of precision medicine and potentially reduce healthcare costs. However, despite these advantages, several limitations must be considered. First, the calculation of SHR and AISI was based on test results obtained within 24 hours of ICU admission, meaning we were unable to capture the impact of dynamic changes in these indicators over time. Second, we did not include data on the use of anti-inflammatory or hypoglycemic drugs, highlighting the need for future research to incorporate this information. Additionally, the cohort in our study consisted solely of patients from the United States and central China, which warrants caution when generalizing the findings to broader populations. Larger-scale, multicenter studies will be necessary to further validate these results. Lastly, as an observational study, our research cannot establish causal relationships.

Conclusion

This study found that both SHR and AISI are strongly associated with total mortality risk, in-hospital mortality risk, and 28-day mortality risk in sepsis patients. Moreover, the combined effect of these two factors not only amplifies the risk of death but also was associated with the prolonged hospital stay in the ICU as recorded. These findings suggest that early control of stress glucose levels and reduction of inflammation in sepsis patients could not only decrease mortality risk but also shorten ICU stays, thereby reducing healthcare costs. The results have important clinical implications and considerable economic benefits. Future research should include more multi-center prospective studies to further confirm these findings and to test the effectiveness of intervention measures based on this comprehensive indicator.

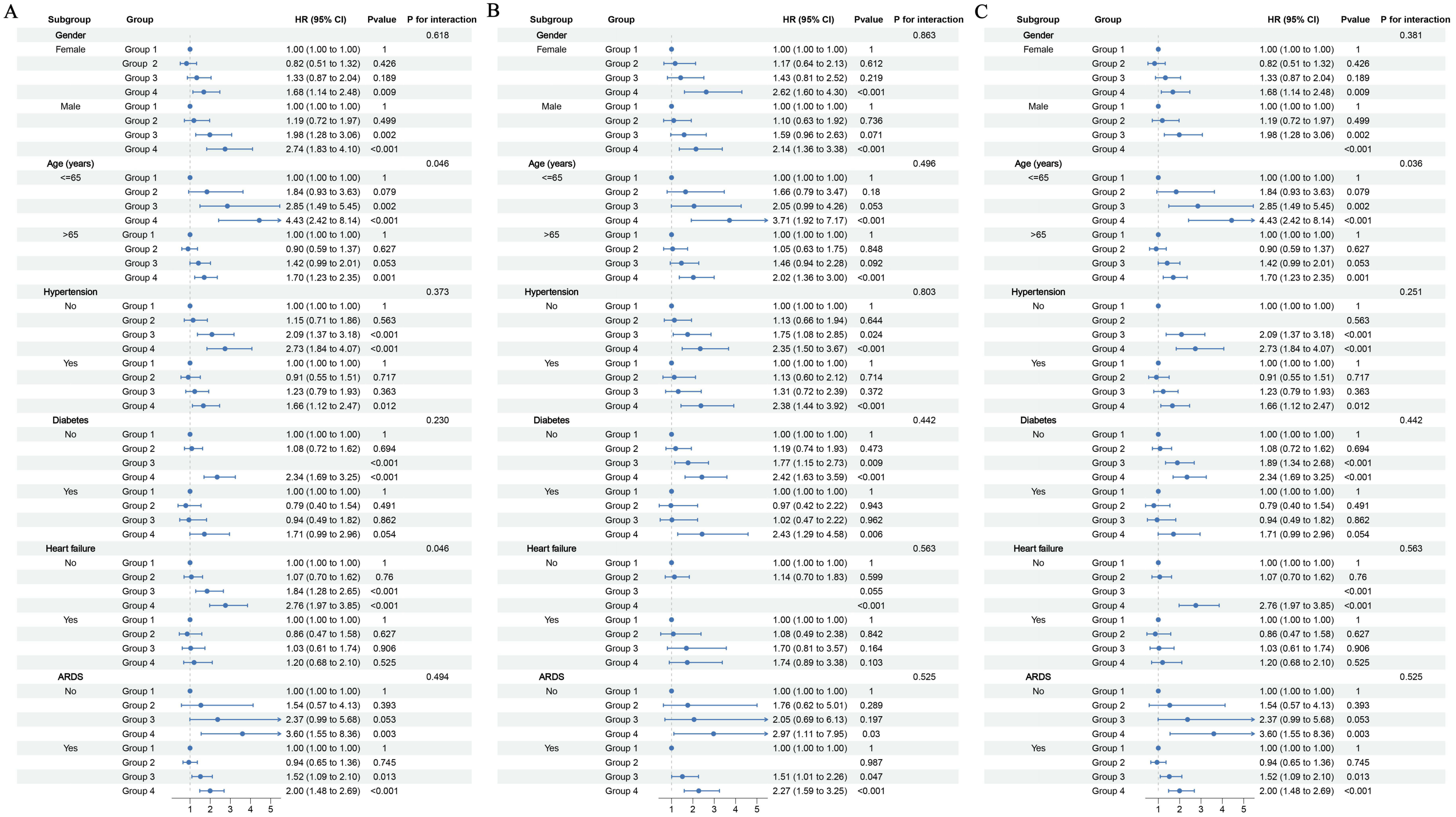

Figure 7 Subgroup analysis based on different basic conditions and disease statuses. (**A**) Overall mortality; (**B**) In-hospital mortality; (**C**), 28-day mortality.

Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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