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Development and external validation of a prognostic model for 28-day mortality in sepsis: incorporating glycemic variability and the systemic immune-inflammation index

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Abstract

Background: Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection, is clinically and biologically heterogeneous. Immune dysregulation and metabolic disturbances contribute to poor outcomes but may not be fully captured by the Sequential Organ Failure Assessment (SOFA) score. We evaluated the joint prognostic value of glycemic variability (GV) and the systemic immune-inflammation index (SII). We also developed a 28-day mortality prediction model.

Methods: Adults with sepsis from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database formed the development and internal validation cohort. The eICU Collaborative Research Database (eICU-CRD) and Zigong cohorts provided external validation. Outcomes were 28-day all-cause and intensive care unit mortality; eICU-CRD used 28-day in-hospital mortality as a proxy. Associations of GV, log-transformed SII (LogSII), and their

combinations with mortality were examined using Kaplan–Meier analysis, Cox regression, restricted cubic splines, subgroup analyses, and interaction tests. Predictive value was assessed using receiver operating characteristic curves and reclassification measures. A logistic model with Boruta-assisted predictor selection was evaluated for discrimination, calibration, and decision-curve net benefit.

Results: The MIMIC-IV, eICU-CRD, and Zigong cohorts included 5564, 4302, and 538 patients, respectively. Group 4 (high GV/high LogSII) had the largest adjusted hazard ratio point estimate for 28-day mortality relative to Group 1 (low GV/low LogSII): 1.95 (95% confidence interval 1.63–2.34; $\boldsymbol{P < 0.001}$). Both markers showed nonlinear associations with mortality. Areas under the receiver operating characteristic curve (AUROCs) were 0.601 for GV, 0.582 for LogSII, and 0.619 for their combination. The combined AUROC exceeded that of GV ($\boldsymbol{P = 0.017}$) or LogSII ($\boldsymbol{P < 0.001}$) alone. The final model included GV, LogSII, age, blood urea nitrogen, respiratory rate, vasopressor use, and peripheral oxygen saturation. Training and internal validation AUROCs were 0.704 and 0.741, respectively, both higher than those of SOFA. External AUROCs were 0.678 in eICU-CRD and 0.651 in Zigong.

Conclusions: Joint GV and LogSII assessment provided additional prognostic information over either marker alone. The model showed modest discrimination in internal and external validation. It was implemented as a web-based risk calculator.

Keywords: Sepsis, Glycemic variability, Systemic immune-inflammation index, Nomogram

1 Background

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, remains a major contributor to the global burden of disease and mortality [1, 2]. It is clinically and biologically heterogeneous, with pathophysiological processes involving inflammation, immunosuppression, coagulation abnormalities, endothelial dysfunction, and metabolic alterations [3, 4]. These complex, interrelated host responses complicate prognostic assessment and risk stratification in patients with sepsis.

The Sequential Organ Failure Assessment (SOFA) score is widely used to evaluate organ dysfunction in patients with sepsis [1, 5]. Inflammatory responses and disturbances in glucose metabolism are also closely associated with adverse outcomes. The systemic immune-inflammation index (SII) combines neutrophil, lymphocyte, and platelet counts in a composite inflammatory index [6]. Previous studies have reported associations between SII and mortality in patients with sepsis, although the direction and shape of these associations have varied across cohorts [7, 8]. Glycemic variability (GV) describes fluctuations in blood

glucose levels over time and is associated with impaired glucose homeostasis. A systematic review and cohort studies in sepsis have associated higher GV with adverse outcomes [9–12].

SII and GV reflect different physiological disturbances in sepsis: SII primarily captures systemic immune-inflammatory status, whereas GV reflects fluctuations in blood glucose during critical illness. To date, these markers have largely been examined separately in sepsis. However, whether their joint assessment provides additional prognostic information remains unclear. Evaluating GV and SII together may help identify patients with sepsis who are at increased risk of death.

In this study, we examined the associations of GV, the natural logarithm of SII (LogSII), and their joint categories with mortality in patients with sepsis. We assessed whether their combination improved prognostic performance relative to either marker alone. Following Boruta-assisted predictor selection, we developed a multivariable logistic regression model for 28-day mortality. The model underwent internal validation in the Medical Information Mart for Intensive Care IV (MIMIC-IV) cohort, followed by external validation in the eICU Collaborative Research Database (eICU-CRD) and an independent hospital cohort in China. A web-based interactive calculator was developed to provide individualized risk estimates.

2 Methods

2.1 Study design and data sources

This was a multicohort retrospective study. MIMIC-IV v3.1, which contains electronic health records from Beth Israel Deaconess Medical Center between 2008 and 2022, was used for model development and internal validation [13]. eICU-CRD, comprising deidentified clinical data from multiple intensive care units (ICUs) in 2014–2015, provided a multicenter external validation cohort in the United States [14]. A critical care database of patients with infection at Zigong Fourth People's Hospital, integrating inpatient records with manually obtained follow-up outcomes, provided an external validation cohort in China [15]. All three databases contained deidentified data and were accessed in accordance with their respective data-use requirements.

2.2 Study population

For patients with multiple ICU admissions, only the first ICU stay was retained. Adult patients aged $\geq$ 18 years who met the Sepsis-3 criteria at their first ICU admission were eligible for inclusion. Exclusion criteria were death within 48 h of ICU admission, ICU length of stay $<$ 48 h, end-stage renal disease, cirrhosis or malignancy, fewer than three blood glucose measurements during the ICU stay, and missing neutrophil, platelet, or lymphocyte counts within 24 h of ICU admission. Identical eligibility criteria were applied across the MIMIC-IV, eICU-CRD, and Zigong cohorts. The study population and cohort allocation are shown in Fig. 1.

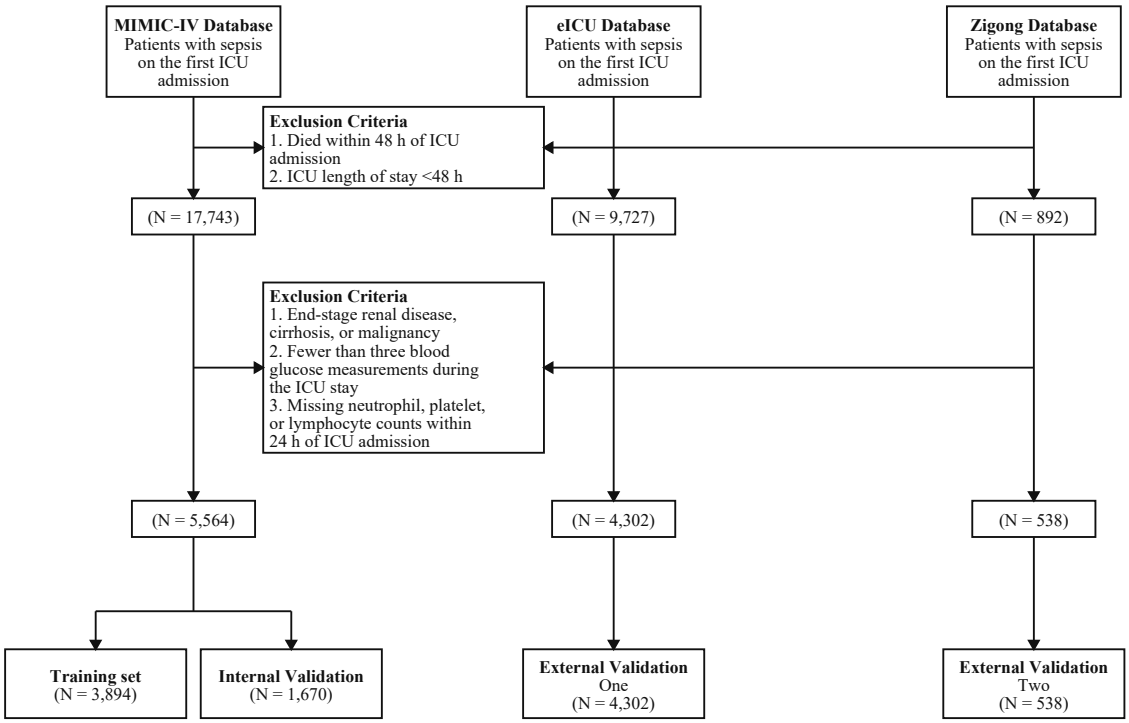


Fig. 1 Flow chart of patient selection and cohort allocation. MIMIC-IV was used for model development and internal validation; eICU-CRD and the Zigong cohort served as external validation cohorts 1 and 2, respectively. MIMIC-IV, Medical Information Mart for Intensive Care IV; eICU-CRD, eICU Collaborative Research Database.

2.3 Data extraction and variable definitions

Demographic characteristics, vital signs, comorbidities, treatments, and laboratory measurements were extracted using Structured Query Language through DecisionLinnc 1.1.7.4 software. Unless otherwise specified, baseline vital signs and laboratory measurements were obtained within 24 h of ICU admission. Standard MIMIC-IV code is available in the MIMIC code repository maintained by the Massachusetts Institute of Technology Laboratory for Computational Physiology.

The primary exposures were GV and SII. GV was calculated using all available blood glucose measurements throughout the ICU stay, consistent with previous studies of GV in sepsis [11, 16]. GV was defined as the standard deviation of glucose measurements divided by their mean, multiplied by 100%:

$$\mathrm{GV} = \frac{\mathrm{SD}_{\mathrm{glucose}}}{\mathrm{Mean}_{\mathrm{glucose}}} \times 100\%.$$

Here, SD denotes the standard deviation of glucose measurements. SII was calculated as follows:

$$SII = \frac{\text{Platelet count} \times \text{Neutrophil count}}{\text{Lymphocyte count}},$$

with all counts in $10^9/L$.

Because SII was right-skewed, its natural logarithm (LogSII) was used in regression and prediction analyses. Accordingly, effect estimates are reported for LogSII, whereas SII is used when defining the index or discussing its biological interpretation.

2.4 Outcomes

The primary outcome was 28-day all-cause mortality, and the secondary outcome was ICU mortality. In MIMIC-IV, 28-day all-cause mortality was defined as death from any cause within 28 days after the first ICU admission. ICU mortality was defined as death occurring during the ICU stay.

Because reliable post-discharge mortality information is not available in eICU-CRD, 28-day in-hospital mortality was used as a proxy for 28-day mortality, consistent with Yang et al. [17]. This endpoint comprised in-hospital deaths within 28 days of the first ICU admission. Patients discharged alive before day 28 were treated as survivors.

In the Zigong cohort, ascertainment of 28-day all-cause mortality incorporated post-discharge follow-up information [15]. Patients who died within 28 days were classified as nonsurvivors; those alive at day 28 were classified as survivors. This outcome was consistent with previous studies using data from Zigong Fourth People's Hospital [18].

2.5 Statistical analysis

Continuous variables are presented as medians with interquartile ranges, and categorical variables as counts and percentages. Between-group comparisons used the Wilcoxon rank-sum test or Pearson's χ^2 test, as appropriate. Candidate variables with more than 20% missing values were excluded from the main analysis. Variables with $\leq 20\%$ missing values underwent multiple imputation by chained equations using the `mice` package in R [19]. Outliers were winsorized at prespecified cutoffs.

For prediction model development, the MIMIC-IV cohort was randomly divided into training and internal validation sets in a 7:3 ratio. Candidate predictor selection and model fitting were performed in the training set; the internal validation set was not used for model development.

GV and LogSII were each categorized using their empirical tertiles in the MIMIC-IV analysis cohort, with the highest tertile defined as high and the lower two tertiles as low. Their combinations defined 4 groups: Group 1, low GV/low LogSII; Group 2, low GV/high LogSII; Group 3, high GV/low LogSII; and Group 4, high GV/high LogSII.

Kaplan–Meier curves described survival across these groups, with survival distributions compared using the log-rank test. Cox proportional hazards regression assessed associations of GV, LogSII, and their joint categories with mortality. Results are reported as hazard ratios (HRs) with 95% confidence intervals (CIs). The unadjusted model included no covariates. Model I adjusted for age and sex; Model II additionally adjusted for vital signs and comorbidities; Model III further adjusted for hemoglobin,

creatinine, blood urea nitrogen, lactate, SOFA score, and insulin use. Variance inflation factors were used to assess multicollinearity among covariates. The proportional hazards assumption for the joint-category Model III analyses was assessed using scaled Schoenfeld residuals.

Restricted cubic spline (RCS) analyses examined potential nonlinear associations of GV and LogSII with 28-day mortality. Prespecified subgroup analyses assessed the consistency of associations across clinical subgroups. Potential effect modification was evaluated using interaction terms, with corresponding interaction P values reported. To account for multiple subgroup comparisons, a sensitivity analysis applying false discovery rate (FDR) correction was also performed.

Statistical interaction between GV and LogSII was further evaluated [20]. Multiplicative interaction between the binary high/low marker categories was assessed with a Wald test of the corresponding log-HR contrast. Additive interaction was summarized by the relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (SI), using HRs from the fully adjusted joint-category Cox model and its exact coefficient covariance matrix [21]. The multivariate delta method was used for RERI and AP, and a log-scale delta interval for SI.

Receiver operating characteristic (ROC) analysis assessed the discrimination of GV, LogSII, and their combination for mortality outcomes. Areas under the ROC curve (AUROCs) were compared using DeLong's test [22]. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated to assess the incremental predictive value of the combined GV+LogSII Cox model over models containing either GV or LogSII alone. Categorical NRI used exploratory mortality-risk thresholds of 10%, 20%, and 30%. Continuous NRI and IDI were calculated from individual predicted risks at the corresponding outcome time points. Percentile 95% CIs and P values were estimated using stratified bootstrap resamples. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

2.6 Model development and validation

The Boruta algorithm was used to select candidate predictors in the training set [23]. A multivariable logistic regression model was then fitted to predict 28-day mortality, and a nomogram was constructed from the final model.

Model performance was evaluated in terms of discrimination, calibration, and exploratory decision-analytic net benefit using decision curve analysis (DCA) [24]. Discrimination was assessed using AUROC. Calibration was evaluated using calibration plots, the Brier score, calibration intercept, and calibration slope. In internal validation, the development models remained locked and patients were resampled with their paired predictions, so the intervals are conditional on the fitted development models.

The final model was first evaluated in the MIMIC-IV internal validation set and subsequently externally validated in the independent eICU-CRD and Zigong cohorts.

2.7 Development of the web-based risk calculator

A web-based interactive risk calculator was developed in R Shiny using the regression coefficients of the final multivariable logistic regression model. Entering the model's predictor values yields an individualized predicted probability of 28-day mortality.

3 Results

3.1 Study population and baseline characteristics

The MIMIC-IV cohort included 5564 eligible patients with sepsis, of whom 3894 were allocated to the training set and 1670 to the internal validation set. The eICU-CRD and Zigong external validation cohorts included 4302 and 538 patients, respectively. In MIMIC-IV, 4509 patients survived and 1055 died within 28 days, corresponding to a 28-day all-cause mortality rate of 19.0%. There were 681 ICU deaths. Baseline characteristics are presented in Table 1.

Compared with 28-day survivors, nonsurvivors were older and had higher SOFA scores, Simplified Acute Physiology Score II (SAPS II) scores, and Charlson comorbidity indices (all $P < 0.001$). Nonsurvivors also had higher respiratory rates and lower peripheral oxygen saturation (SpO_2), together with more pronounced inflammatory, metabolic, and organ dysfunction-related abnormalities. Median GV was 25.33% (17.32%–35.11%) in nonsurvivors versus 20.30% (14.36%–29.41%) in survivors; corresponding LogSII values were 7.78 (6.95–8.49) and 7.39 (6.62–8.16), respectively (both $P < 0.001$). Heart failure, myocardial infarction, and chronic obstructive pulmonary disease (COPD) were more common in nonsurvivors, who also more frequently received continuous renal replacement therapy (CRRT) and vasopressors (all $P < 0.001$; Table 1).

3.2 Associations of GV and LogSII with mortality

Kaplan–Meier analyses showed significant differences in 28-day and 1-year survival probabilities across the joint GV and LogSII groups (overall log-rank $P < 0.001$; Fig. 2). Group 1 had the highest survival probability, whereas Group 4 had the lowest. Groups 2 and 3 had intermediate survival probabilities.

There was a significant departure from multiplicativity between GV and LogSII for both 28-day all-cause mortality and ICU mortality (both $P_{\text{interaction}} = 0.016$). The joint associations were lower than expected from the associations of GV and LogSII considered separately. No significant additive interaction was observed for either outcome (Additional file 1). Cox proportional hazards regression further characterized mortality risk across the prespecified groups (Table 2). In the fully adjusted model, Groups 2, 3, and 4 all had higher 28-day mortality risk than the reference group (Group 1), with HRs of 1.64 (95% CI 1.39–1.94), 1.60 (95% CI 1.35–1.90), and 1.95 (95% CI 1.63–2.34), respectively (all

Table 1 Baseline characteristics according to 28-day survival status

Variables	Total ($n = 5564$)	Survivors ($n = 4509$)	Nonsurvivors ($n = 1055$)	P value
Demographics				
Age (years)	66 (54, 77)	65 (53, 76)	73 (63, 83)	< 0.001
Sex				0.614
Female	2377 (42.72%)	1919 (42.56%)	458 (43.41%)	
Male	3187 (57.28%)	2590 (57.44%)	597 (56.59%)	
Weight (kg)	81.80 (68.10, 98.60)	82.73 (68.80, 99.70)	77.90 (65.00, 93.40)	< 0.001
Vital signs				
Mean blood pressure (mmHg)	80 (68, 92)	80 (69, 92)	80 (67, 93)	0.887
Respiratory rate (breaths/min)	19 (16, 24)	19 (15, 24)	21 (17, 26)	< 0.001
Heart rate (beats/min)	90 (79, 106)	90 (79, 106)	91 (78, 107)	0.072
SpO_2 (%)	98 (95, 100)	98 (95, 100)	97 (94, 100)	< 0.001
Temperature (°C)	36.83 (36.44, 37.22)	36.83 (36.44, 37.28)	36.78 (36.44, 37.11)	< 0.001
Comorbidities				
Hypertension	2246 (40.37%)	1846 (40.94%)	400 (37.91%)	0.071
Cerebrovascular disease	438 (7.87%)	342 (7.58%)	96 (9.10%)	0.100
Diabetes mellitus	1662 (29.87%)	1341 (29.74%)	321 (30.43%)	0.661
Hyperlipidemia	2016 (36.23%)	1634 (36.24%)	382 (36.21%)	0.985
Heart failure	1865 (33.52%)	1445 (32.05%)	420 (39.81%)	< 0.001
Myocardial infarction	627 (11.27%)	462 (10.25%)	165 (15.64%)	< 0.001
Ischemic heart disease	2156 (38.75%)	1726 (38.28%)	430 (40.76%)	0.137
COPD	864 (15.53%)	649 (14.39%)	215 (20.38%)	< 0.001
Laboratory results				
Hemoglobin (g/dL)	10.60 (8.90, 12.20)	10.60 (8.90, 12.20)	10.50 (8.80, 12.20)	0.472
Platelet count ($\times 10^9$/L)	186 (129, 258)	185 (130, 257)	189 (126, 264)	0.923
RBC ($\times 10^{12}$/L)	3.53 (2.99, 4.14)	3.54 (3.00, 4.13)	3.52 (2.96, 4.15)	0.587
WBC ($\times 10^9$/L)	12.70 (8.80, 17.70)	12.60 (8.80, 17.40)	13.20 (9.00, 19.40)	< 0.001
Anion gap (mEq/L)	14 (12, 17)	14 (12, 17)	15 (13, 19)	< 0.001
Glucose (mg/dL)	134 (110, 176)	132 (109, 170)	148 (115, 202)	< 0.001
Potassium (mEq/L)	4.10 (3.70, 4.60)	4.10 (3.70, 4.60)	4.20 (3.70, 4.80)	0.006
Sodium (mEq/L)	139 (136, 142)	139 (136, 141)	139 (135, 142)	0.034
Creatinine (mg/dL)	1.10 (0.80, 1.60)	1.00 (0.80, 1.60)	1.30 (0.90, 2.00)	< 0.001
Blood urea nitrogen (mg/dL)	21 (14, 35)	20 (14, 32)	29 (18, 48)	< 0.001
Lactate (mmol/L)	1.80 (1.20, 2.80)	1.80 (1.20, 2.70)	2.10 (1.40, 3.40)	< 0.001
Neutrophils (%)	82.30 (75.00, 88.00)	82.00 (74.60, 87.30)	84.30 (77.00, 89.70)	< 0.001
Lymphocytes (%)	8.90 (5.00, 14.50)	9.30 (5.50, 15.10)	6.60 (3.80, 11.10)	< 0.001
Study exposures				
GV (%)	21.19 (14.75, 30.46)	20.30 (14.36, 29.41)	25.33 (17.32, 35.11)	< 0.001
LogSII	7.45 (6.67, 8.23)	7.39 (6.62, 8.16)	7.78 (6.95, 8.49)	< 0.001
Scoring systems				
SOFA score	6 (4, 9)	6 (4, 9)	8 (5, 11)	< 0.001
SAPS II score	40 (31, 50)	38 (30, 47)	49 (39, 58)	< 0.001
Charlson comorbidity index	5 (3, 6)	4 (2, 6)	6 (4, 8)	< 0.001
Therapy				
Invasive ventilation	5192 (93.31%)	4221 (93.61%)	971 (92.04%)	0.065
CRRT	558 (10.03%)	334 (7.41%)	224 (21.23%)	< 0.001
Vasopressor use	3971 (71.37%)	3129 (69.39%)	842 (79.81%)	< 0.001
Insulin	3182 (57.19%)	2583 (57.29%)	599 (56.78%)	0.764

Values are median (first quartile, third quartile) or number (percentage). Abbreviations: COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; GV, glycemic variability; ICU, intensive care unit; LogSII, natural logarithm of the systemic immune-inflammation index; RBC, red blood cell; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; SpO_2, peripheral oxygen saturation; WBC, white blood cell.

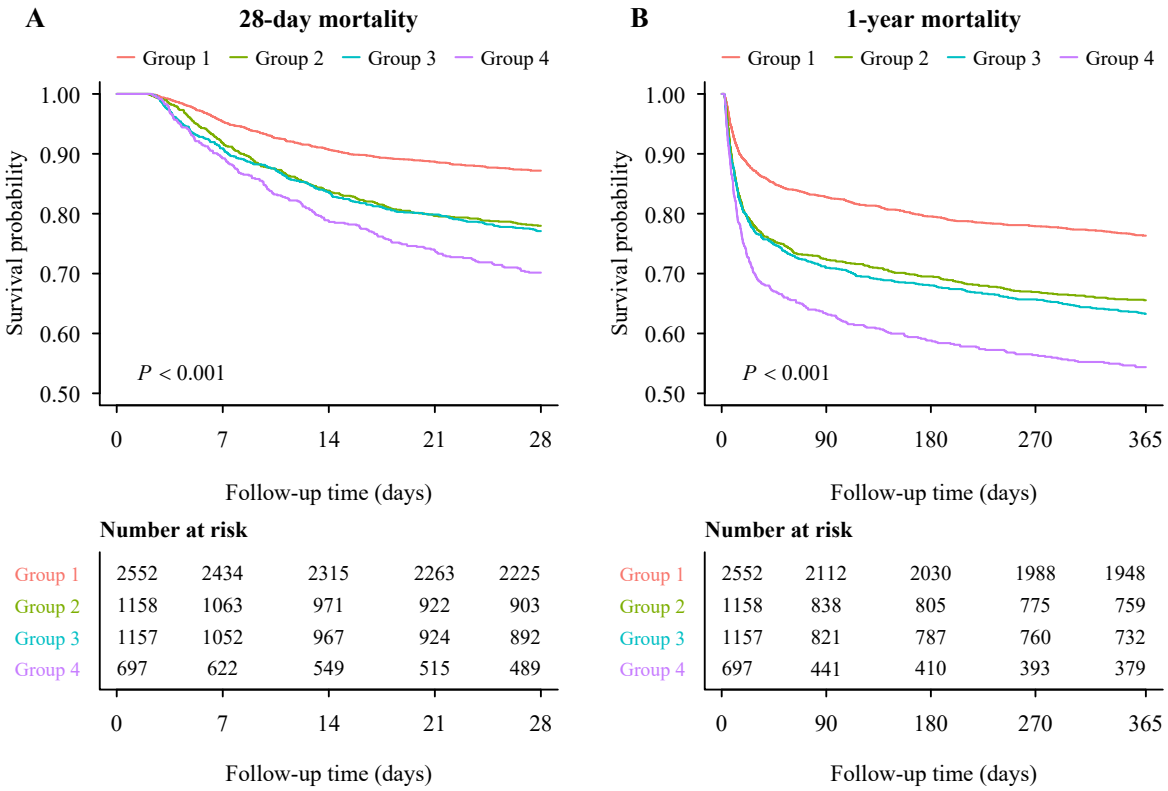


Fig. 2 Kaplan–Meier survival curves according to the joint GV and LogSII categories. (A) 28-day all-cause mortality; (B) 1-year all-cause mortality. Differences among groups were assessed using the log-rank test.

$P < 0.001$). Group 4 had the largest HR point estimate. Corresponding HRs for ICU mortality were 1.67 (95% CI 1.35–2.07), 1.50 (95% CI 1.22–1.86), and 1.73 (95% CI 1.37–2.18), respectively (all $P < 0.001$).

3.3 Incremental predictive value of combined GV and LogSII

ROC analysis assessed the discrimination of GV, LogSII, and their combination for mortality outcomes (Fig. 3). For 28-day mortality, AUROCs were 0.601 (95% CI 0.583–0.620), 0.582 (95% CI 0.562–0.602), and 0.619 (95% CI 0.601–0.638), respectively. The combined assessment had a higher AUROC than GV alone (DeLong $P = 0.017$) or LogSII alone ($P < 0.001$).

For ICU mortality, AUROCs for GV, LogSII, and their combination were 0.627 (95% CI 0.605–0.648), 0.576 (95% CI 0.552–0.600), and 0.634 (95% CI 0.613–0.656), respectively. The combined assessment had a higher AUROC than LogSII alone (DeLong $P < 0.001$), whereas the difference from GV alone was not statistically significant ($P = 0.355$).

NRI and IDI further described the incremental predictive value of the combined GV+LogSII Cox model over models containing GV or LogSII alone (Table 3). Categorical NRI used exploratory mortality-risk thresholds of 10%, 20%, and 30%; continuous NRI and IDI were calculated from individual predicted risks at the corresponding outcome time points. For 28-day mortality, categorical NRI, continuous NRI, and IDI were positive, with bootstrap 95% CIs above zero for both comparisons. For 1-year mortality, the corresponding intervals were above zero for comparison with the LogSII-only model. Compared with the

Table 2 Association of joint GV and LogSII categories with 28-day all-cause and ICU mortality

Group	Unadjusted		Model I		Model II		Model III	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
28-day all-cause mortality								
Group 1	1	Ref	1	Ref	1	Ref	1	Ref
Group 2	1.81 (1.54–2.14)	< 0.001	1.80 (1.53–2.13)	< 0.001	1.61 (1.37–1.90)	< 0.001	1.64 (1.39–1.94)	< 0.001
Group 3	1.90 (1.62–2.24)	< 0.001	1.87 (1.59–2.19)	< 0.001	1.88 (1.59–2.22)	< 0.001	1.60 (1.35–1.90)	< 0.001
Group 4	2.57 (2.16–3.06)	< 0.001	2.42 (2.03–2.88)	< 0.001	2.16 (1.80–2.58)	< 0.001	1.95 (1.63–2.34)	< 0.001
ICU mortality								
Group 1	1	Ref	1	Ref	1	Ref	1	Ref
Group 2	1.63 (1.32–2.00)	< 0.001	1.70 (1.38–2.10)	< 0.001	1.60 (1.29–1.98)	< 0.001	1.67 (1.35–2.07)	< 0.001
Group 3	1.57 (1.29–1.93)	< 0.001	1.54 (1.26–1.89)	< 0.001	1.60 (1.30–1.97)	< 0.001	1.50 (1.22–1.86)	< 0.001
Group 4	1.90 (1.52–2.37)	< 0.001	1.79 (1.44–2.24)	< 0.001	1.70 (1.35–2.14)	< 0.001	1.73 (1.37–2.18)	< 0.001

Values are HRs (95% CIs), with Group 1 as the reference (HR=1). Group 1: low GV/low LogSII; Group 2: low GV/high LogSII; Group 3: high GV/low LogSII; Group 4: high GV/high LogSII. High was defined as the highest tertile and low as the lower two tertiles.
Model I: adjusted for age and sex.
Model II: additionally adjusted for vital signs and comorbidities.
Model III: additionally adjusted for hemoglobin, creatinine, blood urea nitrogen, lactate, SOFA score, and insulin use.

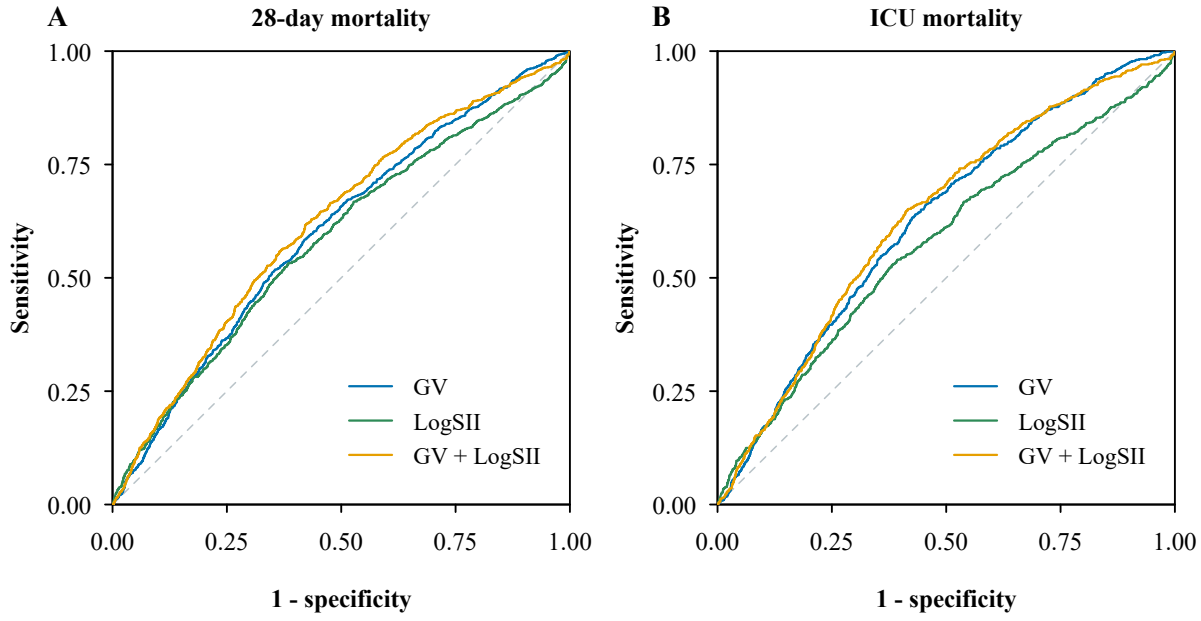


Fig. 3 ROC curves for mortality prediction using GV, LogSII, and their combination. (A) 28-day all-cause mortality; (B) ICU mortality.

GV-only model, continuous NRI and IDI had intervals above zero, whereas the categorical NRI interval included zero. Separate partial-likelihood ratio tests supported an additional contribution of either marker to the corresponding single-marker Cox model at both horizons (all model-comparison $P < 0.001$).

Table 3 Exploratory reclassification estimates and nested-model comparisons for combined GV and LogSII

Comparator	Categorical NRI (95% CI)	Continuous NRI (95% CI)	IDI (95% CI)	Model LRT P
28-day mortality				
GV	0.065 (0.023–0.123)	0.257 (0.187–0.331)	0.008 (0.003–0.014)	< 0.001
LogSII	0.082 (0.027–0.124)	0.277 (0.220–0.344)	0.011 (0.006–0.018)	< 0.001
1-year mortality				
GV	−0.003 (−0.024–0.030)	0.220 (0.162–0.273)	0.007 (0.003–0.013)	< 0.001
LogSII	0.076 (0.039–0.123)	0.283 (0.229–0.336)	0.016 (0.010–0.023)	< 0.001

CI, confidence interval; IDI, integrated discrimination improvement; LRT, likelihood ratio test; NRI, net reclassification improvement.

3.4 Nonlinear associations and subgroup analyses

RCS analyses showed significant overall associations of both GV and LogSII with 28-day mortality (overall $P < 0.001$ for both), with significant nonlinearity (GV, $P_{\text{nonlinearity}} = 0.001$; LogSII, $P_{\text{nonlinearity}} < 0.001$; Fig. 4). HRs generally increased at higher levels of both markers.

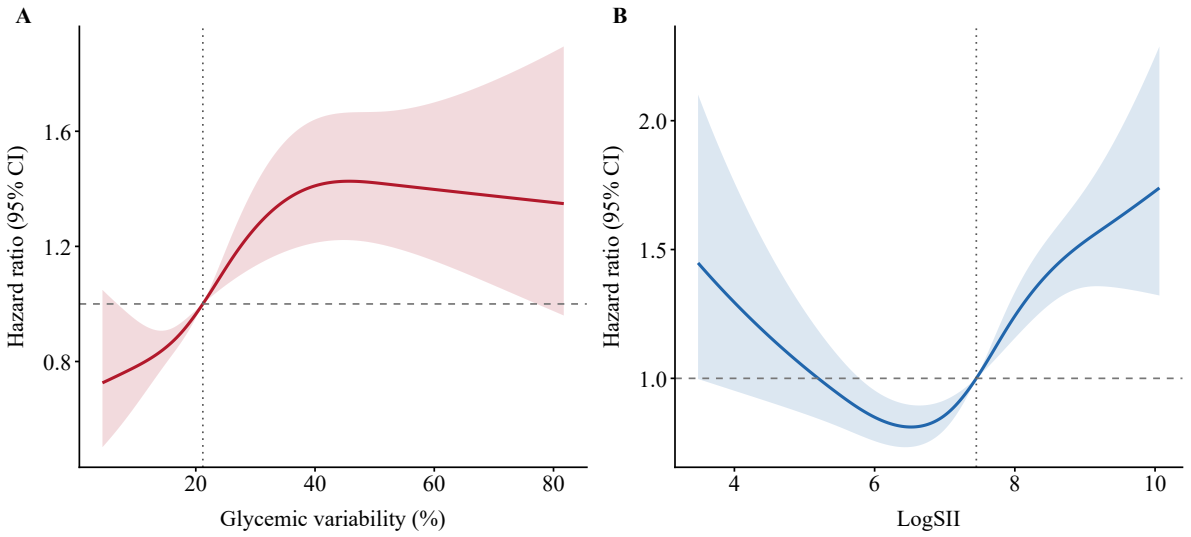
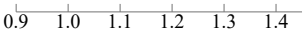


Fig. 4 Restricted cubic splines for GV and LogSII in relation to 28-day all-cause mortality. (A) GV; (B) LogSII. Curves were derived from fully adjusted Cox models. Solid lines show HRs and shaded areas show 95% CIs. Horizontal dashed lines denote HR=1, and vertical dashed lines indicate reference values.

The directions of the associations of GV and LogSII with 28-day mortality were consistent across most clinical subgroups (Fig. 5). Unadjusted interaction P values for GV across age and sex subgroups were 0.017 and 0.007, respectively, but neither remained significant after FDR correction. The interaction between LogSII and insulin use had an unadjusted P value of 0.049 and was also nonsignificant after correction (FDR-adjusted $P = 0.261$). Thus, no effect modifier remained statistically significant after adjustment for multiple comparisons.

A GV

Subgroup	Category	HR (95% CI)	P	Interaction P	FDR P
Overall		**1.12 (1.07–1.16)**	< 0.001		
Age				0.017	0.069
	<60	1.17 (1.08–1.28)	<0.001		
	≥60	1.10 (1.05–1.15)	<0.001		
Sex				0.007	0.060
	Female	1.04 (0.98–1.11)	0.190		
	Male	1.18 (1.12–1.24)	<0.001		
SOFA				0.963	0.963
	<6	1.11 (1.03–1.20)	0.006		
	≥6	1.12 (1.07–1.18)	<0.001		
Hypertension				0.792	0.963
	No	1.11 (1.06–1.17)	<0.001		
	Yes	1.12 (1.05–1.19)	<0.001		
COPD				0.927	0.963
	No	1.11 (1.06–1.16)	<0.001		
	Yes	1.13 (1.03–1.23)	0.009		
Diabetes				0.156	0.417
	No	1.13 (1.07–1.18)	<0.001		
	Yes	1.10 (1.02–1.18)	0.017		
Heart failure				0.341	0.593
	No	1.13 (1.08–1.19)	<0.001		
	Yes	1.08 (1.01–1.16)	0.020		
Insulin use				0.371	0.593
	No	1.12 (1.05–1.19)	<0.001		
	Yes	1.10 (1.04–1.16)	<0.001		



B LogSII

Subgroup	Category	HR (95% CI)	P	Interaction P	FDR P
Overall		**1.15 (1.09–1.22)**	< 0.001		
Age				0.472	0.755
	<60	1.14 (1.00–1.29)	0.042		
	≥60	1.16 (1.10–1.23)	<0.001		
Sex				0.098	0.261
	Female	1.22 (1.13–1.33)	<0.001		
	Male	1.10 (1.03–1.18)	0.007		
SOFA				0.074	0.261
	<6	1.25 (1.11–1.40)	<0.001		
	≥6	1.10 (1.03–1.16)	0.003		
Hypertension				0.582	0.776
	No	1.15 (1.08–1.24)	<0.001		
	Yes	1.16 (1.06–1.26)	<0.001		
COPD				0.851	0.955
	No	1.15 (1.08–1.22)	<0.001		
	Yes	1.19 (1.05–1.35)	0.006		
Diabetes				0.955	0.955
	No	1.16 (1.09–1.23)	<0.001		
	Yes	1.16 (1.04–1.29)	0.006		
Heart failure				0.362	0.724
	No	1.19 (1.11–1.27)	<0.001		
	Yes	1.09 (1.00–1.19)	0.043		
Insulin use				0.049	0.261
	No	1.10 (1.02–1.19)	0.015		
	Yes	1.19 (1.11–1.28)	<0.001		

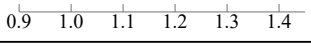


Fig. 5 Forest plots for subgroup analyses of (A) GV and (B) LogSII with 28-day all-cause mortality.

3.5 Sensitivity analysis

After excluding 21 patients with fewer than three eligible glucose measurements within 72 h after ICU admission, 5543 patients were included in the sensitivity analysis. The associations using early GV were consistent in direction with those in the main analysis. In Model III, the HRs (95% CIs) for Group 4 versus Group 1 were 1.78 (1.49–2.14) for 28-day all-cause mortality and 1.71 (1.36–2.16) for ICU mortality (both $P < 0.001$; Additional file 2, Table S2).

3.6 Model development and internal validation

Boruta-assisted predictor selection was performed in the training set (Additional file 3). Based on variable importance, multicollinearity, clinical interpretability, and availability, 7 variables—GV, LogSII, blood urea nitrogen, age, respiratory rate, vasopressor use, and SpO_2—were included in the final multivariable logistic regression model. A nomogram was constructed from this model (Fig. 6).

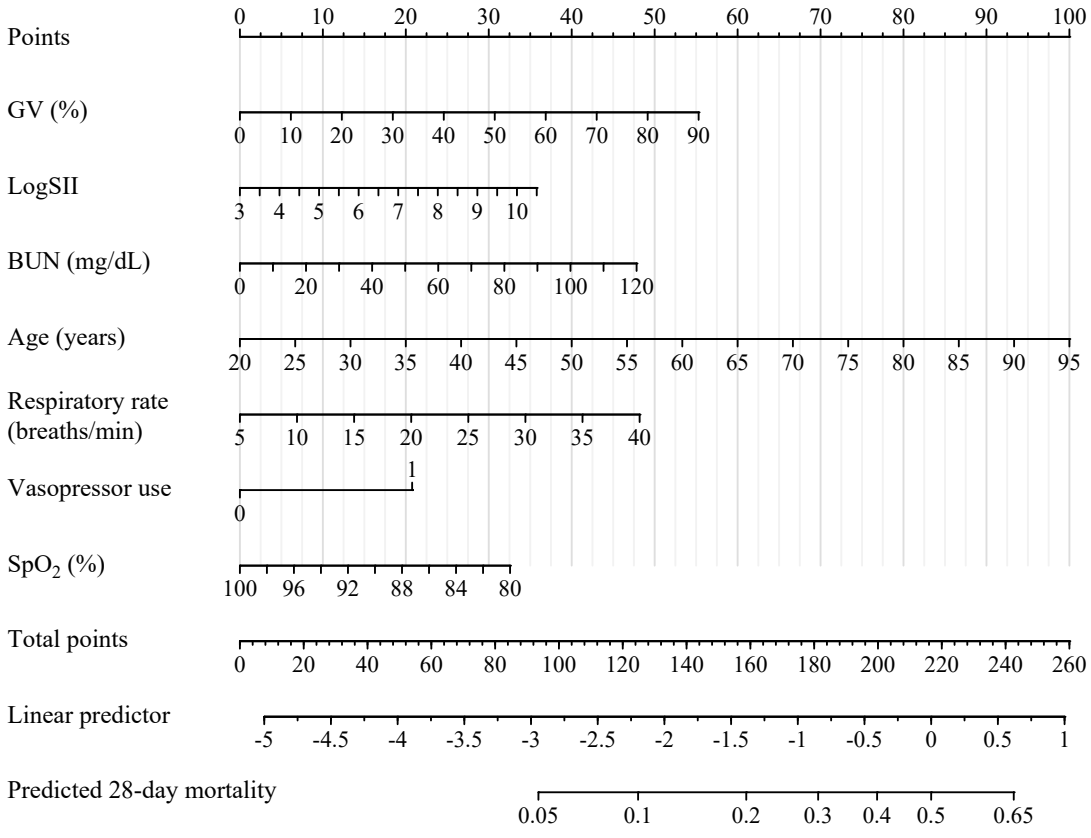


Fig. 6 Nomogram prediction model

Model performance is presented in Table 4 and Fig. 7. In the training set, the nomogram had an AUROC of 0.704 (95% CI 0.683–0.724), compared with 0.622 (95% CI 0.599–0.644) for SOFA (DeLong $P < 0.001$). Corresponding AUROCs in the internal validation set were 0.741 (95% CI 0.712–0.770) and 0.647 (95% CI 0.613–0.681), respectively ($P < 0.001$). The Brier score and calibration slope were 0.141

and 1.000 in the training set, and 0.137 and 1.177 in the internal validation set, respectively. Hosmer–Lemeshow tests did not indicate significant lack of fit in either set. Exploratory DCA suggested greater estimated net benefit for the nomogram than for SOFA and the treat-all and treat-none strategies over threshold probabilities of approximately 0.02–0.45 within the training and internal validation sets.

Compared with SOFA, the nomogram yielded continuous NRI values of 0.372 and 0.391 and IDI values of 0.051 and 0.062 in the training and internal validation sets, respectively; their bootstrap 95% CIs were above zero (Table 4). These exploratory estimates described gains in reclassification and separation of predicted risks.

Table 4 Comparison of the nomogram and SOFA for predicting 28-day all-cause mortality

Cohort	Model	AUROC (95% CI)	DeLong *P*	IDI (95% CI)	Continuous NRI (95% CI)
Training set	Nomogram	0.704 (0.683–0.724)			
	SOFA	0.622 (0.599–0.644)	< 0.001	0.051 (0.033–0.073)	0.372 (0.263–0.497)
Internal validation set	Nomogram	0.741 (0.712–0.770)			
	SOFA	0.647 (0.613–0.681)	< 0.001	0.062 (0.046–0.078)	0.391 (0.270–0.510)

DeLong *P* values compare paired AUROCs within each cohort. SOFA was the reference model for IDI and continuous NRI. AUROC, area under the receiver operating characteristic curve; CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification improvement; SOFA, Sequential Organ Failure Assessment.

3.7 External validation

External validation in two independent cohorts assessed model transportability across healthcare settings (Fig. 8). The AUROC was 0.678 (95% CI 0.657–0.699) in eICU-CRD and 0.651 (95% CI 0.599–0.702) in Zigong. Discrimination was lower than in internal validation, although the model retained some ability to distinguish patients at different levels of mortality risk.

3.8 Deployment of the web-based risk calculator

The final seven-variable logistic regression model was deployed as a web-based risk calculator for individualized estimation of 28-day mortality in patients with sepsis (Additional file 4, Figure S2). Users enter GV, LogSII, blood urea nitrogen, age, respiratory rate, vasopressor use, and SpO_2 to obtain the predicted probability of 28-day mortality and the corresponding survival probability. The interface also displays risk categories, points assigned to each predictor, the total point score, and a summary of the

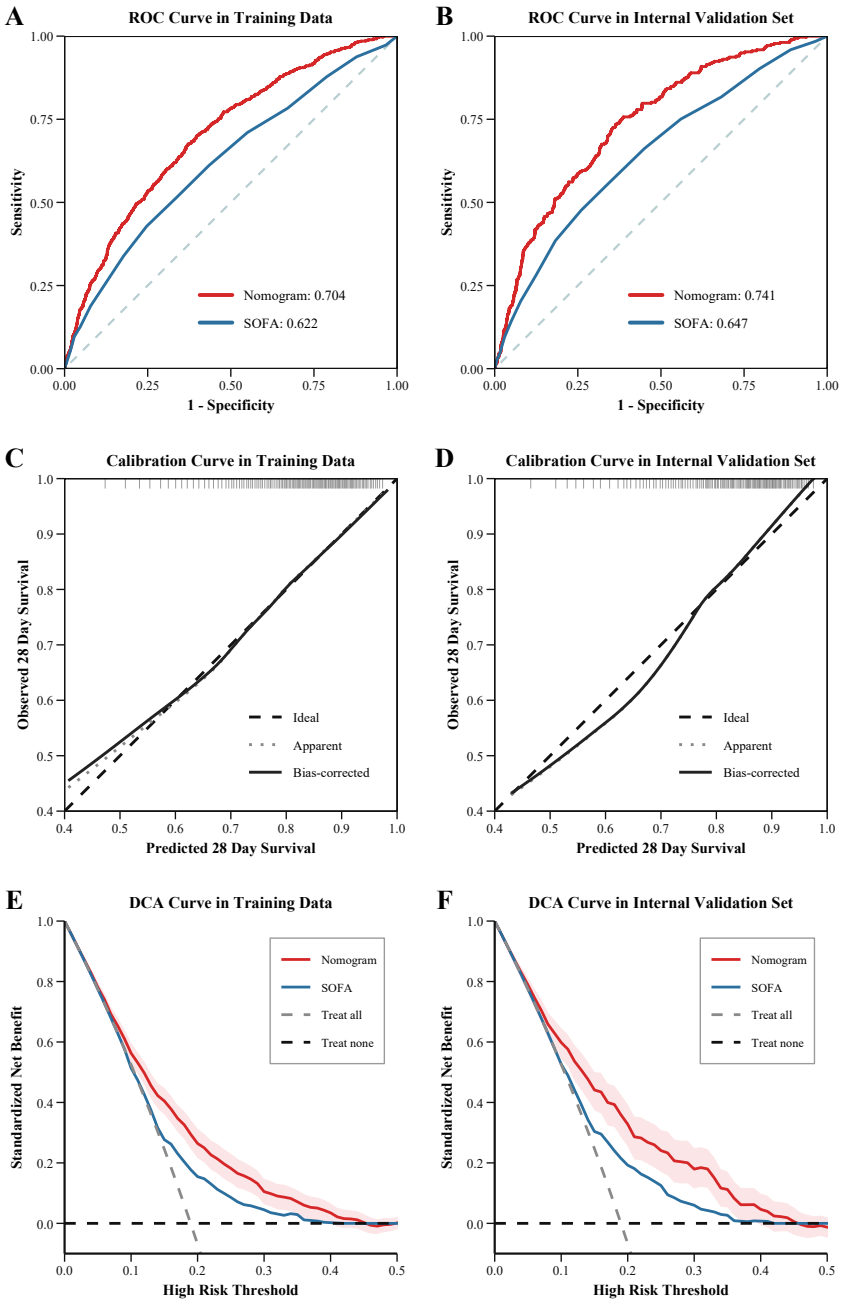


Fig. 7 Internal performance of the seven-variable nomogram. (A, B) ROC curves in the training and internal validation sets, respectively. (C, D) Calibration curves for 28-day survival probability (one minus the predicted mortality probability) in the training and internal validation sets. (E, F) Decision curves in the training and internal validation sets.

input values. Figure S2 uses demonstration inputs and does not represent a real patient record. The calculator is available at: https://stitches.shinyapps.io/icu-28day-seven-variable-nomogram/. It is intended to support risk estimation and stratification, but should not serve as the sole basis for clinical decisions.

4 Discussion

This study evaluated the associations of GV, LogSII, and their joint categories with mortality in patients with sepsis. We also developed and validated a model to predict 28-day mortality. Both markers were

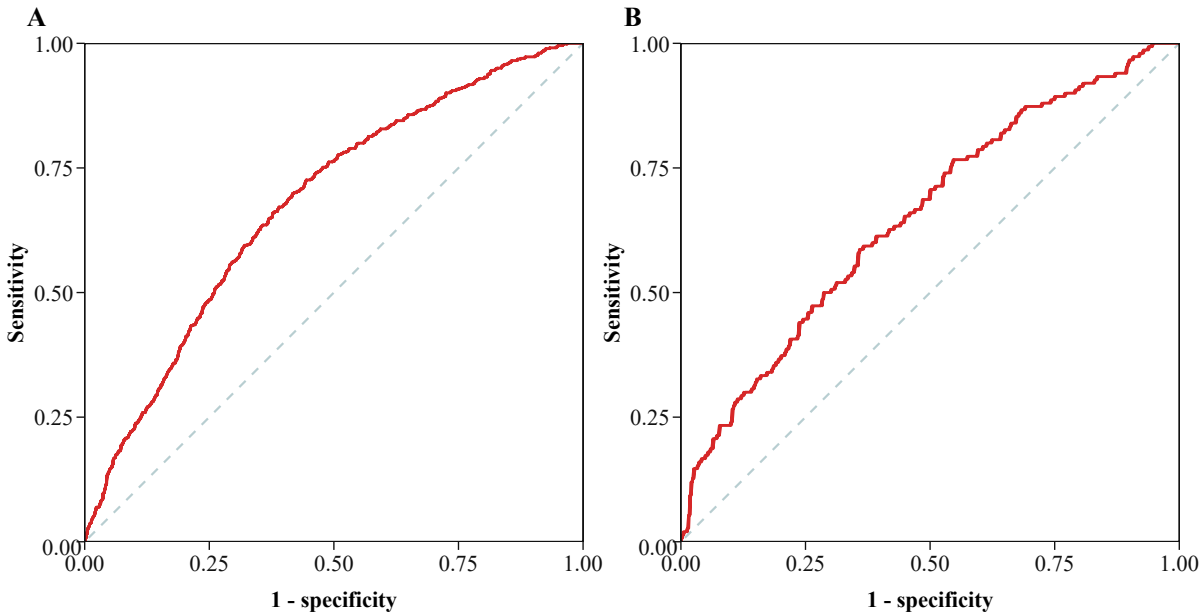


Fig. 8 External validation ROC curves for the seven-variable model. (A) eICU-CRD external validation cohort; (B) Zigong hospital external validation cohort. eICU-CRD, eICU Collaborative Research Database; ROC, receiver operating characteristic.

independently associated with this outcome after multivariable adjustment, with the numerically largest adjusted HR in Group 4. Their combined assessment achieved a higher AUROC than either marker alone, with positive exploratory NRI and IDI estimates for 28-day mortality. The resulting seven-variable model underwent internal validation in MIMIC-IV, followed by external validation in eICU-CRD and an independent cohort in China. These findings suggest that concurrent assessment of glucose fluctuations and systemic immune-inflammatory status may improve risk stratification in patients with sepsis.

GV captures glycemic fluctuations shaped by the stress response, insulin resistance, inflammation, nutritional support, and glucose-lowering treatment during critical illness. A systematic review and sepsis cohort studies have linked higher GV to adverse outcomes [9–12]. Metabolic reprogramming and mitochondrial dysfunction provide a pathological context for altered glucose regulation in sepsis [4, 25]. Separately, studies in people with type 2 diabetes and experimental glucose-clamp settings have associated glucose fluctuations with oxidative stress and impaired endothelial function [26, 27]. Whether GV directly contributes to endothelial injury in sepsis cannot be determined from these data. In this study, GV remained associated with 28-day mortality after adjustment for demographic characteristics, vital signs, comorbidities, laboratory measurements, and SOFA score. RCS analysis further indicated a nonlinear association with mortality. This pattern is broadly consistent with previous research on GV and prognosis in critical illness.

Recalculating GV from measurements obtained during the first 72 h yielded associations in the same direction as the main analysis. Group 4 remained associated with higher mortality than Group 1 for both outcomes after full adjustment. This finding supports the consistency of the joint-category associations across the two GV assessment windows.

SII integrates peripheral neutrophil, lymphocyte, and platelet counts to reflect systemic immune-inflammatory status. Neutrophil activation, lymphopenia, and altered platelet function and coagulation contribute to the dysregulated host response in sepsis. SII may therefore provide more comprehensive prognostic information than a single blood cell measurement. Previous MIMIC-IV studies have reported associations between SII and mortality in patients with sepsis [7, 8]. In our study, LogSII remained associated with 28-day mortality after full adjustment; RCS analysis indicated that this association was nonlinear. SOFA primarily assesses organ dysfunction, whereas LogSII reflects systemic immune-inflammatory status. LogSII may thus complement existing severity scores.

Joint assessment of GV and LogSII may provide additional prognostic information for 28-day all-cause mortality. The combined model had a higher AUROC than either marker alone. Significant negative multiplicative interactions between GV and LogSII were observed for both 28-day all-cause mortality and ICU mortality, whereas interactions on the additive scale were not statistically significant.

Previous studies have generally used single or composite inflammatory, nutritional, and metabolic indices for risk stratification, whereas comprehensive clinical prediction requires consideration of baseline characteristics, physiological status, and organ function [28–30]. We therefore integrated GV and LogSII with age, blood urea nitrogen, respiratory rate, vasopressor use, and SpO_2 to develop a seven-variable model. Age is closely related to physiological reserve and comorbidity burden. Blood urea nitrogen may reflect impaired renal function and increased catabolism during critical illness. Respiratory rate reflects respiratory workload, whereas SpO_2 indicates oxygenation. Vasopressor use indicates circulatory dysfunction requiring hemodynamic support. These variables are routinely available in ICU practice and have clear clinical interpretations.

The final model achieved AUROCs of 0.704 and 0.741 in the training and internal validation sets, respectively, both exceeding those of SOFA. Exploratory NRI and IDI estimates suggested gains in risk reclassification and discrimination relative to SOFA. DCA suggested greater estimated net benefit over part of the examined threshold range, but clinical benefit from model-guided intervention was not evaluated.

External validation assesses whether a prediction model retains its performance across populations and healthcare settings. Previous work on sepsis risk prediction has used geographically distinct cohorts for this purpose [31]. We evaluated our model in the multicenter US eICU-CRD cohort and an independent hospital cohort in China. Differences in case mix, illness severity, treatment practices, variable measurement, and outcome ascertainment may affect model performance. Further prospective validation and, where appropriate, model recalibration remain necessary.

To facilitate use of the model, we implemented the final logistic regression equation in a web-based interactive risk calculator. The interface returns individualized 28-day mortality probabilities from 7 predictors, together with the corresponding risk categories and point scores.

This study has several strengths. We examined the individual and joint associations of GV and LogSII with mortality using complementary analytical approaches. Model performance was assessed using discrimination, calibration, and decision curve analysis. In addition to internal validation in MIMIC-IV, external validation was performed in the multicenter eICU-CRD cohort and an independent hospital cohort in China. A publicly accessible web-based calculator was also developed.

This study has several limitations. The retrospective design precludes causal inference, and residual confounding cannot be excluded despite multivariable adjustment. Excluding patients who stayed in the ICU for less than 48 h or died within 48 h of admission may have introduced selection bias and limited applicability to patients who die early.

SII was derived from early ICU measurements and did not capture changes over time. Outcome ascertainment also differed across cohorts: the Zigong database included follow-up information, whereas eICU-CRD relied on 28-day in-hospital mortality [15, 17]. This difference may limit comparisons of model performance. Temporal validation and prospective multicenter studies are needed to further assess model stability, calibration, and clinical utility.

5 Conclusions

GV and LogSII were associated with 28-day all-cause mortality in patients with sepsis. Their combined assessment showed higher discrimination for this outcome than either marker alone. A seven-variable model combining these markers with routine clinical variables showed modest discrimination in MIMIC-IV internal validation and two independent external cohorts. The model was implemented as a web-based interactive calculator for individualized estimation of 28-day mortality risk.

List of abbreviations

AUROC: area under the receiver operating characteristic curve

CI: confidence interval

DCA: decision curve analysis

eICU-CRD: eICU Collaborative Research Database

FDR: false discovery rate

GV: glycemic variability

HR: hazard ratio

ICU: intensive care unit

IDI: integrated discrimination improvement

LogSII: natural logarithm of SII

MIMIC-IV: Medical Information Mart for Intensive Care IV

NRI: net reclassification improvement

ROC: receiver operating characteristic

SII: systemic immune-inflammation index

SOFA: Sequential Organ Failure Assessment

SpO_2: peripheral oxygen saturation

Declarations

Ethics approval and consent to participate

The use of the MIMIC-IV and eICU-CRD databases was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology. The use of the Zigong dataset was approved by the Ethics Committee of Zigong Fourth People's Hospital. All patient data were de-identified, and individual informed consent was not required for this secondary analysis.

Consent for publication

Not applicable.

Availability of data and materials

The original databases used in this study are available through PhysioNet, including MIMIC-IV, eICU-CRD, and the Critical Care Database Comprising Patients With Infection at Zigong Fourth People's Hospital. The data processed and analyzed in this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

Y.G. and H.S. contributed equally to this work. H.S. and Y.W. extracted the data from the MIMIC-IV database. Y.G. and C.Y. performed the data analysis. X.L. and Z.L. organized and supervised the

study. H.S. wrote the manuscript with supervision from Z.L. All authors reviewed and approved the final manuscript.

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We thank all the administrators who collected, organized and maintained the MIMIC-IV, eICU-CRD and Zigong datasets. This manuscript complies with all instructions to authors. Authorship requirements have been met and the final manuscript was approved by all authors. This manuscript has not been published elsewhere and is not under consideration by another journal.

Additional files

Additional file 1 (.pdf): Table S1. Additive and multiplicative interactions between GV and LogSII. Interaction estimates for 28-day and ICU mortality in fully adjusted Cox models.

Additional file 2 (.pdf): Table S2. Joint early-GV and LogSII categories and mortality. Sensitivity analysis using GV calculated within 72 h of ICU admission.

Additional file 3 (.pdf): Figure S1. Boruta feature selection in the training set. Importance of candidate predictors relative to shadow features.

Additional file 4 (.pdf): Figure S2. Web-based calculator for predicting 28-day mortality. Screenshots illustrating the calculator with demonstration inputs.

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