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Association between the low-density lipoprotein to high-density lipoprotein ratio and prognosis in critically ill intracerebral hemorrhage patients: a retrospective cohort study from the MIMIC-IV database

Yuchen Liu[1†], Houxin Fu[2†], Yue Wang[3], Yi Zhong[1], Rongting Zhang[1], Jingxuan Sun[1], Tianquan Yang[1], Yong Han[1], Yongjun Xiang[1], Bin Yuan[1], Ruxuan Zhou[1], Min Chen[1] and Hangzhou Wang[1*]

Abstract

Background The relationship between lipid profiles and intracranial hemorrhage (ICH) has garnered increasing attention. The ratio of low-density lipoprotein to high-density lipoprotein (LHR) is one of the key lipid profile indices. However, studies investigating the association between LHR and the prognosis of critically ill ICH patients remain limited.

Methods Data for this study were obtained from the MIMIC-IV 3.1 database. Initially, the association between LHR and short-term outcomes in ICH patients, including ICU mortality, in-hospital mortality, and 28-day mortality, was analyzed using Cox regression in both continuous and categorical models. Additionally, restricted cubic spline (RCS), subgroup, and sensitivity analyses were conducted to further validate our findings.

Results The study included 873 critically ill ICH patients, among whom 20.3% (177/873) succumbed within 28 days. Higher LHR was independently associated with lower short-term mortality in ICH patients (28-day mortality: HR = 0.82, 95% CI: 0.68 ~ 0.99, $P = 0.039$; In-hospital mortality: HR = 0.7, 95% CI: 0.55 ~ 0.89, $P = 0.004$; ICU mortality: HR = 0.66, 95% CI: 0.48 ~ 0.92, $P = 0.015$). The RCS revealed a linear relationship between LHR and short-term all-cause mortality. Subgroup analyses demonstrated consistent results. The optimal cutoff value for LHR was determined to be 1.21. Comparing the mortality risk between the low-LHR and high-LHR groups, the high-LHR group exhibited higher survival rates (28-day mortality, $P = 0.0052$; In-hospital mortality, $P = 0.019$; ICU mortality, $P = 0.044$). Furthermore, higher LHR was also correlated with lower disease severity scores (SAPS-II: r = -0.158, $P < 0.001$, OASIS: r = -0.117, $P = 0.006$).

Conclusion LHR was negatively associated with short-term mortality in critically ill ICH patients. It may aid clinicians in identifying high-risk individuals and providing timely interventions.

[†]Yuchen Liu and Houxin Fu have contributed equally to this work and share the first authorship.

*Correspondence:
Hangzhou Wang
wanghangzhoudr@126.com
Full list of author information is available at the end of the article

Keywords Low-density lipoprotein to high-density lipoprotein ratio (LHR), MIMIC-IV, Intracerebral hemorrhage, Lipid metabolism, Prognosis

Introduction

Stroke is the second leading cause of death worldwide and a primary contributor to long-term disability globally [1–3]. Although hemorrhagic stroke accounts for only one-fifth of all stroke cases, it is responsible for nearly half of stroke-related deaths, with intracerebral hemorrhage (ICH) being the most common subtype [4–6]. As the global population continues to age, the burden of stroke is increasing [7]. Patients with ICH admitted to the ICU face inferior outcomes. Approximately 30% of ICH patients require ICU admission for further supportive treatment, and nearly half succumb within one month [8]. Consequently, identifying prognostic markers to predict outcomes in ICH patients is critical.

In recent years, the association between lipid metabolism and the onset and progression of ICH has been widely reported [9–12]. Low-density lipoprotein (LDL) has been negatively associated with the occurrence and mortality of ICH in several large prospective cohort studies [9–11]. Additionally, high-density lipoprotein (HDL) has been reported to prevent stroke occurrence, attributed to its role in maintaining endothelial barrier integrity and its antioxidative and anti-inflammatory properties [6].

LDL and HDL are indicative of pro-atherosclerotic and anti-atherosclerotic effects, respectively. Consequently, the LDL/HDL ratio (LHR) serves as an integrated marker, reflecting the balance between oxidative stress and antioxidant defense mechanisms.

Ratios such as LDL/HDL and non-HDL/HDL are emerging as novel composite lipid biomarkers of atherogenic susceptibility and have been directly linked to the risk of atherosclerosis [13–15]. The LHR has been reported as a predictor of recurrent stroke in patients with minor stroke or transient ischemic attack [14]. However, limited research exists regarding the impact of these ratios on survival outcomes in critically ill ICH patients. Therefore, this study aims to investigate the potential association between LHR and mortality risk in ICH patients, providing a more accurate basis for prognostic evaluation and personalized treatment in clinical practice.

Methods

Data source

This study performed a retrospective analysis utilizing the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 3.1) database. This publicly available dataset encompasses comprehensive medical records of patients admitted to intensive care units (ICU) at Beth Israel Deaconess Medical Center in Boston, Massachusetts, from 2008 to 2019. The database includes extensive clinical details such as patient demographics, laboratory data, medication usage, vital signs, surgical interventions, diagnoses, and treatment outcomes. Yuchen Liu, who completed the necessary training and obtained certification for database access and use (Record ID: 13,284,033), conducted the data extraction. Rigorous protocols were implemented throughout the extraction process to ensure precision and uniformity.

Study population

This study focused on patients diagnosed with ICH, as classified by the International Classification of Diseases (ICD), including ICD-9 code 431 and ICD-10 codes I610–I619 and I62.9. Exclusion criteria were: (1) absence of LDL and HDL data; (2) hospitalization duration of less than 24 h or death within 24 h of admission. For patients with multiple admissions, only data from their initial admission were included.

Clinical data collection

(1) Demographics: gender, age, weight, and ethnicity; (2) Clinical severity: Glasgow Coma Scale (GCS), Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score II (SAPS-II), and Oxford Acute Severity of Illness Score (OASIS).(3) Comorbidities: intraventricular hemorrhage (IVH), hypertension, diabetes, chronic obstructive pulmonary disease (COPD), myocardial infarction, congestive heart failure (CHF), peripheral vascular disease, renal failure, hepatic disorders, sepsis; (4) Laboratory results: hemoglobin, white blood cell count (WBC), hematocrit, sodium, potassium, platelets, serum creatinine, blood urea nitrogen, prothrombin time (PT), activated partial thromboplastin time (APTT), LDL, and HDL; (5) Treatment: mechanical ventilation and use of vasopressor and statins; (6)Prognosis: survival information, the length of hospital and ICU stay.

Outcomes

The primary outcome of the present study was 28-day all-cause mortality, while the secondary outcomes were ICU

mortality and In-hospital mortality. Furthermore, we extended our investigation to explore long-term all-cause mortality at 90 and 180 days.

Statistical analysis

The proportion of missing data was less than 10% for all variables, and multiple imputation was applied to address the missing values. The proportion of missing variables is presented in Supplementary Table 1. Subjects were stratified into tertiles based on their LHR values (T1-T3). Quantitative variables were reported as mean ± standard deviation or median with interquartile range (IQR), based on the distribution of the data, while qualitative variables were summarized as counts and percentages. Continuous variables following a normal distribution were analyzed using the t-test or analysis of variance, whereas the Mann–Whitney U test or Kruskal–Wallis test was applied to those with a non-normal distribution. Categorical variables were compared using Pearson's chi-squared test.

Cox regression models were employed to evaluate the association between LHR and all-cause mortality in critically ill ICH patients, providing hazard ratios (HR) and 95% confidence intervals (CI). Model 1 included no adjustments. Model 2 adjusted for baseline characteristics, including age, ethnicity, sex, and weight. Spearman's rank correlation test was conducted to assess multicollinearity in the Cox regression analysis, and the variance inflation factor (VIF) was calculated (Supplementary Table 2). Variables with a VIF greater than 10 were excluded. Therefore, Model 3 further adjusted for GCS, SOFA, IVH, CHF, Hepatic disorders, Sepsis, WBC, platelets, glucose, serum creatinine, urea nitrogen, PT, cerebral surgery, mechanical ventilation, vasopressor, and statins. Restricted cubic spline (RCS) was applied to elucidate the linear relationship between LHR and all-cause mortality in critically ill ICH patients. Additionally, interaction and stratified analyses were conducted to validate the consistency of findings across subgroups, including age, gender, diabetes, CHF, cerebral surgery, and sepsis. Sensitivity analysis was undertaken to ensure the robustness of the findings. The optimal cutoff value of LHR was determined as 1.21 based on the Receiver Operating Characteristic Curve. ICH patients were categorized into low-LHR and high-LHR groups accordingly. Kaplan–Meier survival curves were utilized to compare the survival outcomes between the two groups. Spearman correlation analysis was used to explore the relationship between LHR and disease severity scores.

R software (version 4.2.1; R Foundation for Statistical Computing; http://www.R-project.org), the R survey package (version 4.1-1), and Free Statistics software (version 1.9.2; Beijing Free Clinical Medical Technology Co., Ltd.) were used for analyses. A two-sided p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 873 patients were included for analysis. Figure 1 shows the selection process for patients. The baseline characteristics of the 28-day survival and mortality groups were summarized in Table 1. The 28-day all-cause mortality rate was 20.3% (177/873). Non-survivors had a lower LHR (1.5 vs. 1.8) and were older (median age 79 vs. 69). They also had lower weights (73 vs. 79 kg) and included fewer males (44.6% vs. 56.5%). Disease severity scores, such as GCS (8 vs. 13), SOFA (5 vs. 3), SAPS-II (39 vs. 29), and OASIS (38 vs. 31), were markedly worse in the mortality group. Non-survivors had a higher prevalence of IVH (22.6% vs. 13.1%), hepatic disorders (2.8% vs. 0.7%), and sepsis (52.5% vs. 28.6%), while CHF was more common in non-survivors as well (22% vs. 14.9%). Laboratory findings showed elevated WBC counts (10.0 vs. 8.6×10^9/L), glucose levels (163.1 vs. 133.9 mg/dL), and urea nitrogen (18 vs. 14 mg/dL) in non-survivors. Conversely, hemoglobin (11.6 vs. 12.4 g/L), hematocrit (35.4% vs. 37.4%), and platelet counts (184 vs. 204×10^9/L) were lower. Regarding treatments, non-survivors underwent more frequent cerebral surgeries (15.8% vs. 9.5%), received less often statins (26.7% vs. 37.6%), and were almost universally treated with mechanical ventilation (99.4% vs. 25.3%) and vasopressors (99.4% vs. 7%). The characteristics of included patients stratified by LHR tertiles were presented in Table 2.

Association of LHR and all-cause mortality

The association between LHR and mortality risk in critically ill ICH patients was evaluated using continuous variable and tertile-based categorical models. The results indicated that higher LHR was associated with a reduced risk of short-term mortality in critically ill ICH patients. This association remained significant in Model 3, which adjusted for age, gender, ethnicity, weight, GCS, SOFA, IVH, CHF, Hepatic disorders, Sepsis, WBC, platelets, glucose, serum creatinine, urea nitrogen, PT, cerebral surgery, mechanical ventilation, vasopressor, and statins (28-day mortality: HR = 0.82, 95% CI: 0.68 ~ 0.99, $P = 0.039$; In-hospital mortality: HR = 0.7, 95% CI: 0.55 ~ 0.89, $P = 0.004$; ICU mortality: HR = 0.66, 95% CI: 0.48 ~ 0.92, $P = 0.015$). Similarly, the categorical models yielded consistent findings, as detailed in Table 3. The RCS was used for further investigation, revealing a linear relationship between LHR and short-term all-cause mortality (28-day mortality: P for non-linearity = 0.283;

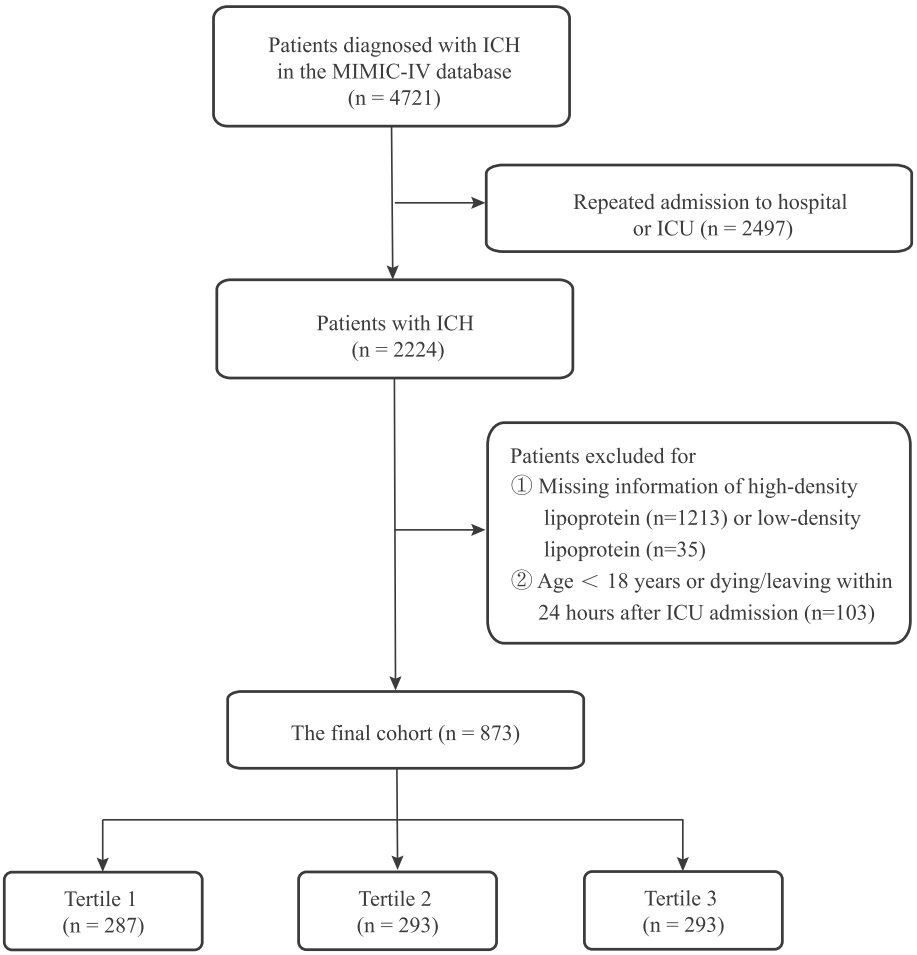

Fig. 1 Flow chart for inclusion of participants

In-hospital mortality: P for non-linearity = 0.596; ICU mortality: P for non-linearity = 0.431) (Fig. 2).

We further explored the association between LHR and long-term all-cause mortality. However, no statistically significant differences were observed in Model 3 (90-day mortality: HR = 0.9, 95% CI: 0.76 ~ 1.05, $P = 0.185$; 180-day mortality: HR = 0.96, 95% CI: 0.83 ~ 1.11, $P = 0.54$) (Supplementary Table 3).

Subgroup analysis

Subgroup analyses were conducted to evaluate the stability of the results. The association between LHR and 28-day all-cause mortality remained consistent across different subgroups (Fig. 3).

Sensitivity analysis

To evaluate the robustness of the association between LHR and mortality risk in ICH patients, the cohort was divided into two groups based on the threshold value (1.21) determined by the ROC curve. As shown in Fig. 4, Kaplan–Meier survival curves at different time points demonstrated that patients in the high LHR group exhibited higher survival rates (28-day mortality, $P = 0.0052$; In-hospital mortality, $P = 0.019$; ICU mortality, $P = 0.044$). Furthermore, spearman correlation analyses were performed to investigate the relationship between LHR and various severity indices (Fig. 5). LHR showed a negative correlation with SAPS-II ($r = -0.158$, $P < 0.001$) and OASIS ($r = -0.117$, $P = 0.006$), but no significant correlation with the SOFA score ($r = -0.0582$, $P = 0.0856$).

Discussion

This study investigates the association between lipid levels and outcomes in critically ill ICH patients. Higher LHR was independently associated with lower short-term mortality in ICH patients, demonstrating a linear relationship. This association remains consistent across various subgroups. To enhance clinical applicability, the optimal cutoff value for LHR was determined to be 1.21 based on ROC curve analysis. Participants were

Table 1 The characteristics of included patients stratified by 28-day survival outcomes

Variables	Total (*n* = 873)	28-day survival (*n* = 696)	28-day non-survival (*n* = 177)	*p*-value
LHR	1.7 (1.2, 2.4)	1.8 (1.3, 2.6)	1.5 (1.1, 2.0)	**< 0.001**
Demographic variables				
Age, years	71 (60, 81)	69 (58, 80)	79 (69, 85)	**< 0.001**
Weight, kg	77.8 (64.5, 93.0)	79.0 (65.7, 95.0)	73.0 (58.5, 83.4)	**< 0.001**
Male	472 (54.1)	393 (56.5)	79 (44.6)	**0.005**
Ethnicity (White)	482 (55.2)	390 (56)	92 (52)	0.332
Clinical severity				
GCS	12 (8, 14)	13 (9, 14)	8 (6, 13)	**< 0.001**
SOFA	4 (2, 6)	3 (2, 5)	5 (4, 7)	**< 0.001**
SAPS-II	31 (24, 39)	29 (24, 36)	39 (33, 45)	**< 0.001**
OASIS	32 (26, 38)	31 (25, 36)	38 (33, 43)	**< 0.001**
Comorbidities				
IVH	131 (15.0)	91 (13.1)	40 (22.6)	**0.002**
Hypertension	158 (18.1)	132 (19)	26 (14.7)	0.187
Diabetes	250 (28.6)	195 (28)	55 (31.1)	0.422
COPD	94 (10.8)	79 (11.4)	15 (8.5)	0.27
Myocardial infarct	92 (10.5)	69 (9.9)	23 (13)	0.233
CHF	143 (16.4)	104 (14.9)	39 (22)	**0.023**
PVD	54 (6.2)	47 (6.8)	7 (4)	0.168
Renal failure	125 (14.3)	93 (13.4)	32 (18.1)	0.11
Hepatic disorders	10 (1.1)	5 (0.7)	5 (2.8)	**0.034**
Sepsis	292 (33.4)	199 (28.6)	93 (52.5)	**< 0.001**
Laboratory tests				
WBC, 10^9/L	9.0 (7.1, 11.4)	8.6 (7, 11)	10 (7.6, 13)	**< 0.001**
Hb, g/L	12.2 ± 1.9	12.4 ± 1.9	11.6 ± 2.0	**0.003**
Hematocrit, vol%	37.0 ± 5.5	37.4 ± 5.4	35.4 ± 5.8	**0.014**
Platelets, 10^9/L	201 (161, 250)	204 (166, 251.2)	184 (137, 233)	**< 0.001**
Glucose, mg/dL	139.8 ± 61.2	133.9 ± 54.4	163.1 ± 78.8	**< 0.001**
Sodium, mmol/L	138.2 ± 4.0	138.3 ± 3.9	138.2 ± 4.5	0.776
Potassium, mmol/L	3.8 (3.5, 4.1)	3.8 (3.5, 4.1)	3.9 (3.4, 4.2)	0.527
Serum creatinine, mg/dL	0.9 (0.7, 1.1)	0.8 (0.7, 1.0)	0.9 (0.7, 1.4)	**0.03**
Urea nitrogen, mg/dL	15 (11, 20)	14 (11, 20)	18 (13, 23)	**< 0.001**
PT, s	12.2 (11.3, 13.2)	12.1 (11.3, 13.0)	12.7 (11.8, 13.8)	**< 0.001**
APTT, s	27.3 (24.8, 30.0)	27.3 (25.1, 29.9)	26.7 (24.0, 30.2)	0.175
Treatments				
Cerebral surgery	94 (10.8)	66 (9.5)	28 (15.8)	**0.015**
Mechanical ventilation	352 (40.3)	176 (25.3)	176 (99.4)	**< 0.001**
Statins	307 (35.4)	260 (37.6)	47 (26.7)	**0.007**
Vasopressor	225 (25.8)	49 (7)	176 (99.4)	**< 0.001**

LHR low-density lipoprotein to high-density lipoprotein ratio, *GCS* Glasgow Coma Scale, *SOFA* Sequential Organ Failure Assessment, *SAPS-II* Simplified Acute Physiology Score II, *OASIS* Oxford Acute Severity of Illness Score, *IVH* intraventricular hemorrhage, *COPD* chronic obstructive pulmonary disease, *PVD* Peripheral vascular disease, *CHF* congestive heart failure, *WBC* white blood cell count, *PT* prothrombin time, *APTT* activated partial thromboplastin time

subsequently divided into two groups. Kaplan–Meier survival curves confirmed that the high-LHR group had a significantly lower risk of short-term mortality. Furthermore, LHR negatively correlates with severity scores, including SAPS II and OASIS, underscoring its robustness as a prognostic marker.

The association between low LDL levels, statin use, and the risk of ICH has been a subject of debate for decades [16]. Several studies have reported an association

Table 2 Characteristics of included patients stratified by LHR tertiles

Variables	Total ($n=873$)	T1 ($n=287$)	T2 ($n=293$)	T3 ($n=293$)	*p*-value
LHR	1.7 (1.2, 2.4)	1.0 (0.8, 1.2)	1.7 (1.6, 1.9)	2.8 (2.4, 3.4)	**<0.001**
Demographic variables					
Age, years	71 (60, 81)	75 (65, 83)	74 (61, 82)	65 (54, 75)	**<0.001**
Weight, kg	77.8 (64.5, 93)	71.2 (59.8, 84)	77.8 (63.8, 93)	84 (72, 99.3)	**<0.001**
Male	472 (54.1)	135 (47)	161 (54.9)	176 (60.1)	**0.007**
Ethnicity (White)	482 (55.2)	167 (58.2)	167 (57)	148 (50.5)	0.134
Clinical severity					
GCS	12 (8, 14)	12 (8, 14)	12 (9, 14)	13 (9, 14)	0.29
SOFA	4 (2, 6)	4 (3, 6)	4 (2, 6)	4 (2, 6)	0.142
SAPS-II	31 (24, 39)	33 (26, 39)	33 (26, 40)	28 (21, 36)	**<0.001**
OASIS	32 (26, 38)	33 (27.5, 39)	33 (27, 38)	31 (25, 36)	**<0.001**
Comorbidities					
IVH	131 (15.0)	49 (17.1)	44 (15)	38 (13)	0.384
Hypertension	158 (18.1)	48 (16.7)	62 (21.2)	48 (16.4)	0.246
Diabetes	250 (28.6)	71 (24.7)	96 (32.8)	83 (28.3)	0.101
COPD	94 (10.8)	37 (12.9)	28 (9.6)	29 (9.9)	0.363
Myocardial infarct	92 (10.5)	32 (11.1)	26 (8.9)	34 (11.6)	0.515
CHF	143 (16.4)	59 (20.6)	43 (14.7)	41 (14)	0.064
PVD	54 (6.2)	16 (5.6)	21 (7.2)	17 (5.8)	0.689
Renal failure	125 (14.3)	38 (13.2)	46 (15.7)	41 (14)	0.686
Hepatic disorders	10 (1.1)	1 (0.3)	5 (1.7)	4 (1.4)	0.357
Sepsis	292 (33.4)	104 (36.2)	86 (29.4)	102 (34.8)	0.178
Laboratory tests					
WBC, 10^9/L	9.0 (7.1, 11.4)	8.7 (6.8, 11.2)	8.6 (7.0, 11.0)	9.2 (7.5, 11.8)	**0.041**
Hb, g/L	12.2 ± 1.9	11.8 ± 1.9	12.1 ± 1.9	12.7 ± 1.9	**<0.001**
Hematocrit, vol%	37.0 ± 5.5	35.8 ± 5.4	36.6 ± 5.4	38.5 ± 5.4	**<0.001**
Platelets, 10^9/L	201 (161, 250)	183 (150, 238.5)	201 (162, 243)	211 (174, 259)	**<0.001**
Glucose, mg/dL	139.8 ± 61.2	137.7 ± 53.5	139.7 ± 66.7	142.0 ± 62.7	0.7
Sodium, mmol/L	138.2 ± 4.0	137.8 ± 4.0	138.4 ± 4.0	138.5 ± 4.0	**0.049**
Potassium, mmol/L	3.8 (3.5, 4.1)	3.8 (3.5, 4.1)	3.8 (3.5, 4.1)	3.8 (3.5, 4.1)	0.834
Serum creatinine, mg/dL	0.9 (0.7, 1.1)	0.8 (0.6, 1.0)	0.8 (0.7, 1.0)	0.9 (0.7, 1.1)	**0.003**
Urea nitrogen, mg/dL	15 (11, 20)	15 (11, 20)	15 (11, 20)	15 (11, 21)	0.909
PT, s	12.2 (11.3, 13.2)	12.2 (11.3, 13.3)	12.1 (11.3, 13.1)	12.2 (11.4, 13.1)	0.631
APTT, s	27.3 (24.8, 30.0)	27.4 (25.2, 30.2)	27.1 (24.3, 29.8)	27.3 (24.9, 30.1)	0.501
Treatments					
Cerebral surgery	94 (10.8)	28 (9.8)	28 (9.6)	38 (13)	0.328
Mechanical ventilation	352 (40.3)	130 (45.3)	116 (39.6)	106 (36.2)	0.078
Statins	307 (35.4)	86 (30.4)	101 (34.6)	120 (41.1)	**0.026**
Vasopressor	225 (25.8)	94 (32.8)	73 (24.9)	58 (19.8)	**0.002**

LHR low-density lipoprotein to high-density lipoprotein ratio, *GCS* Glasgow Coma Scale, *SOFA* Sequential Organ Failure Assessment, *SAPS-II* Simplified Acute Physiology Score II, *OASIS* Oxford Acute Severity of Illness Score, *IVH* intraventricular hemorrhage, *COPD* chronic obstructive pulmonary disease, *CHF* congestive heart failure, *PVD* Peripheral vascular disease, *WBC* white blood cell count, *PT* prothrombin time, *APTT* activated partial

between LDL levels and an increased risk of ICH in populations from the United States, Europe, and Asia [9, 12, 17–19]. A meta-analysis comprising 23 prospective studies also reported consistent findings [12]. However, some randomized controlled trials on statin therapy have failed to identify such a relationship [20]. A 2015 meta-analysis of 26 randomized trials demonstrated that patients in the statin therapy group who experienced significant reductions in LDL cholesterol levels (approximately 0.5 mmol/L for more intensive versus less intensive therapy) did not exhibit a significant increase in hemorrhagic stroke during follow-up (RR 1.12, 95% CI 0.93–1.35;

Table 3 The correlation between LHR and short-term all-cause mortality

Variable	Model 1		Model 2		Model 3	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
28-day mortality						
LHR	0.69 (0.58 ~ 0.83)	**< 0.001**	0.81 (0.67 ~ 0.98)	**0.029**	0.82 (0.68 ~ 0.99)	**0.039**
Tertiles						
T1	Reference		Reference		Reference	
T2	0.72 (0.51 ~ 1)	0.051	0.78 (0.56 ~ 1.09)	0.151	0.8 (0.55 ~ 1.17)	0.248
T3	0.45 (0.3 ~ 0.66)	**< 0.001**	0.62 (0.42 ~ 0.93)	**0.019**	0.64 (0.42 ~ 0.99)	**0.044**
P for trend		**< 0.001**		**0.016**		**0.041**
In-hospital mortality						
LHR	0.65 (0.53 ~ 0.8)	**< 0.001**	0.7 (0.56 ~ 0.87)	**0.002**	0.7 (0.55 ~ 0.89)	**0.004**
Tertiles						
T1	Reference		Reference		Reference	
T2	0.77 (0.51 ~ 1.15)	0.196	0.8 (0.54 ~ 1.21)	0.292	0.68 (0.44 ~ 1.06)	0.088
T3	0.43 (0.27 ~ 0.67)	**< 0.001**	0.51 (0.32 ~ 0.81)	**0.005**	0.48 (0.29 ~ 0.8)	**0.005**
P for trend		**< 0.001**		**0.005**		**0.004**
ICU mortality						
LHR	0.61 (0.47 ~ 0.81)	**0.001**	0.64 (0.48 ~ 0.85)	**0.002**	0.66 (0.48 ~ 0.92)	**0.015**
Tertiles						
T1	Reference		Reference		Reference	
T2	0.94 (0.57 ~ 1.53)	0.793	0.97 (0.59 ~ 1.6)	0.91	0.86 (0.5 ~ 1.48)	0.586
T3	0.39 (0.22 ~ 0.71)	**0.002**	0.43 (0.23 ~ 0.8)	**0.007**	0.43 (0.22 ~ 0.83)	**0.011**
P for trend		**0.002**		**0.011**		**0.014**

Model 1: unadjusted; Model 2: adjusted for age, gender, ethnicity, and weight; Model 3: adjusted for Model 2 and GCS, SOFA, IVH, CHF, Hepatic disorders, Sepsis, WBC, platelets, glucose, serum creatinine, urea nitrogen, PT, cerebral surgery, mechanical ventilation, vasopressor, statins

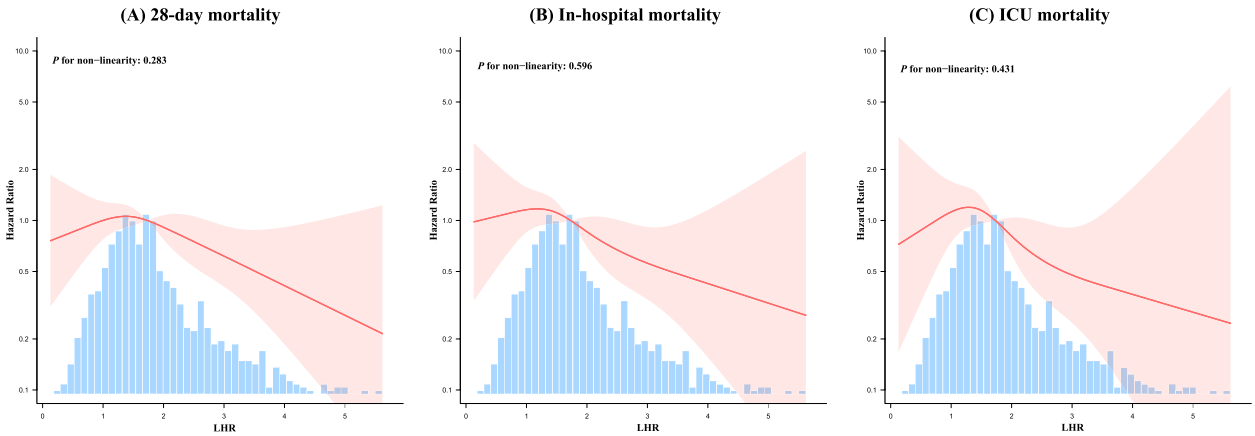

Fig. 2 The restricted cubic spline analysis for the nonlinear association between the LHR and short-term all-cause mortality (**A**) 28-day, (**B**) In-hospital, and (**C**) ICU

P = 0.20) [21]. The IMPROVE-IT trial further explored the long-term safety of extremely low LDL cholesterol levels (< 30 mg/dL) achieved through intensive statin therapy. The results showed no significant difference in the incidence of ICH (0.6% vs. 0.8%; HR 1.38, *P* = 0.11) [22].

Compared to previous studies, our research exclusively included ICU-admitted ICH patients and focused on exploring the association between lipid levels and prognosis in critically ill ICH patients. A large Japanese population-based cohort study observed a significant association between reduced LDL cholesterol levels and

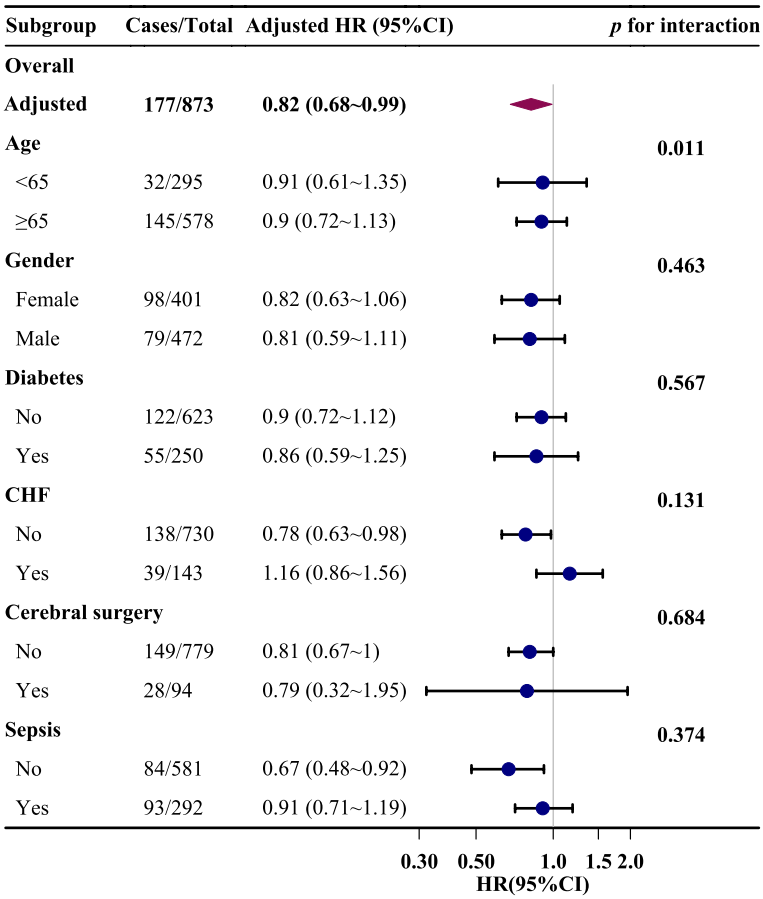

Fig. 3 Subgroup analysis for the correlation between the LHR and 28-day all-cause mortality in patients with ICH

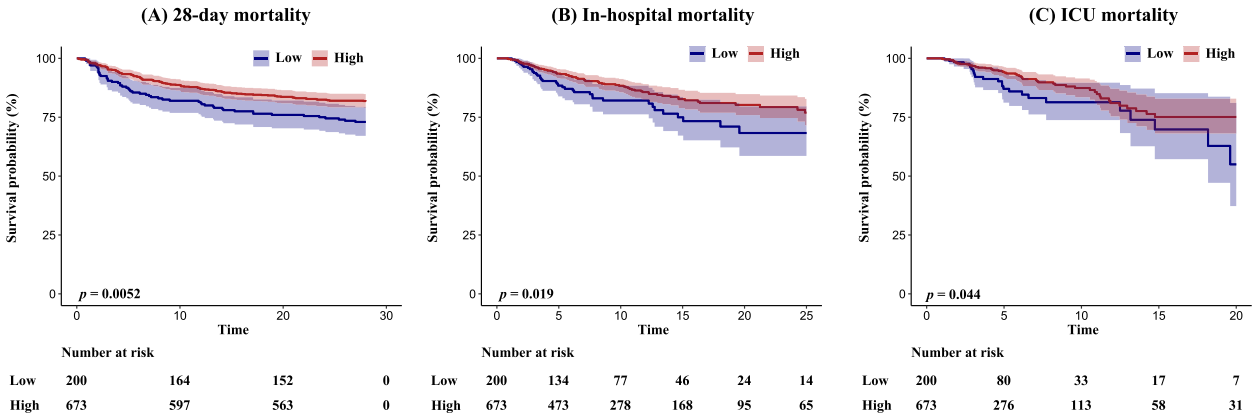

Fig. 4 Kaplan–Meier survival analysis curves for all-cause mortality, the cohort was divided into two groups based on the threshold value (1.21) determined by the ROC curve. **A** 28-day, **B** In-hospital, and (**C**) ICU

increased mortality in patients with ICH [9]. Similarly, a Spanish study reported consistent findings, showing that patients with low LDL cholesterol levels had a significantly increased risk of mortality (HR = 3.07) [23]. This is also consistent with our findings. Lower LDL cholesterol levels have also been found to be significantly associated with hematoma expansion in ICH patients [24]. In this study, an LDL cholesterol level < 95 mg/dL was identified as an independent predictor of hematoma growth, early neurological deterioration, and early mortality in ICH

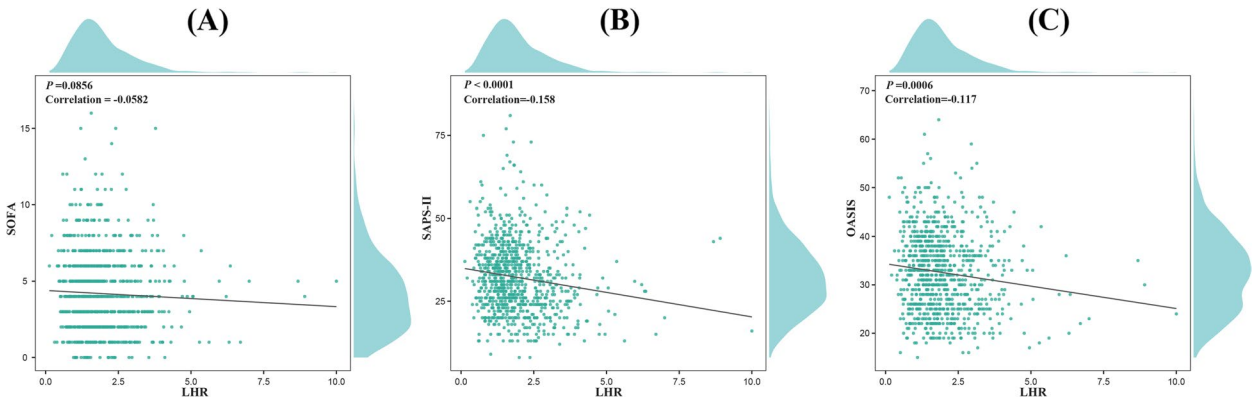

Fig. 5 The correlation of LHR and the disease severity scores of patients with ICH (**A**) SOFA, **B** SAPS-II, and (**C**) OASIS

patients [24]. The same study also pointed out that the relationship between LDL cholesterol levels and long-term outcomes was not significant, which is consistent with our findings in the ICU population. Although these studies suggest that low LDL-C levels are associated with poor ICH prognosis, other research indicates that low LDL-C levels are not always directly related to the severity or prognosis of ICH. A systematic review and meta-analysis found that low LDL-C levels were associated with a 3-month mortality rate in ICH patients but not with in-hospital mortality [25]. However, the majority of participants included in this analysis were Han Chinese, limiting the generalizability of the findings. Therefore, further research is needed.

In this context, several potential mechanisms can be considered as possible explanations. Atherosclerosis is marked by the necrosis of vascular smooth muscle cells and the accumulation of basement membrane-like material in the outer layers of smooth muscle cells within intracerebral arteries, predominantly in the basal ganglia, thalamus, and brainstem [26, 27]. Cholesterol within LDL can be taken up by macrophages to form foam cells, a critical process in the development of atherosclerosis [28]. Additionally, LDL cholesterol can induce leukocyte-endothelial adhesion, stimulate the expression of inflammatory markers, and trigger platelet aggregation [29–31]. This suggests that elevated LDL levels may have a beneficial effect in hemorrhagic conditions. HDL is thought to prevent atherosclerosis by facilitating reverse cholesterol transport and inhibiting LDL oxidation [32]. LDL and HDL correspond to pro-atherosclerotic and anti-atherosclerotic roles, respectively. Thus, the LHR functions as a holistic marker of oxidative stress levels and the body's antioxidant defense capacity.

It should be acknowledged that this study has several limitations. First, due to the retrospective nature of the study, we are unable to establish a causal relationship for this association definitively. Second, although we attempted to adjust for known confounders, the limitations of the database prevented us from obtaining additional clinical information, such as hematoma location, hematoma volume, and the presence of cerebral edema. Lastly, the inability to determine the reasons why these patients underwent lipid metabolism tests may introduce selection bias. Therefore, future studies should include these variables to further validate our findings.

Conclusion

This study identified a negative association between LHR and short-term mortality in critically ill ICH patients. LHR may serve as a valuable tool for risk stratification in critically ill ICH patients, aiding clinicians in identifying high-risk individuals and providing timely interventions.

Abbreviations

ICH	Intracerebral hemorrhage
ICU	Intensive care units
LDL	Low-density lipoprotein
HDL	High-density lipoprotein
LHR	Low-density lipoprotein to high-density lipoprotein ratio
GCS	Glasgow Coma Scale
SOFA	Sequential Organ Failure Assessment
SAPS-II	Simplified Acute Physiology Score II
OASIS	Oxford Acute Severity of Illness Score
IVH	Intraventricular hemorrhage
COPD	Chronic obstructive pulmonary disease
PVD	Peripheral vascular disease
CHF	Congestive heart failure
WBC	White blood cell count
PT	Prothrombin time
APTT	Activated partial thromboplastin time
NRI	Net reclassification improvement
IDI	Integrated discrimination improvement

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Authors' contributions
Yuchen Liu and Houxin Fu conducted data curation, statistical analysis, visualization, and original draft writing. All authors contributed to the conceptualization and supervision. All authors have approved the submitted version and agreed both to be personally accountable for the author's contributions and to ensure that questions related to the accuracy or integrity of any part of the work.

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Data availability
The data are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was performed according to the guidelines of the Helsinki Declaration. The use of the MIMIC-IV database was approved by the review committee of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. The data is publicly available (in the MIMIC-IV database), therefore, the ethical approval statement and the requirement for informed consent were waived for this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Neurosurgery, Children's Hospital of Soochow University, Suzhou, Jiangsu 215006, China. [2]Department of Pediatric Hematology and Oncology, Children's Hospital of Soochow University, Suzhou, Jiangsu 215006, China. [3]Institute of Pediatric Research, Children's Hospital of Soochow University, Suzhou, Jiangsu 215006, China.

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