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Research Article

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Prognostic value of the haptoglobin to lactate ratio in sepsis patients with elevated troponin: a retrospective cohort study.

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Abstract

Background: Elevated troponin is a frequent and life-threatening complication among critically ill patients with sepsis. While lactate is a classic marker of tissue hypoperfusion and metabolic stress, haptoglobin (Hp) serves as a vital scavenger of toxic cell-free hemoglobin, reflecting the host's antioxidative defense capacity. Consequently, the haptoglobin-to-lactate ratio (HLR) may represent a novel composite index capturing the balance between physiological reserve and pathological insult. However, the prognostic value of HLR has not been systematically evaluated in the high-risk population of troponin-positive sepsis patients.This study aimed to examine the association between the HLR and both short- and long-term all-cause mortality in troponin-positive sepsis patients, and to assess its prognostic value in this high-risk population.

Methods: This retrospective cohort study was conducted using the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 3.1) database. Adult patients who met Sepsis-3 criteria and were admitted to the intensive care unit (ICU) were included. The troponin-positive sepsis subgroup was defined as an elevated serum troponin T (> 0.01 ng/mL) within the first 24 hours of ICU admission in the absence of acute coronary syndrome or other non-septic causes. The HLR was calculated as Hp (mg/dL) divided by serum lactate (mmol/L) on the first ICU day and analyzed both as a continuous variable and in quartiles. Baseline characteristics were compared across HLR quartiles. Survival differences were estimated using Kaplan–Meier curves. Cox proportional hazards regression models were applied to assess the independent association between HLR and 28-day and 90-day all-cause mortality. Non-linear relationships were explored using restricted cubic splines (RCS). Subgroup analyses were performed to test the consistency of associations across clinical strata.

Results: A total of 609 troponin-positive sepsis patients were included. Patients in higher HLR quartiles had lower SOFA scores and significantly lower lactate levels compared with those in lower quartiles. Kaplan–Meier analysis demonstrated significantly improved survival with increasing HLR quartiles (log-rank $P < 0.001$). In the fully adjusted multivariable Cox model including continuous lactate (Model E), the highest HLR quartile remained an independent predictor of 28-day mortality (HR 0.61, P=0.031). Adding HLR to lactate significantly improved risk reclassification (Continuous NRI = 0.199) . RCS analysis revealed an L-shaped non-linear relationship between HLR and mortality risk, with optimal breakpoints identified at 7.864 for 28-day mortality and 2.125 for 90-day mortality. Subgroup analysis indicated that the prognostic value of HLR was particularly pronounced in elderly patients aged ≥ 65 years (P for interaction = 0.035).

Conclusions: The HLR is an independent prognostic biomarker for predicting short- and long-term mortality in troponin-positive sepsis patients. This simple, inflammation–metabolism–based index may serve as a convenient tool for risk stratification and prognostic assessment in critical care settings.

Keywords: sepsis, myocardial injury, haptoglobin, lactate, biomarker, prognosis, MIMIC-IV, sepsis patients with elevated troponin,HLR

Introduction

Sepsis remains a leading cause of morbidity and mortality in intensive care units (ICUs) worldwide and is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection[1][2]. Among the multiple organ dysfunctions associated with sepsis, sepsis-associated myocardial injury (typically identified by elevated troponin) is particularly concerning. Sepsis-associated myocardial injury is characterized by reversible myocardial depression and elevated cardiac biomarkers, such as troponin, in the absence of acute coronary syndrome[3][4]. It has been reported that elevated troponin occurs in 30–50% of patients with sepsis and is independently associated with a significantly increased risk of death[5][6]. Therefore, early and accurate risk stratification in this population is essential to guide clinical decision-making.

Haptoglobin (Hp) is an acute-phase plasma protein that binds free hemoglobin (Hb), thereby reducing Hb-induced oxidative damage. Clinical data have shown that higher serum Hp levels are associated with lower 28-day mortality in patients with septic shock, suggesting a potential protective role[7]. Recent studies have further demonstrated that terminal fucosylation of Hp (Fu-Hp) at Asn207 and Asn211 is significantly elevated in the plasma of patients with sepsis. Fu-Hp can interact with macrophage C-type lectin receptors such as Mincle (CLEC4E), activating the NF-κB and MAPK pathways and inducing the release of pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α), as well as activating the NLRP3 inflammasome[8].Hp is synthesized and degraded primarily in the liver, its expression is regulated by inflammation, and its plasma levels have been used as a biomarker for tissue damage and infection[9].

Lactate is a sensitive indicator of metabolic stress and circulatory decompensation. In sepsis, pro-inflammatory cytokines such as IL-1β promote lactate production by inducing a shift toward aerobic glycolysis; elevated lactate levels therefore are not solely due to tissue hypoxia[10].Moreover, lactate itself may modulate immune responses by acting via lactate transporters and epigenetic mechanisms to influence immune cell function[11]. Thus, lactate integrates both hemodynamic and immunometabolic derangements in sepsis.

To date, no study has systematically investigated the prognostic value of the haptoglobin-to-lactate ratio (HLR) in troponin-positive sepsis patients. We hypothesized that the HLR, which combines an index of antioxidative and hemoglobin-scavenging capacity (Hp) with a marker of metabolic stress (lactate), may provide superior prognostic information compared with either parameter alone. Using data from the large, publicly available MIMIC-IV database, this study aimed to evaluate whether the HLR is associated with short- and long-term mortality and to determine its potential role in risk stratification among patients with sepsis-associated myocardial injury.

Methods

Data Source

This retrospective cohort study was conducted using data from the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 3.1) database. MIMIC-IV contains comprehensive, de-identified health-related data for patients admitted to the ICUs of Beth Israel Deaconess Medical Center in Boston, USA[12].The use of MIMIC-IV has been approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center, and the requirement for individual informed consent was waived because all data are de-identified. The authors completed the required training and obtained access to the database prior to data extraction(record number:72371138).

Study Population

We initially identified all adult patients (aged ≥ 18 years) who were admitted to the ICU and met the Sepsis-3 criteria (suspected or documented infection plus an acute increase in SOFA score ≥ 2) in the MIMIC-IV database. A total of 41,295 ICU admissions with sepsis were screened. The patient selection process was as follows: (1) patients younger than 18 years were excluded; (2) patients with an ICU length of stay less than 24 hours were excluded; (3) patients with missing measurements of either serum lactate or haptoglobin on the first day of ICU admission were excluded; (4) non-first ICU admissions for the same patient were excluded; and (5) patients with a history of heart failure, myocardial infarction, chronic obstructive pulmonary disease, or acute myocarditis were excluded. After these exclusions, 1,272 adult patients with sepsis and complete Hp and lactate data were included in the cohort.

Definition of sepsis patients with elevated troponin

Sepsis patients with elevated troponin was defined as an elevated serum troponin T concentration > 0.01 ng/mL within the first 24 hours of ICU admission, in the absence of acute coronary syndrome or other non-septic causes of myocardial injury[13]. According to troponin T measurements and values, patients were categorized as follows: (1) troponin T not measured (n = 644); (2) troponin T ≤ 0.01 ng/mL (n = 19); and (3) troponin T > 0.01 ng/mL, fulfilling the definition of the troponin-positive sepsis subgroup (n = 609). The primary analytical sample for this study consisted of the 609 troponin-positive sepsis patients.

Exposure: Haptoglobin-to-Lactate Ratio

The primary exposure of interest was the haptoglobin-to-lactate ratio (HLR). Haptoglobin (Hp) and serum lactate were both measured within the first 24 hours of ICU admission. The HLR was calculated as Hp (mg/dL) divided by lactate (mmol/L). Troponin-positive sepsis patients were further stratified into quartiles according to HLR values: Q1 ($0.18 \leq HLR \leq 19.71$, n = 153), Q2 ($20.00 \leq HLR \leq 57.32$, n = 152), Q3 ($60.00 \leq HLR \leq 136.25$, n = 152), and Q4 ($136.36 \leq HLR \leq 716.00$, n = 152).

Outcomes

The primary outcomes were 28-day and 90-day all-cause mortality after ICU admission. Mortality status and dates of death were obtained from in-hospital records and linked long-term follow-up data in MIMIC-IV.

$$Hp/LA\ Ratio = \frac{\text{Initial Haptoglobin (mg/dL)}}{\text{Initial Lactate (mmol/L)}}$$

Covariates

Baseline variables extracted from the database included demographics (Age, Gender), vital signs, comorbidities (e.g., Diabetes , Chronic Kidney Disease (CKD)), laboratory parameters (Albumin, Creatinine, Glucose, Hemoglobin, Platelet count, activated partial thromboplastin time（APTT), white blood cell count(WBC), peak troponin T, and severity scores (SOFA). Therapeutic interventions recorded during the first 24 hours included the use of Mechanical Ventilation, Vasopressors, and continuous renal replacement therapy (CRRT).

Handling of Missing Data

Prior to analysis, the extent of missing data for all baseline variables was evaluated. Variables with more than 20% missingness were excluded to ensure data quality. For variables with less than 20% missingness, missing values were assumed to be missing at random. Multiple imputation by chained equations (MICE) was performed using the mice package in R. Five imputed datasets were generated using predictive mean matching for continuous variables to preserve the original data distribution. Regression analyses were conducted separately in each imputed dataset, and results were pooled according to Rubin's rules. Multicollinearity among covariates was assessed using the variance inflation factor (VIF), and variables with VIF > 5 were removed from the final models.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate, and compared across HLR quartiles using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test. Categorical variables were presented as counts (percentages) and compared using the chi-square test. Kaplan–Meier survival curves were constructed for 28-day and 90-day mortality according to HLR quartiles, and differences were assessed using the log-rank test.

Five multivariable Cox proportional hazards models were constructed to evaluate the independence of HLR. Model A was unadjusted. Model B was adjusted for SOFA score and age. Model C and D were further adjusted for continuous lactate and haptoglobin, respectively, to evaluate the incremental value of the ratio over its individual components. Model E was the fully adjusted model including all aforementioned covariates. Restricted cubic spline (RCS) functions with four knots at the 5th, 35th, 65th, and 95th percentiles of the HLR distribution were used to evaluate potential non-linear relationships between HLR and mortality risk. Subgroup analyses were performed according to age, sex, and CKD status, and multiplicative interactions were tested by including product terms in the Cox models. A two-sided *P*-value < 0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 609 troponin-positive sepsis patients were included in the final analysis. The flowchart of patient selection from the MIMIC-IV database is shown in Figure 1. Baseline demographic characteristics, comorbidities, laboratory findings, and clinical outcomes stratified by HLR quartiles are summarized in Table 1. Among the included patients, 357 (58.6%) were male, 95 (15.6%) had diabetes mellitus, and 222 (36.4%) had CKD. Vasopressors were administered to 479 (78.7%) patients, and 570 (93.6%) required mechanical ventilation.

Patients were categorized into four HLR quartiles: Q1 ($0.18 \leq HLR \leq 19.71$, n = 153), Q2 ($20.00 \leq HLR \leq 57.32$, n = 152), Q3 ($60.00 \leq HLR \leq 136.25$, n = 152), and Q4 ($136.36 \leq HLR \leq 716.00$, n = 152). Compared with patients in the highest quartile (Q4), those in lower quartiles (Q1–Q3) generally had higher SOFA scores, higher lactate levels, increased white blood cell counts, prolonged APTT, and higher peak troponin T levels. In contrast, platelet counts and Hp concentrations were higher in the Q4 group. Both 28-day and 90-day mortality rates were significantly lower in Q4 than in the lower quartiles, particularly Q1 ($P < 0.05$).

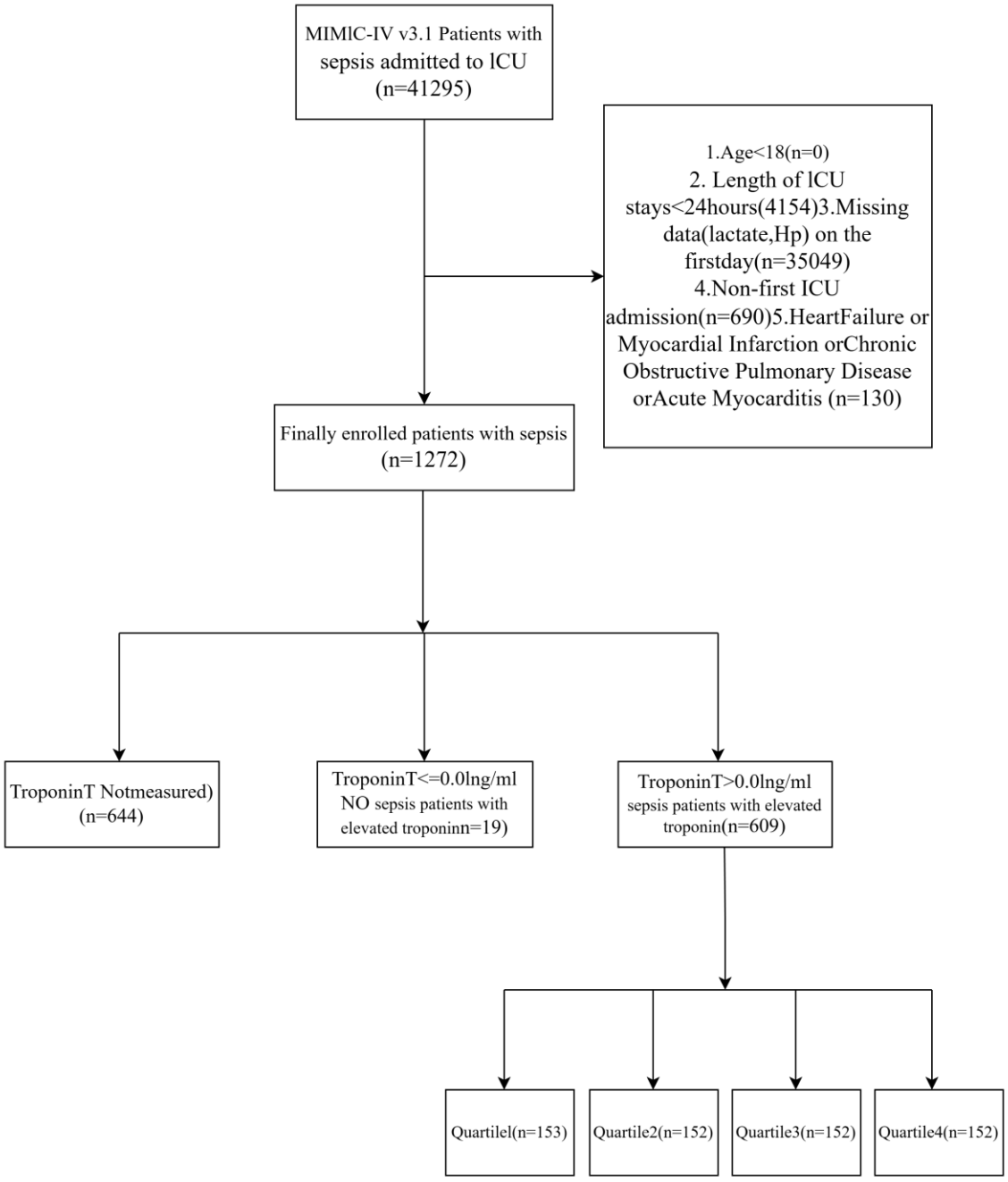


Fig.1Selection of the study population from the MIMIC-IV database

Table 1: **Baseline characteristics of study population stratified by Haptoglobin/Lactate Ratio**

Characteristic	Q1 (N = 153)	Q2 (N = 152)	Q3 (N = 152)	Q4 (N = 152)	*P*-value
Demographics					
Gender, Male n (%)	96 (62.7%)	80 (52.6%)	92 (60.5%)	89 (58.6%)	0.315
Age, median (IQR)	62.0 (46.0, 70.0)	67.0 (54.5, 80.0)	68.0 (55.0, 81.0)	69.0 (57.5, 76.5)	<0.001
Comorbidities, n (%)					
Diabetes	20 (13.1%)	16 (10.5%)	28 (18.4%)	31 (20.4%)	0.063
Chronic Kidney Disease	40 (26.1%)	54 (35.5%)	49 (32.2%)	79 (52.0%)	<0.001
Clinical Status					
CRRT Use, n (%)	74 (48.4%)	75 (49.3%)	85 (55.9%)	78 (51.3%)	0.560
Mech. Ventilation, n (%)	147 (96.1%)	139 (91.4%)	142 (93.4%)	142 (93.4%)	0.430
Vasopressor Use, n (%)	129 (84.3%)	130 (85.5%)	118 (77.6%)	102 (67.1%)	<0.001
SOFA Score, median	12.0 (9.0, 14.0)	10.0 (7.0, 13.0)	8.0 (6.0, 10.0)	7.0 (5.0, 10.0)	<0.001
Outcomes, n (%)					
28-day Mortality	81 (52.9%)	65 (42.8%)	62 (40.8%)	48 (31.6%)	0.002
90-day Mortality	91 (59.5%)	83 (54.6%)	73 (48.0%)	64 (42.1%)	0.014
Laboratory Findings					
Lactate (mmol/L)	6.1 (3.5, 9.4)	2.8 (1.8, 4.2)	2.1 (1.4, 2.6)	1.2 (1.0, 1.5)	<0.001
Haptoglobin (mg/dL)	43 (24, 78)	103 (62, 158)	183 (143, 238)	257 (215, 344)	<0.001
Haptoglobin/Lactate Ratio	9.2 (4.4, 13.5)	34.1 (27.6, 45.6)	94.8 (76.4, 113.6)	220.0 (167.4, 261.1)	<0.001
Albumin (g/dL)	2.9 (2.4, 3.3)	2.9 (2.4, 3.3)	2.9 (2.5, 3.3)	2.8 (2.4, 3.2)	0.520
Creatinine (mg/dL)	1.8 (1.2, 2.8)	1.9 (1.2, 3.3)	1.4 (1.0, 2.8)	1.8 (1.0, 3.4)	0.164
Glucose (mg/dL)	159 (102, 230)	142 (110, 179)	131 (106, 163)	136 (105, 178)	<0.001
Hemoglobin (g/dL)	10.0 (8.4, 12.5)	10.0 (8.1, 11.8)	9.6 (8.1, 11.3)	9.2 (7.4, 11.0)	<0.001
Platelets ($\times 10^9$/L)	127 (58, 194)	138 (78, 219)	152 (88, 248)	186 (103, 280)	<0.001
WBC ($\times 10^9$/L)	12.4 (7.6, 21.2)	12.9 (8.3, 20.3)	11.4 (8.3, 16.4)	11.7 (7.5, 16.6)	0.024

Data are presented as n (%) or median (interquartile range).

CRRT: Continuous Renal Replacement Therapy; SOFA: Sequential Organ Failure Assessment.

Association Between HLR and Mortality

Kaplan–Meier survival curves revealed a clear gradient of risk across HLR quartiles for both 28-day and 90-day mortality, with patients in Q4 exhibiting the highest survival probability and those in Q1 the lowest (log-rank $P < 0.001$ for both endpoints).

Five progressive multivariate Cox proportional hazards models were constructed to evaluate the independence and incremental prognostic value of HLR. In the unadjusted Model A, higher HLR

was significantly associated with a lower risk of 28-day mortality (Q4 vs. Q1: HR 0.46, 95% CI 0.32–0.66, $P < 0.001$). After adjusting for baseline severity (SOFA score and age) in Model D, the highest HLR quartile (Q4) remained a robust independent protector (HR 0.55, 95% CI 0.38–0.81, $P = 0.002$) (**Table 2 and Table 3)**.

Crucially, in the head-to-head comparison with lactate (Model E), the prognostic significance of HLR Q4 persisted even after adjusting for absolute lactate concentrations as a continuous variable (HR 0.61, 95% CI 0.38–0.95, $P = 0.031$). Notably, in this combined model, the independent association of lactate with 28-day mortality was no longer statistically significant ($P = 0.449$), suggesting that HLR captures unique prognostic information beyond tissue hypoperfusion alone. For the 90-day mortality analysis, HLR demonstrated superior prognostic stability across all models. In the baseline model (Model D), HLR Q4 was significantly associated with reduced 90-day mortality (HR 0.58, 95% CI 0.41–0.82, P=0.002). The most striking finding was observed in Model E: after simultaneously adjusting for SOFA score, age, and continuous lactate levels, HLR Q4 remained a significant independent predictor (HR 0.62, 95% CI 0.41–0.93, P=0.021). In contrast, the absolute lactate level lost its independent prognostic value in this combined model (P=0.635). These results reinforce that HLR provides distinct and more durable prognostic information for long-term survival than lactate alone(**Table 4 and Table 5)**.

Table 2: Multivariate Cox proportional hazards models for 28-day mortality (Part 1: Models A–C).

Variables	Model A	Model B	Model C
	HR (95% CI), *P*	HR (95% CI), *P*	HR (95% CI), *P*
SOFA score	–	1.11 (1.08–1.15), < 0.001	1.13 (1.10–1.17), < 0.001
Age (years)	–	1.02 (1.01–1.03), < 0.001	1.02 (1.01–1.03), < 0.001
Target Biomarker (Quartiles)			
Q1 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	0.69 (0.50–0.96), 0.028	1.54 (1.06–2.25), 0.025	0.90 (0.64–1.27), 0.556
Q3	0.66 (0.48–0.92), 0.015	1.57 (1.08–2.28), 0.018	0.84 (0.59–1.20), 0.336
Q4	0.46 (0.32–0.66), < 0.001	2.02 (1.39–2.91), < 0.001	0.91 (0.64–1.29), 0.601

Note: Model A: Unadjusted HLR; Model B: Lactate quartiles + SOFA + Age;
Model C: Haptoglobin quartiles + SOFA + Age.

Table 3: Multivariate Cox proportional hazards models for 28-day mortality (Part 2: Models D–E).

Variables	Model D	Model E
	HR (95% CI), *P*	HR (95% CI), *P*
SOFA score	1.12 (1.08–1.16), < 0.001	1.12 (1.08–1.15), < 0.001
Age (years)	1.02 (1.01–1.03), < 0.001	1.02 (1.01–1.03), < 0.001
Target Biomarker (Quartiles)		
Q1 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	0.68 (0.49–0.95), 0.025	0.73 (0.50–1.06), 0.096
Q3	0.77 (0.54–1.10), 0.155	0.84 (0.55–1.27), 0.400
Q4	0.55 (0.38–0.81), 0.002	0.61 (0.38–0.95), 0.031
Continuous Adjustment		
Lactate	–	1.02 (0.98–1.06), 0.449

Note: Model D: HLR quartiles + SOFA + Age;
Model E: HLR quartiles + SOFA + Age + continuous Lactate.

Table 4: Multivariate Cox proportional hazards models for 90-day mortality (Part 1: Models A–C).

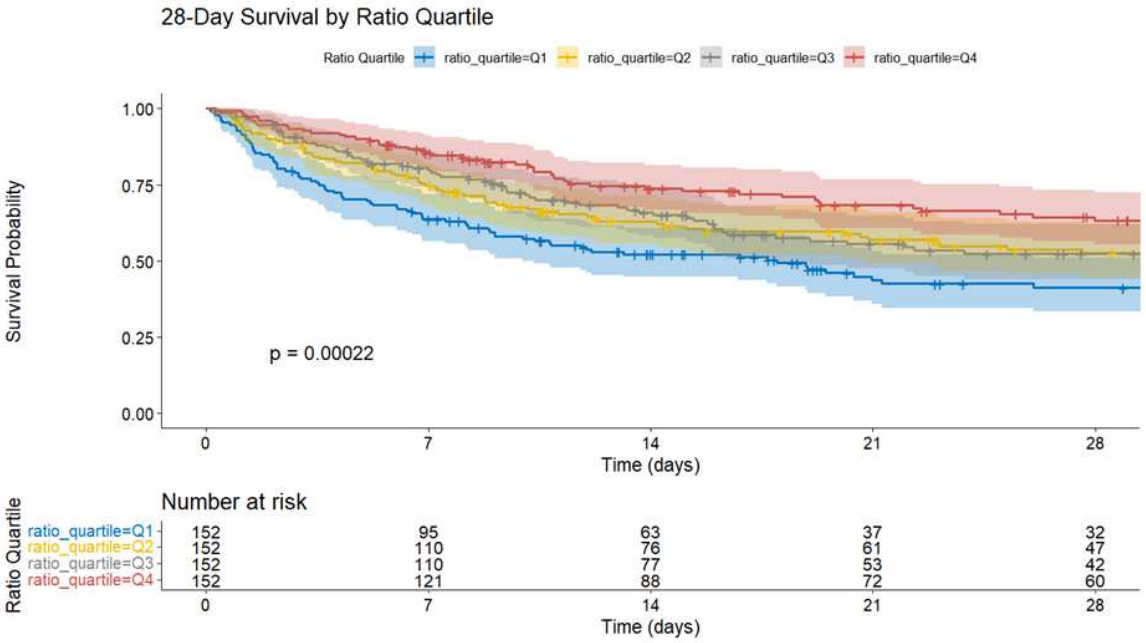
Variables	Model A	Model B	Model C
	HR (95% CI), P	HR (95% CI), P	HR (95% CI), P
SOFA score	–	1.10 (1.07–1.14), < 0.001	1.12 (1.08–1.15), < 0.001
Age (years)	–	1.02 (1.01–1.02), < 0.001	1.02 (1.01–1.02), < 0.001
Target Biomarker (Quartiles)			
Q1 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	0.73 (0.54–0.99), 0.042	1.60 (1.15–2.23), 0.005	0.80 (0.58–1.09), 0.160
Q3	0.65 (0.48–0.88), 0.006	1.58 (1.14–2.21), 0.006	0.82 (0.59–1.12), 0.212
Q4	0.49 (0.35–0.67), < 0.001	1.83 (1.31–2.56), < 0.001	0.81 (0.59–1.12), 0.203

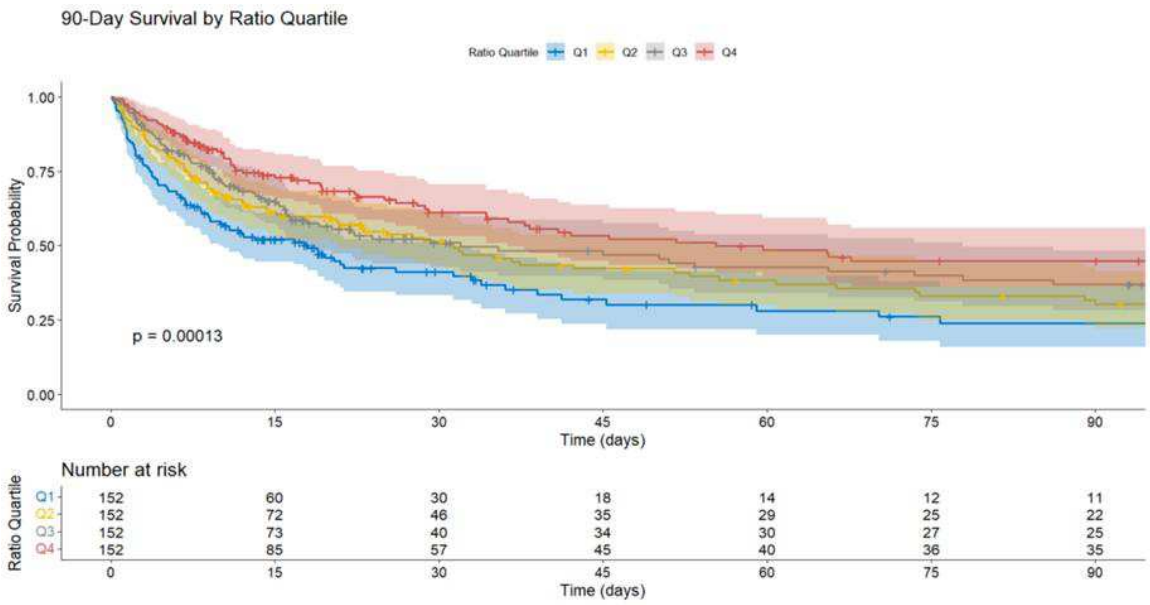
Note: Model A: Unadjusted HLR; Model B: Lactate quartiles + SOFA + Age;
Model C: Haptoglobin quartiles + SOFA + Age.

Table 5: Multivariate Cox proportional hazards models for 90-day mortality (Part 2: Models D–E).

Variables	Model D	Model E
	HR (95% CI), P	HR (95% CI), P
SOFA score	1.10 (1.07–1.14), < 0.001	1.10 (1.07–1.14), < 0.001
Age (years)	1.02 (1.01–1.03), < 0.001	1.02 (1.01–1.03), < 0.001
Target Biomarker (Quartiles)		
Q1 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	0.72 (0.53–0.98), 0.040	0.75 (0.53–1.06), 0.100
Q3	0.75 (0.54–1.04), 0.081	0.78 (0.53–1.14), 0.204
Q4	0.58 (0.41–0.82), 0.002	0.62 (0.41–0.93), 0.021
Continuous Adjustment		
Lactate	–	1.01 (0.97–1.05), 0.635

Note: Model D: HLR quartiles + SOFA + Age;
Model E: HLR quartiles + SOFA + Age + continuous Lactate.

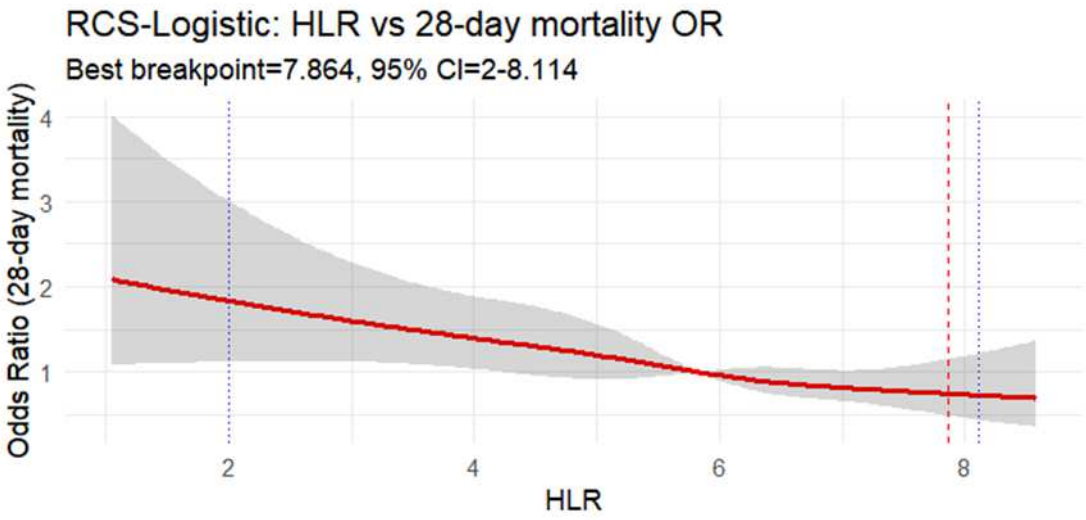


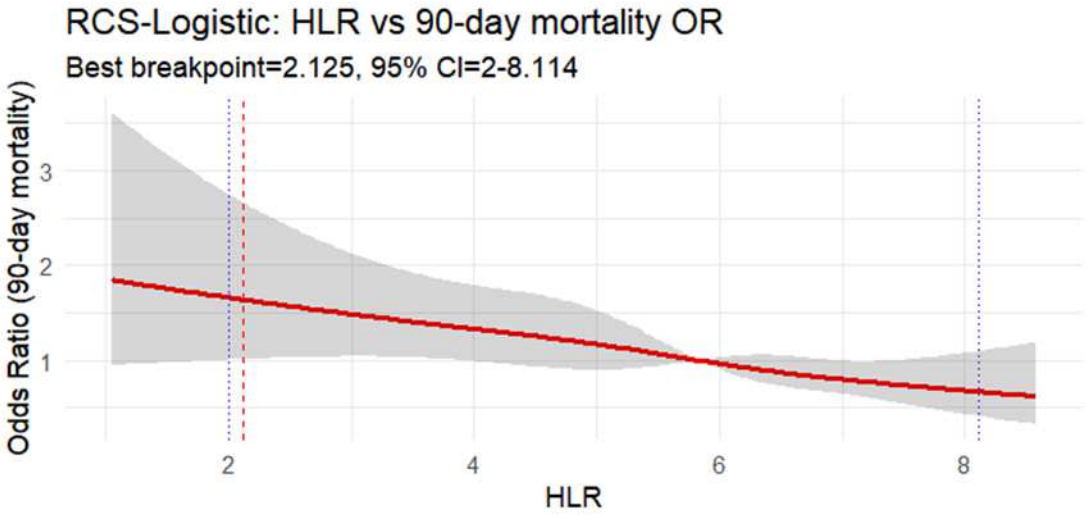


Non-linear Relationship Between HLR and Mortality

To visually assess the non-linear dose-response relationship between the HLR and the risk of mortality, we utilized restricted cubic spline (RCS) models based on logistic regression. The model was fitted using the rms package in R. We placed 4 knots at the 5th, 35th, 65th, and 95th percentiles of the HLR distribution to effectively capture the potential non-linear shape. The reference value was set at the median (or the first quartile) of the HLR. A test for non-linearity was performed by assessing the significance of the non-linear terms (*P* for non-linearity). Furthermore, we calculated the optimal cutoff value (breakpoint) where the protective association significantly plateaued or changed trajectory, based on the shape of the spline curve.

- 28-day Mortality: The risk of death decreased sharply as the HLR increased, plateauing after a breakpoint of 7.864 (95% CI: 2–8.114).
- 90-day Mortality: A similar L-shaped curve was observed:with a best breakpoint calculated at 2.125 (95% CI: 2–8.114). This suggests that maintaining an HLR above these thresholds is critical for survival.





Incremental Predictive Performance

We further evaluated the incremental value of HLR over lactate alone. The combined model (Lactate + HLR) yielded an AUC of 0.611 compared to 0.610 for lactate alone (**Figure5**). Importantly, adding HLR to the lactate model significantly improved risk reclassification with a Continuous NRI of 0.199 and an IDI of 0.001. Calibration plots indicated good model fit (**Figure6**). Furthermore, DCA demonstrated that incorporating HLR provided a superior net clinical benefit across relevant threshold probabilities compared to lactate alone (**Figure7**).

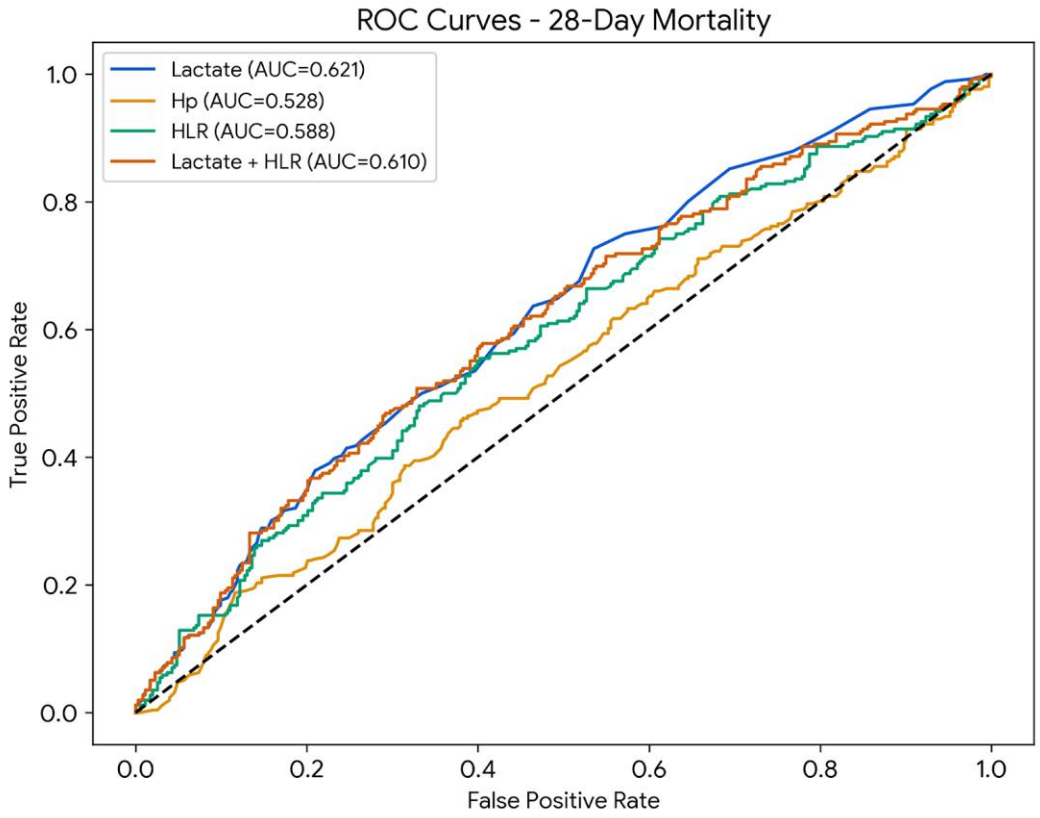


Figure5: Receiver operating characteristic (ROC) curves for 28-day mortality. The curves illustrate the predictive performance of Lactate, Haptoglobin (Hp), the Haptoglobin-to-Lactate Ratio (HLR), and the combined model (Lactate + HLR) in troponin-positive sepsis patients.. The area under the curve (AUC) values for each predictor are detailed in the legend.

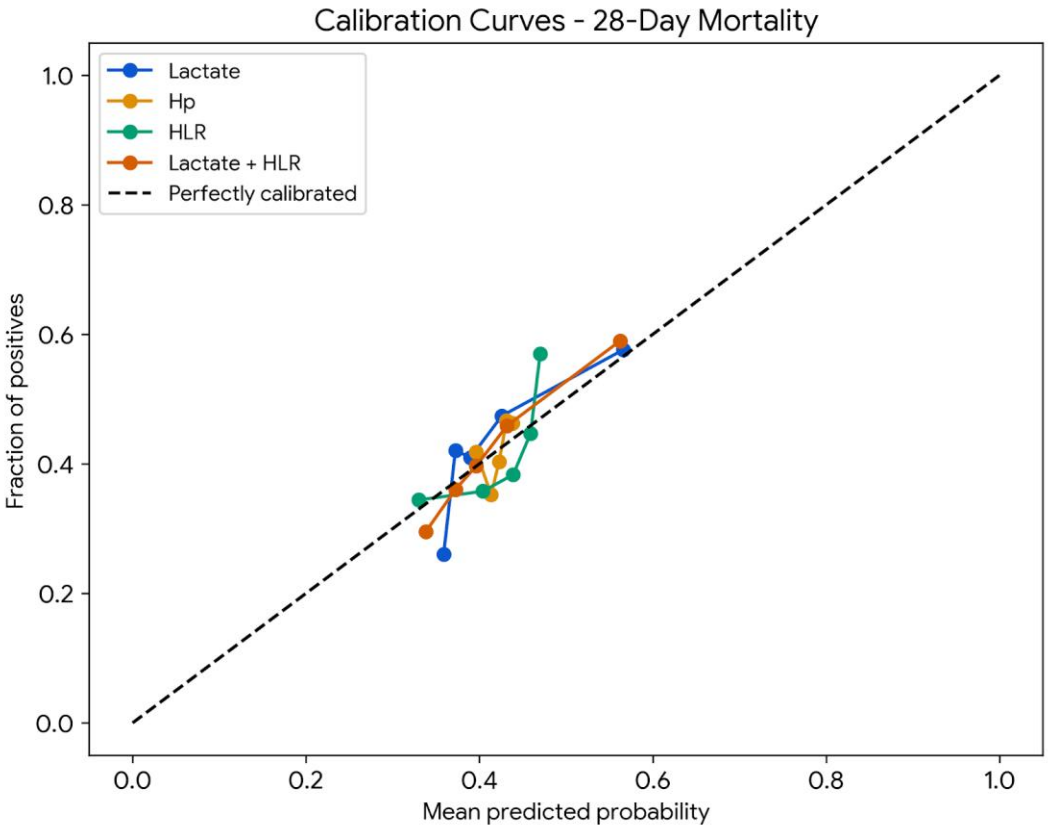


Figure6: Calibration curves of the predictive models for 28-day mortality. The dashed line represents perfect calibration, where predicted probabilities match observed proportions. Curves for Lactate (blue), Hp (yellow), HLR (green), and the combined Lactate + HLR model (orange) are shown.

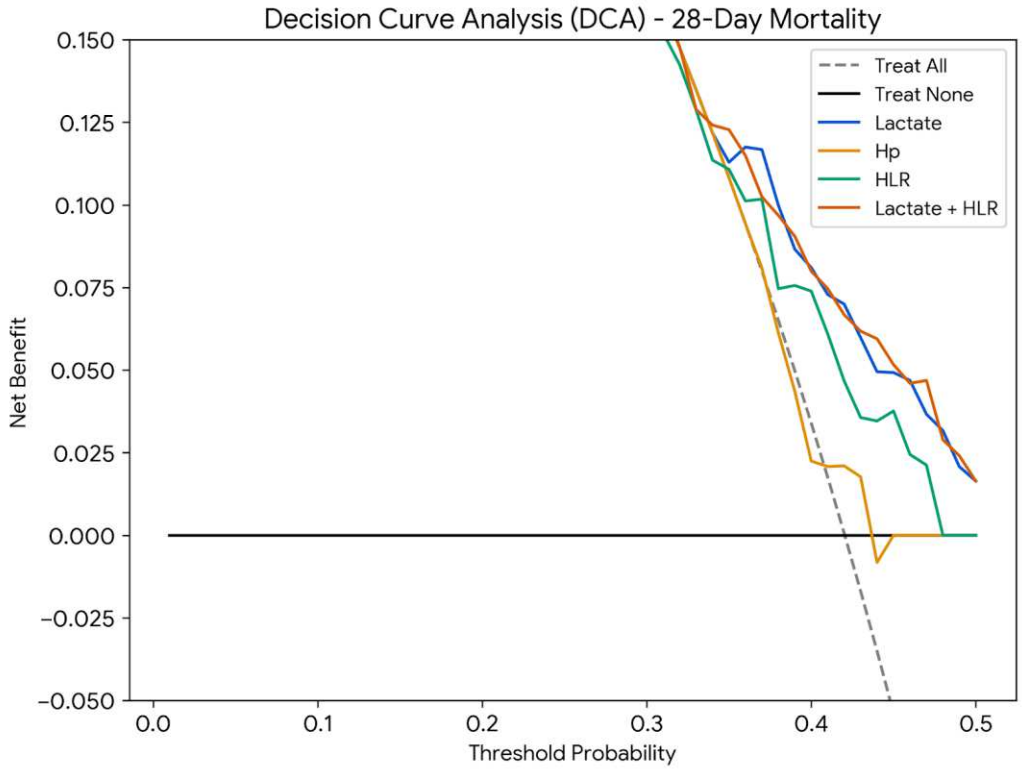


Figure7: Decision curve analysis (DCA) for 28-day mortality.

Sensitivity Analysis for Unmeasured Confounding

The E-value for the association between the highest HLR quartile and 28-day mortality in the fully adjusted Model E was 2.66 (lower CI limit: 1.28), suggesting robust resistance to potential unmeasured confounding

Subgroup Analyses

Subgroup analyses for 90-day mortality showed that the inverse association between higher HLR and mortality was generally consistent across sex and CKD subgroups (*P* for interaction > 0.05 for both). However, a significant interaction was observed for age (P for interaction = 0.035). In patients aged ≥ 65 years, the protective effect of higher HLR was particularly pronounced; in this group, Q4 was associated with a substantially reduced risk of death (HR 0.35, 95% CI 0.23–0.54). Forest plots of subgroup analyses for 28-day and 90-day mortality are presented in Figures 8 and 9.

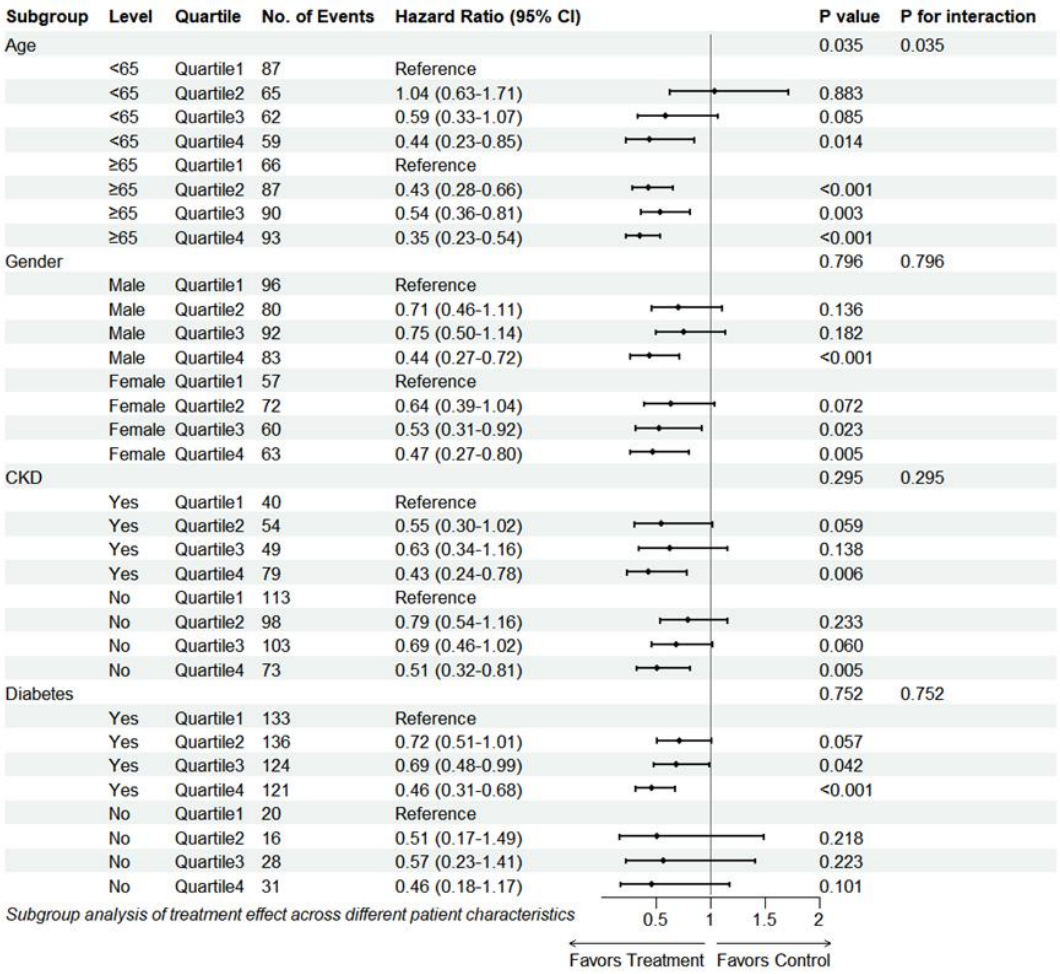


Fig.8 Subgroup forest plots for 28-day all-cause mortality. Adjusted for age, gender, CKD,Diabetes,.HLR: the Quartile1 ($0.18 \leq HLR \leq 19.71$, N=153), the Quartile2 ($20.00 \leq HLR \leq 57.32$, N=152), the Quartile3 ($60.00 \leq HLR \leq 136.25$, N=152), and the Quartile4 ($136.36 \leq HLR \leq 716.00$, N=152)..HR hazard rati o, CI confidence interval

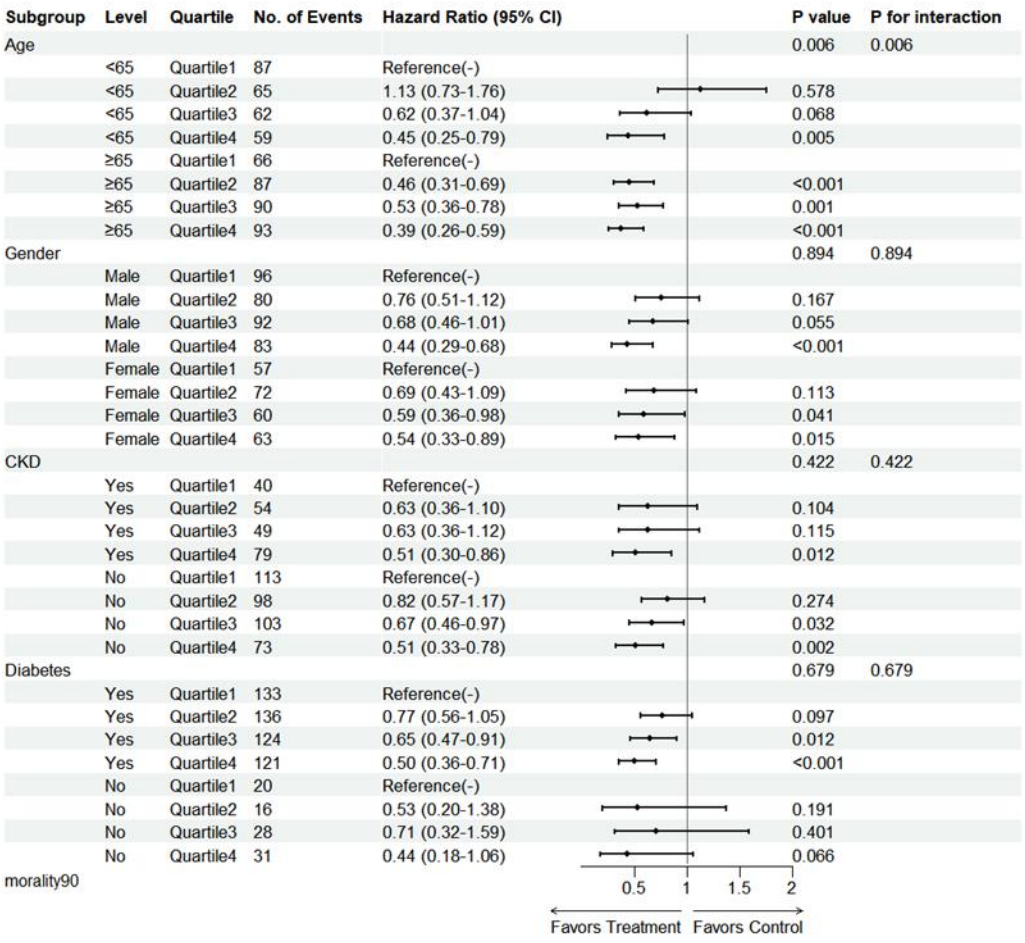


Fig.9 Subgroup forest plots for 90-day all-cause mortality. Adjusted for age, gender, CKD,Diabetes,.HLR: the Quartile1 ($0.18 \leq Hp/LA \leq 19.71$, N=153), the Quartile2 ($20.00 \leq Hp/LA \leq 57.32$, N=152), the Quartile3 ($60.00 \leq Hp/LA \leq 136.25$, N=152), and the Quartile4 ($136.36 \leq Hp/LA \leq 716.00$, N=152)..HR hazard rati o, CI confidence interval

Discussion

In this large, retrospective cohort study based on the MIMIC-IV database, we demonstrated for the first time that the haptoglobin-to-lactate ratio is a strong and independent predictor of both short- and long-term mortality in troponin-positive sepsis patients. Lower HLR values were associated with substantially higher 28-day and 90-day mortality, and RCS analysis revealed a distinct L-shaped relationship, indicating that mortality risk increases steeply below specific HLR thresholds.

The non-linear relationship identified in our RCS analysis suggests that mortality risk increases sharply when HLR falls below a certain level, though the exact breakpoints (e.g., 7.864) are likely cohort-specific and require prospective validation[14][47].

Mechanistically, a low HLR likely reflects the convergence of two detrimental processes: impaired antioxidative and hemoglobin-scavenging capacity (low Hp) and heightened metabolic

stress (high lactate). In sepsis, hyperlactatemia is a composite marker of tissue hypoperfusion, mitochondrial dysfunction, and adrenergic stimulation, and is closely linked to adverse outcomes and myocardial dysfunction[15][16]. Concurrently, sepsis is frequently accompanied by intravascular hemolysis, leading to the release of cell-free hemoglobin (CFH) and heme, which promote oxidative stress, vasoconstriction, endothelial injury, and organ dysfunction[17][18][19][20][21]. From a pathophysiological perspective, the clinical significance of a suppressed HLR may be interpreted through the theoretical lens of intravascular hemolysis and metabolic distress. Previous literature has established that as haptoglobin reserves are exhausted, the accumulation of cell-free hemoglobin can scavenge nitric oxide (NO), potentially triggering vasoconstriction and microcirculatory impairment [22][23]. Although our study did not directly measure cell-free hemoglobin or NO levels, the observed association between low HLR and adverse outcomes aligns with the established role of haptoglobin in mitigating heme-mediated toxicity [21][28]. Furthermore, existing experimental evidence suggests that heme-driven oxidative stress may involve pathways like ferroptosis, to which cardiomyocytes are particularly sensitive [24][25][26]. While these specific molecular pathways were not directly quantified in this retrospective cohort, the HLR may serve as a circulating proxy reflecting the exhaustion of these protective scavenger systems. Consequently, a low HLR could signal a state of 'double hit'—unmitigated oxidative insult paired with profound metabolic failure—thereby explaining its robust prognostic value in troponin-positive sepsis patients. Thus, a suppressed HLR not only reflects systemic ischemia but serves as a circulating proxy for the specific risk of myocardial iron toxicity and mitochondrial collapse.Parallel to this, the lactate component of HLR signals mitochondrial distress. In septic cardiomyopathy, cardiomyocytes undergo profound metabolic reprogramming and mitochondrial suppression, which can blunt contractility regardless of oxygen supply[27] . Hp is the principal intravascular scavenger of CFH, forming Hp–Hb complexes that facilitate clearance via CD163-expressing macrophages and mitigate hemoglobin-mediated toxicity[21][28][29].Low Hp concentrations in this context indicate an overwhelmed scavenger system and are associated with greater CFH burden and worse clinical outcomes[19][20][30].Therefore, a low HLR signals a “double hit” of severe metabolic derangement and inadequate antioxidative defense, which may be particularly deleterious for myocardial tissue.

Our findings also resonate with the growing interest in composite biomarker ratios in sepsis. Ratios such as the lactate/albumin ratio (LAR) have been shown to outperform lactate alone for mortality prediction in sepsis and septic shock, likely because they integrate multiple pathophysiological domains into a single index[31][32]. The HLR follows a similar conceptual framework. Compared with albumin, Hp is more specifically linked to the hemolysis and oxidative stress pathway, whereas albumin is a general negative acute-phase reactant influenced by inflammation, capillary leak, hepatic function, and nutritional status[33][34][35]. Although cardiac troponin remains the diagnostic cornerstone for myocardial injury, its prognostic precision in sepsis is frequently clouded by issues like reduced renal clearance or non-ischemic leakage. HLR offers a different perspective by integrating two upstream drivers of injury: hemolytic oxidative stress and metabolic failure. Rather than merely reflecting established cellular damage, this ratio captures the ongoing systemic toxicity burden, potentially providing a more dynamic gauge of physiological reserve than static biomarkers alone[36].In our cohort, HLR remained significantly

associated with mortality after adjustment for SOFA score and other confounders, suggesting that it captures unique information not fully reflected in conventional organ failure scores. From a translational perspective, the clinical utility of HLR lies in its pragmatic accessibility. While novel biomarkers for sepsis, such as mid-regional pro-adrenomedullin (MR-proADM) or soluble urokinase plasminogen activator receptor (suPAR), show promise, their high cost and limited availability restrict routine implementation in resource-limited settings[37][38]. In contrast, haptoglobin and lactate are standard components of admission panels in most intensive care units. The prognostic signal of HLR suggests it may provide supplementary risk stratification information upon admission. Identifying patients with a disproportionately low HLR upon admission could trigger earlier, more aggressive hemodynamic monitoring or adjunctive therapies aimed at mitigating hemolysis [39].

The observed interaction between age and HLR suggests a potentially more pronounced prognostic value in older patients (**Figure 9**). However, this finding should be interpreted with caution as an exploratory interaction that might represent statistical noise within a modest sample size. Should this association be validated in larger cohorts, several age-related physiological factors reported in previous literature could be considered as potential contributors. For instance, advancing age is associated with increased erythrocyte fragility and accumulated oxidative damage[40][41][42], which may influence circulating hemoglobin dynamics. Haptoglobin plays a critical role in these hemolytic states [43][44], and diminished hepatic functional reserve in the elderly could theoretically impair haptoglobin synthesis and lactate clearance [45]. This framework aligns with earlier observations that lactate-based indices carry strong prognostic weight in metabolically fragile populations [46][47]. Nevertheless, these mechanistic links remain purely speculative in our study, and further research is needed to determine if age truly modifies the clinical utility of HLR.

This study has several strengths. First, we leveraged a large, high-quality, publicly available critical care database with detailed clinical and laboratory data. Second, we performed comprehensive adjustment for potential confounders and used advanced statistical techniques, including multiple imputation for missing data and RCS modelling to explore non-linear relationships. Third, we conducted subgroup and interaction analyses to examine the robustness and generalizability of the findings across clinically relevant strata.

Several limitations should also be acknowledged. First, as haptoglobin is not routinely measured in all sepsis patients, our final cohort represents a highly selected, sicker subgroup where clinicians likely suspected hemolysis or liver dysfunction (indication bias). Second, we excluded patients with a history of heart failure, MI, or COPD to reduce baseline confounders for myocardial injury. We acknowledge that this blunt exclusion reduces the generalizability of our findings, as these pre-existing conditions are highly prevalent in real-world ICU sepsis populations.Due to the retrospective observational design, residual confounding cannot be fully excluded despite extensive adjustment. External validation in independent datasets is lacking, and our findings may not be generalizable to populations or settings where Hp and lactate are not routinely measured. Additionally, the requirement for concurrent measurements of Hp and lactate on ICU admission may have introduced selection bias. Finally, there is no universally accepted diagnostic standard for sepsis patients with elevated troponin; troponin T is highly sensitive but

not specific for sepsis patients with elevated troponin, and some degree of misclassification is possible.

Implications and Future Directions

Our findings suggest that the HLR is a promising, readily available biomarker for risk stratification in troponin-positive sepsis patients. Because Hp and lactate are routinely measured in many ICUs, the HLR can be calculated at minimal additional cost and may complement existing severity scores such as SOFA. Future studies should aim to (i) validate the prognostic value and optimal thresholds of HLR in independent multicenter cohorts; (ii) evaluate its incremental predictive performance over established risk models; (iii) characterize dynamic changes in HLR during the ICU stay; and (iv) explore whether therapeutic interventions targeting hemolysis, oxidative stress, or tissue perfusion can favorably modify HLR and improve clinical outcomes.

Conclusions

The haptoglobin-to-lactate ratio is a independent prognostic biomarker for 28-day and 90-day mortality in troponin-positive sepsis patients. Lower HLR values are associated with significantly worse survival, whereas higher ratios confer a protective effect. By integrating information on metabolic stress and host defense against hemoglobin-mediated toxicity, HLR offers a simple and potentially valuable tool for refined risk stratification in the ICU.

Declarations

Clinical trial number: not applicable.

The data used in this study were obtained from the MIMIC-IV database. The establishment of this database and the waiver for individual informed consent were approved by the Institutional Review Boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. All participants in the database were de-identified to protect their privacy, and the study was conducted in accordance with the Declaration of Helsinki. The data used in this study were obtained from the MIMIC-IV database. The establishment of this database was approved by the Institutional Review Boards (IRB) of the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC). All participants in the database were de-identified to protect their privacy, and the requirement for informed consent was waived by the IRB. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication Not applicable.

Availability of data and materials The data that support the findings of this study are available from the MIMIC-IV database (https://physionet.org/content/mimiciv/). Access to the database requires user certification.

Competing interests The authors declare that they have no competing interests.

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Authors' contributions Chaoyue Yu performed the data analysis and prepared the figures. Chaoyue Yu and Shaobo Cui wrote the manuscript. Dongrong Li, Yinghui Li, Jun Jin, Qi Ding, and Xinjing Yang reviewed the manuscript. All authors read and approved the final manuscript.These authors have contributed equally to this work.

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