DATABASE ANALYSIS

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Machine-Learning-Based Evaluation of the Prognostic Significance of the Non-High-Density Lipoprotein to High-Density Lipoprotein Cholesterol Ratio in Critical Ischemic Stroke

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Background: This study examined associations of the non-high-density lipoprotein to high-density lipoprotein cholesterol ratio (NHHR) with short-term (28-day) and long-term (365-day) mortality in critically ill patients with ischemic stroke.

Material/Methods: This retrospective cohort study utilized data from the MIMIC-IV database and focused on critically ill patients with ischemic stroke. Cox proportional hazards, restricted cubic spline, and Kaplan-Meier analyses were performed to examine the relationship between NHHR and mortality. Machine learning models were developed to improve predictive performance; model discrimination and clinical utility were evaluated using time-dependent receiver operating characteristic curves and decision curve analysis.

Results: Overall, 2492 critically ill patients with ischemic stroke were included. For 28-day mortality, NHHR levels below 2.122 were associated with a 24.9% increase in risk per unit decrease, whereas values above 2.122 conferred a 13.0% increase in risk per unit increment. For 365-day mortality, NHHR levels below 2.111 were associated with a 20.9% increase in mortality risk per unit decrease; values above this threshold were associated with a 14.1% increase in risk per unit increase. Among 6 machine learning algorithms, the random survival forest model demonstrated the best performance, demonstrating superior discrimination, calibration, and clinical utility for predicting both short- and long-term mortality.

Conclusions: In critically ill patients with ischemic stroke, NHHR demonstrated a nonlinear and independent association with mortality; the lowest risk was observed at intermediate values. Random survival forest modeling supports NHHR as a robust and clinically meaningful prognostic biomarker in this population.

Keywords: cholesterol, HDL • cholesterol, LDL • ischemic stroke • machine learning • neurology • prognosis

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Introduction

The ongoing global burden of ischemic stroke continues to serve as a leading cause of death and disability worldwide [1]. In 2021, there were approximately 784 449 new cases of ischemic stroke globally, representing 62.4% of all newly diagnosed stroke cases and causing an estimated 3.29 million deaths [2]. By 2030, ischemic stroke is projected to cause 4.9 million deaths worldwide [1].

Recent research suggests that non-conventional lipid metrics, such as the non-high-density lipoprotein to high-density lipoprotein cholesterol ratio (NHHR), can predict cardiovascular risk more effectively than conventional lipid profiles [3]. NHHR has emerged as a promising composite biomarker for atherosclerosis, with accumulating evidence linking it to a broad spectrum of conditions, including depression [4], suicidality in adults [5], cardiovascular disease [3], ischemic stroke [6], hyperuricemia [7], and diabetes [8]. Data increasingly indicate the potential of NHHR as a predictor of cardiovascular and non-cardiovascular outcomes, supporting its inclusion in routine clinical evaluations. A recent cohort study highlighted the prognostic significance of NHHR by identifying an L-shaped association with cardiovascular mortality [9]. Although the association between NHHR and ischemic stroke incidence has been established, its utility in predicting mortality among patients with stroke remains poorly characterized.

Despite growing evidence supporting NHHR as a predictor of cardiovascular and metabolic disorders, its prognostic value in patients with ischemic stroke remains unclear. Because conventional biomarkers often fail to adequately capture the complex and nonlinear interactions underlying stroke outcomes, increasing attention has shifted toward machine learning approaches to improve clinical prediction accuracy [10,11]. Modern algorithms (eg, neural networks, support vector machines, and random forest models) have demonstrated substantial promise in predicting mortality across diverse clinical settings, including glioblastoma [12], esophageal cancer [13], and cervical cancer [14]. Here, we conducted a retrospective cohort study to investigate the associations of NHHR with 28-day and 365-day mortality in critically ill patients with ischemic stroke. We also incorporated advanced machine learning techniques to enhance risk stratification and evaluate the prognostic utility of NHHR within a comprehensive predictive modeling framework.

Material and Methods

Data Source and Study Cohort

This retrospective observational study used intensive care unit data from an updated version of the Medical Information Mart for Intensive Care IV (MIMIC-IV), which includes revised patient information and reorganized data tables. Data collection and research activities were approved by the BIDMC Institutional Review Board, which waived the requirement for informed consent due to the retrospective nature of the study. Ke Shi (co-corresponding author) completed the Collaborative Institutional Training Initiative program and obtained certified database access (Certificate No. 68968318).

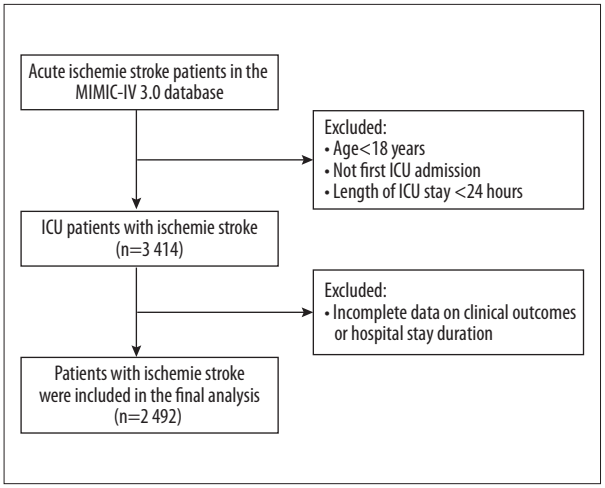

Figure 1. Flowchart of sample selection. Abbreviation: ICU, intensive care unit.

Among 523 740 ICU admissions recorded in the MIMIC-IV version 3.0 database, we identified adult patients (aged ≥ 18 years) during their first ICU admission. Eligible patients had a diagnosis of ischemic stroke based on International Classification of Diseases, Ninth Revision/International Classification of Diseases, Tenth Revision (ICD-9/ICD-10) codes. Patients were excluded if they: (1) were younger than 18 years; (2) were not in their first ICU admission; (3) had an ICU stay shorter than 24 hours; or (4) had incomplete data regarding clinical outcomes or hospital length of stay. For patients with multiple ICU admissions, only the first admission was included in the analysis. After applying all inclusion and exclusion criteria, the final cohort comprised 2492 patients with ischemic stroke (**Figure 1**).

Variable Selection and Data Collection

Relevant clinical variables were extracted using structured SQL scripts. Demographic variables encompassed age, sex, language, marital status, and race. Vital signs at admission included heart rate, blood pressure, respiratory rate, body temperature, and SpO_2. Laboratory parameters were glucose, hematocrit, hemoglobin, platelet count, white blood cell (WBC) count, anion gap, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, sodium, potassium, high-density lipoprotein (HDL) cholesterol, total cholesterol, triglycerides, and bilirubin. Coagulation markers included the international normalized ratio (INR), prothrombin

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time, and partial thromboplastin time. Clinical severity was assessed using the Charlson Comorbidity Index, the Acute Physiology and Chronic Health Evaluation III (APACHE III), the Simplified Acute Physiology Score II (SAPS II), and the Oxford Acute Severity of Illness Score (OASIS). Data regarding comorbidities—such as hypertension, myocardial infarction, heart failure, vascular disease, dementia, pulmonary disease, rheumatic disorders, mild liver disease, diabetes, paraplegia, chronic kidney disease, malignancy, metastatic cancer, and sepsis—were also collected. Additional variables included admission type, insurance status, and survival outcomes at 28 and 365 days.

Exposure and Outcome Measures

The primary exposure was NHHR, calculated as the ratio of non-HDL cholesterol to HDL cholesterol. The primary outcome was 28-day all-cause mortality, and the secondary outcome was 365-day all-cause mortality.

Statistical Analysis

Continuous variables were summarized as medians and interquartile ranges; they were compared using the Kruskal-Wallis test or 1-way analysis of variance, depending on data distribution. Categorical variables were presented as frequencies and percentages; they were compared using the chi-square test or Fisher's exact test. Multivariable Cox proportional hazards regression models were developed to assess the association between NHHR and mortality. Three sequential models were constructed: Model 1 was unadjusted; Model 2 was adjusted for age, sex, race, language, marital status, insurance status, admission type (emergency, urgent, surgical, observation, and elective), heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, respiratory rate, temperature, and SpO_2; and Model 3 was further adjusted for glucose, hematocrit, hemoglobin, platelet count, WBC count, anion gap, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, sodium, potassium, INR, prothrombin time, partial thromboplastin time, total bilirubin, hypertension, myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, diabetes, paraplegia, renal disease, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, severe liver disease, malignant cancer, metastatic solid tumor, and sepsis.

To identify potential inflection points in the association between NHHR and mortality, restricted cubic spline analyses followed by piecewise linear regression were performed due to the observed nonlinear relationship. Kaplan-Meier survival curves were also generated to visualize differences in cumulative survival across NHHR categories. To improve predictive accuracy, 6 machine learning algorithms were applied: Cox proportional hazards model, conditional inference tree, elastic net regularization, neural network, random survival forest (RSF), and Cox gradient boosting (XGBoost). Least absolute shrinkage and selection operator (LASSO) regression was used to identify informative predictors by penalizing less relevant features and shrinking their coefficients to 0 [15]. Predictive models were trained and validated using a 10-fold cross-validation framework, with hyperparameter tuning performed during model development. Model performance was evaluated using time-dependent receiver operating characteristic curves and area under the curve (AUC); clinical utility was assessed via decision curve analysis and calibration plots. All analyses were conducted using R software (version 4.3.1), and 2-sided *P*-values < 0.05 were considered statistically significant.

Ethics Approval and Consent to Participate

The MIMIC-IV database adheres to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Beth Israel Deaconess Medical Center (Approval No. 2001P-001699/14). This study complied with international research ethics and publication standards; it was conducted in accordance with the Declaration of Helsinki.

Results

Baseline Characteristics

Table 1 presents the baseline characteristics of the study population stratified by NHHR quartiles (Q1 < 1.71, Q2 1.71-2.39, Q3 2.39-3.37, Q4 > 3.37). In total, 2492 critically ill patients with ischemic stroke were included. The median age was 72 years, and women represented 50.32% of the cohort. Higher NHHR levels were associated with younger age and a greater proportion of male participants. Illness severity scores, including SAPS II, OASIS, and the Charlson Comorbidity Index, significantly decreased as NHHR quartile increased. Conversely, higher NHHR levels were associated with increased diastolic blood pressure, mean blood pressure, hemoglobin, WBC count, total cholesterol, and triglyceride levels. Significant interquartile differences were also observed across several laboratory indicators, including body temperature, SpO_2, glucose, hematocrit, platelet count, creatinine, and APACHE III score. Finally, differences were observed in multiple demographic and clinical characteristics (eg, marital status, insurance type, diabetes, chronic kidney disease, and sepsis). The 28-day mortality rate was highest in Q1 (21.67%) and lowest in Q4 (14.74%). The 365-day mortality rate was also highest in Q1 (36.28%) and lowest in Q4 (26.60%).

Associations of NHHR With Primary Outcomes

The association between NHHR and 28-day mortality was evaluated using Cox proportional hazards regression models

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Table 1. Baseline characteristics of the study population categorized by NHHR quartiles.

Characteristic	Total (n = 2492)	Q1 (n = 623)	Q2 (n = 623)	Q3 (n = 622)	Q4 (n = 624)	*P*
Age	72.00 (61.00, 83.00)	78.00 (67.00, 86.00)	76.00 (65.00, 84.00)	71.00 (60.00, 81.75)	65.00 (55.00, 75.00)	< 0.001
Heart rate	78.00 (69.00, 89.00)	78.00 (69.00, 90.00)	77.00 (68.00, 88.00)	77.00 (69.00, 88.00)	80.00 (69.00, 90.00)	0.103
SBP	134.00 (121.00, 147.00)	133.00 (121.00, 146.00)	133.00 (121.00, 147.00)	135.00 (120.00, 148.00)	133.00 (121.75, 146.00)	0.695
DBP	72.00 (63.00, 81.00)	70.00 (62.00, 78.00)	71.00 (63.50, 81.00)	72.00 (64.00, 81.00)	74.00 (64.00, 82.25)	< 0.001
MBP	89.00 (81.00, 98.00)	88.00 (79.00, 96.00)	88.00 (81.00, 97.00)	89.00 (81.00, 99.00)	90.00 (81.00, 99.00)	0.016
Respiratory rate	19.00 (17.00, 21.00)	19.00 (17.00, 21.00)	19.00 (17.00, 21.00)	19.00 (17.00, 21.00)	19.00 (17.00, 21.00)	0.804
Temperature	36.90 (36.70, 37.10)	36.90 (36.70, 37.10)	36.90 (36.70, 37.10)	36.80 (36.70, 37.00)	36.90 (36.70, 37.10)	0.002
SpO2	97.00 (96.00, 98.00)	97.00 (96.00, 98.00)	97.00 (95.00, 98.00)	97.00 (96.00, 98.00)	97.00 (96.00, 98.00)	< 0.001
Glucose	122.00 (104.00, 155.00)	121.00 (104.00, 153.00)	120.00 (105.00, 146.00)	122.00 (104.00, 155.00)	125.00 (105.00, 169.25)	0.021
Hematocrit	36.30 (31.80, 40.10)	34.90 (30.90, 38.90)	36.20 (31.80, 39.70)	37.10 (32.60, 41.10)	36.80 (31.15, 40.82)	< 0.001
Hemoglobin	12.00 (10.30, 13.30)	11.40 (9.90, 12.90)	11.90 (10.40, 13.20)	12.20 (10.80, 13.70)	12.30 (10.20, 13.70)	< 0.001
Platelet count	203.00 (162.00, 253.00)	197.00 (157.00, 249.00)	201.00 (158.00, 251.00)	207.50 (167.00, 249.00)	207.00 (167.00, 263.00)	0.016
WBC count	10.50 (8.20, 13.90)	10.00 (7.60, 12.85)	10.20 (8.00, 13.20)	10.50 (8.30, 14.30)	11.50 (8.67, 15.10)	< 0.001
Anion gap	13.00 (11.00, 15.00)	13.00 (11.00, 15.00)	13.00 (11.00, 15.00)	13.00 (11.00, 15.00)	13.00 (11.00, 15.00)	0.406
Bicarbonate	24.00 (22.00, 26.00)	24.00 (22.00, 26.00)	24.00 (22.00, 26.00)	24.00 (22.00, 26.00)	24.00 (22.00, 26.00)	0.174
Blood urea nitrogen	19.00 (14.00, 26.00)	20.00 (15.00, 28.00)	18.00 (14.00, 25.00)	18.00 (14.00, 26.00)	18.00 (13.00, 27.00)	0.040
Calcium	8.70 (8.20, 9.10)	8.70 (8.30, 9.10)	8.70 (8.30, 9.10)	8.70 (8.30, 9.10)	8.60 (8.10, 9.00)	0.068
Chloride	105.00 (102.00, 108.00)	105.00 (102.00, 108.00)	105.00 (102.00, 107.00)	105.00 (102.00, 108.00)	105.00 (102.00, 108.00)	0.719
Creatinine	1.00 (0.80, 1.30)	1.00 (0.80, 1.30)	1.00 (0.80, 1.20)	1.00 (0.80, 1.30)	1.00 (0.80, 1.40)	0.001
Sodium	140.00 (138.00, 142.25)	140.00 (138.00, 143.00)	140.00 (138.00, 142.00)	140.00 (138.00, 142.00)	140.00 (138.00, 142.00)	0.857
Potassium	3.90 (3.60, 4.20)	3.90 (3.60, 4.20)	3.90 (3.60, 4.20)	3.90 (3.60, 4.20)	3.90 (3.50, 4.20)	0.349
INR	1.20 (1.10, 1.30)	1.20 (1.10, 1.30)	1.20 (1.10, 1.30)	1.20 (1.10, 1.30)	1.20 (1.10, 1.30)	0.820
Prothrombin time	12.90 (11.90, 14.60)	12.90 (11.80, 14.70)	12.90 (11.90, 14.45)	12.90 (11.90, 14.60)	12.90 (11.90, 14.60)	0.887
PTT	30.10 (27.00, 36.52)	30.10 (27.20, 36.30)	29.80 (27.10, 36.00)	30.20 (26.80, 37.00)	30.10 (27.00, 37.47)	0.851

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Table 1 continued. Baseline characteristics of the study population categorized by NHHR quartiles.

Characteristic	Total (n = 2492)	Q1 (n = 623)	Q2 (n = 623)	Q3 (n = 622)	Q4 (n = 624)	*P*
Total bilirubin	0.60 (0.40, 0.80)	0.60 (0.40, 0.80)	0.60 (0.40, 0.80)	0.60 (0.40, 0.80)	0.60 (0.40, 0.80)	0.232
Charlson Comorbidity Index	7.00 (5.00, 9.00)	7.00 (6.00, 9.00)	7.00 (6.00, 9.00)	7.00 (5.00, 9.00)	6.00 (5.00, 8.00)	< 0.001
APACHE III	38.00 (28.00, 52.00)	40.00 (29.00, 55.00)	37.00 (28.00, 49.00)	35.00 (26.00, 50.00)	38.00 (27.00, 55.00)	< 0.001
SAPS II	31.00 (24.00, 40.00)	33.00 (27.00, 41.00)	32.00 (26.00, 40.00)	30.00 (23.00, 38.00)	30.00 (22.00, 39.00)	< 0.001
OASIS	31.00 (26.00, 38.00)	32.00 (26.00, 39.00)	31.00 (26.00, 36.50)	31.00 (25.00, 37.00)	30.00 (24.00, 38.00)	0.004
HDL	44.00 (35.00, 56.00)	59.00 (48.00, 69.00)	48.00 (40.00, 58.00)	42.00 (36.00, 50.00)	35.00 (28.00, 41.00)	< 0.001
Total cholesterol	155.00 (126.00, 187.25)	135.00 (110.00, 159.50)	148.00 (123.50, 176.00)	162.50 (135.25, 188.00)	186.00 (151.75, 218.00)	< 0.001
Triglycerides	107.00 (78.00, 149.00)	76.00 (61.00, 95.00)	93.00 (73.00, 119.00)	121.00 (92.00, 154.00)	159.00 (122.00, 223.00)	< 0.001
Sex, n (%)						< 0.001
Male	1238 (49.68)	262 (42.05)	283 (45.43)	324 (52.09)	369 (59.13)	
Female	1254 (50.32)	361 (57.95)	340 (54.57)	298 (47.91)	255 (40.87)	
Admission type, n (%)						0.678
Emergency	1460 (58.59)	355 (56.98)	367 (58.91)	370 (59.49)	368 (58.97)	
Urgent	302 (12.12)	76 (12.20)	70 (11.24)	84 (13.50)	72 (11.54)	
Surgical	36 (1.44)	5 (0.80)	9 (1.44)	8 (1.29)	14 (2.24)	
Observation	678 (27.21)	183 (29.37)	172 (27.61)	156 (25.08)	167 (26.76)	
Elective	16 (0.64)	4 (0.64)	5 (0.80)	4 (0.64)	3 (0.48)	
Language, n (%)						0.477
English	2193 (88.00)	555 (89.09)	554 (88.92)	543 (87.30)	541 (86.70)	
Other	299 (12.00)	68 (10.91)	69 (11.08)	79 (12.70)	83 (13.30)	
Marital status, n (%)						< 0.001
Married	1365 (54.78)	327 (52.49)	332 (53.29)	343 (55.14)	363 (58.17)	
Divorced	153 (6.14)	34 (5.46)	41 (6.58)	33 (5.31)	45 (7.21)	
Single	593 (23.80)	138 (22.15)	139 (22.31)	156 (25.08)	160 (25.64)	
Widowed	381 (15.29)	124 (19.90)	111 (17.82)	90 (14.47)	56 (8.97)	
Insurance, n (%)						< 0.001
Medicaid	292 (11.72)	53 (8.51)	59 (9.47)	80 (12.86)	100 (16.03)	
Medicare	1568 (62.92)	455 (73.03)	442 (70.95)	365 (58.68)	306 (49.04)	
Private	632 (25.36)	115 (18.46)	122 (19.58)	177 (28.46)	218 (34.94)	

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Table 1 continued. Baseline characteristics of the study population categorized by NHHR quartiles.

Characteristic	Total (n = 2492)	Q1 (n = 623)	Q2 (n = 623)	Q3 (n = 622)	Q4 (n = 624)	*P*
Race, n (%)						0.072
White	1441 (57.83)	355 (56.98)	374 (60.03)	366 (58.84)	346 (55.45)	
Black/African American	277 (11.12)	88 (14.13)	58 (9.31)	66 (10.61)	65 (10.42)	
Other	774 (31.06)	180 (28.89)	191 (30.66)	190 (30.55)	213 (34.13)	
Hypertension, n (%)						0.940
No	533 (21.39)	130 (20.87)	134 (21.51)	138 (22.19)	131 (20.99)	
Yes	1959 (78.61)	493 (79.13)	489 (78.49)	484 (77.81)	493 (79.01)	
Myocardial infarction, n (%)						0.127
No	2128 (85.39)	526 (84.43)	549 (88.12)	531 (85.37)	522 (83.65)	
Yes	364 (14.61)	97 (15.57)	74 (11.88)	91 (14.63)	102 (16.35)	
Congestive heart failure, n (%)						0.006
No	1891 (75.88)	449 (72.07)	466 (74.80)	474 (76.21)	502 (80.45)	
Yes	601 (24.12)	174 (27.93)	157 (25.20)	148 (23.79)	122 (19.55)	
Peripheral vascular disease, n (%)						0.444
No	2223 (89.21)	547 (87.80)	556 (89.25)	564 (90.68)	556 (89.10)	
Yes	269 (10.79)	76 (12.20)	67 (10.75)	58 (9.32)	68 (10.90)	
Dementia, n (%)						0.244
No	2334 (93.66)	581 (93.26)	576 (92.46)	583 (93.73)	594 (95.19)	
Yes	158 (6.34)	42 (6.74)	47 (7.54)	39 (6.27)	30 (4.81)	
Chronic pulmonary disease, n (%)						0.265
No	2087 (83.75)	512 (82.18)	516 (82.83)	522 (83.92)	537 (86.06)	
Yes	405 (16.25)	111 (17.82)	107 (17.17)	100 (16.08)	87 (13.94)	
Rheumatic disease, n (%)						0.092
No	2428 (97.43)	600 (96.31)	608 (97.59)	605 (97.27)	615 (98.56)	
Yes	64 (2.57)	23 (3.69)	15 (2.41)	17 (2.73)	9 (1.44)	
Peptic ulcer disease, n (%)						0.289
No	2464 (98.88)	613 (98.39)	614 (98.56)	617 (99.20)	620 (99.36)	
Yes	28 (1.12)	10 (1.61)	9 (1.44)	5 (0.80)	4 (0.64)	
Mild liver disease, n (%)						0.126
No	2414 (96.87)	600 (96.31)	607 (97.43)	609 (97.91)	598 (95.83)	
Yes	78 (3.13)	23 (3.69)	16 (2.57)	13 (2.09)	26 (4.17)	
Diabetes, n (%)						0.010
No	1662 (66.69)	422 (67.74)	435 (69.82)	422 (67.85)	383 (61.38)	
Yes	830 (33.31)	201 (32.26)	188 (30.18)	200 (32.15)	241 (38.62)	

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Characteristic	Total (n = 2492)	Q1 (n = 623)	Q2 (n = 623)	Q3 (n = 622)	Q4 (n = 624)	*P*
Paraplegia, n (%)						0.018
No	1081 (43.38)	251 (40.29)	259 (41.57)	268 (43.09)	303 (48.56)	
Yes	1411 (56.62)	372 (59.71)	364 (58.43)	354 (56.91)	321 (51.44)	
Renal disease, n (%)						0.005
No	2040 (81.86)	484 (77.69)	515 (82.66)	531 (85.37)	510 (81.73)	
Yes	452 (18.14)	139 (22.31)	108 (17.34)	91 (14.63)	114 (18.27)	
Malignant cancer, n (%)						0.185
No	2313 (92.82)	588 (94.38)	582 (93.42)	571 (91.80)	572 (91.67)	
Yes	179 (7.18)	35 (5.62)	41 (6.58)	51 (8.20)	52 (8.33)	
Severe liver disease, n (%)						0.404
No	2469 (99.08)	617 (99.04)	619 (99.36)	618 (99.36)	615 (98.56)	
Yes	23 (0.92)	6 (0.96)	4 (0.64)	4 (0.64)	69 (1.44)	
Metastatic solid tumor, n (%)						0.091
No	2412 (96.79)	609 (97.75)	603 (96.79)	605 (97.27)	595 (95.35)	
Yes	80 (3.21)	14 (2.25)	20 (3.21)	17 (2.73)	29 (4.65)	
Sepsis, n (%)						< 0.001
No	1716 (68.86)	422 (67.74)	478 (76.73)	435 (69.94)	381 (61.06)	
Yes	776 (31.14)	201 (32.26)	145 (23.27)	187 (30.06)	243 (38.94)	
365-day mortality status, n (%)						0.002
No	1735 (69.62)	397 (63.72)	440 (70.63)	440 (70.74)	458 (73.40)	
Yes	757 (30.38)	226 (36.28)	183 (29.37)	182 (29.26)	166 (26.60)	
28-day mortality status, n (%)						0.006
No	2060 (82.66)	488 (78.33)	526 (84.43)	514 (82.64)	532 (85.26)	
Yes	432 (17.34)	135 (21.67)	97 (15.57)	108 (17.36)	92 (14.74)	

Abbreviations: APACHE III, Acute Physiology and Chronic Health Evaluation III; DBP, diastolic blood pressure; HDL, high-density lipoprotein; INR, international normalized ratio; MBP, mean blood pressure; OASIS, Oxford Acute Severity of Illness Score; PTT, partial thromboplastin time; SAPS II, Simplified Acute Physiology Score II; SBP, systolic blood pressure; WBC, white blood cell.

(**Table 2**). In the fully adjusted Model 3, elevated NHHR was significantly associated with an increased risk of 28-day mortality. When NHHR was analyzed as a continuous variable, each unit increase was associated with a higher risk of death (hazard ratio [HR] = 1.09, 95% confidence interval [CI]: 1.04-1.14, $P < 0.001$). When NHHR was analyzed categorically using the second quartile (Q2) as the reference group, individuals in the lowest quartile (Q1) had a significantly higher risk of 28-day mortality (HR = 1.41, 95% CI: 1.08-1.83, P = 0.011). The third and fourth quartiles also showed HRs greater than 1, although these associations were not statistically significant (Q3: HR = 1.30, 95% CI: 0.99-1.72, P = 0.060; Q4: HR = 1.33, 95% CI: 0.99-1.78, P = 0.060). These findings suggest that the lowest risk was observed in Q2. Both lower and higher NHHR levels were associated with increased mortality risk.

A significant nonlinear association between NHHR and 28-day mortality was also observed (**Table 3**). In the standard linear regression model, higher NHHR was associated with increased mortality risk (effect size = 1.095, 95% CI: 1.044-1.148,

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Table 2. Association between NHHR and 28-day mortality in critically ill patients with ischemic stroke.

Characteristic	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
NHHR (continuous)	1.01 (0.95-1.07)	0.767	1.09 (1.04-1.14)	< 0.001	1.09 (1.04-1.14)	< 0.001
NHHR quartile						
Q2	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q1	1.44 (1.11-1.87)	0.006	1.40 (1.08-1.82)	0.012	1.41 (1.08-1.83)	0.011
Q3	1.11 (0.84-1.46)	0.456	1.28 (0.97-1.69)	0.076	1.30 (0.99-1.72)	0.060
Q4	0.94 (0.71-1.25)	0.660	1.31 (0.98-1.76)	0.069	1.33 (0.99-1.78)	0.060

Abbreviations: CI, confidence interval; HR, hazard ratio; NHHR, non-high-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio. Model 1: Crude model; Model 2: Adjusted for age, sex, race, language, marital status, insurance status, admission type (emergency, urgent, surgical, observation, and elective), heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, respiratory rate, temperature, and SpO_2; Model 3: Adjusted for variables in Model 2 plus glucose, hematocrit, hemoglobin, platelet count, white blood cell count, anion gap, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, sodium, potassium, international normalized ratio, prothrombin time, partial thromboplastin time, total bilirubin, hypertension, myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, diabetes, paraplegia, renal disease, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, severe liver disease, malignant cancer, metastatic solid tumor, and sepsis.

Table 3. Nonlinear association between NHHR and 28-day mortality in critically ill patients with ischemic stroke.

Outcome	Effect size (95% CI)	*P*
Fitted by standard linear regression	1.095 (1.044-1.148)	< 0.001
Fitted by 2-piecewise linear regression		
Inflection point	2.122	
< 2.122	0.751 (0.593-0.951)	0.018
≥ 2.122	1.130 (1.082-1.180)	< 0.001
P for likelihood ratio test	0.002	

Abbreviations: CI, confidence interval; HR, hazard ratio; NHHR, non-high-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio.

P < 0.001). To further characterize this relationship, a 2-piecewise linear regression model was applied. The identified inflection point was NHHR = 2.122. Below this threshold, NHHR was inversely associated with 28-day mortality (effect size = 0.751, 95% CI: 0.593-0.951, *P* = 0.018). Above the inflection point, NHHR was significantly and positively associated with mortality (effect size = 1.130, 95% CI: 1.082-1.180, *P* < 0.001). According to the likelihood ratio test, the piecewise model provided a significantly better fit than the standard linear model (*P* = 0.002).

Restricted cubic spline analyses demonstrated a significant nonlinear relationship between NHHR and short-term mortality in patients with ischemic stroke. For 28-day mortality (**Figure 2**), the overall association was statistically significant (*P* < 0.001), as was the nonlinear component (*P* = 0.001). The spline curve exhibited a J-shaped pattern, with lower mortality risk at moderate NHHR levels and an increasing hazard beyond the inflection point. Kaplan-Meier survival analyses demonstrated significant differences in mortality risk across NHHR quartiles. As shown in **Figure 3**, 28-day survival probabilities significantly differed among the 4 NHHR groups (log-rank *P* = 0.005). Short-term survival was worst among patients in the lowest quartile (Q1). Patient in the highest quartile (Q4) exhibited the most favorable survival outcomes.

Associations of NHHR With Secondary Outcomes

Cox regression analyses were performed to investigate the association between NHHR and 365-day mortality (**Table 4**). In the fully adjusted Model 3, higher NHHR was significantly associated with an increased risk of 365-day mortality. When NHHR was analyzed as a continuous variable, each unit increase

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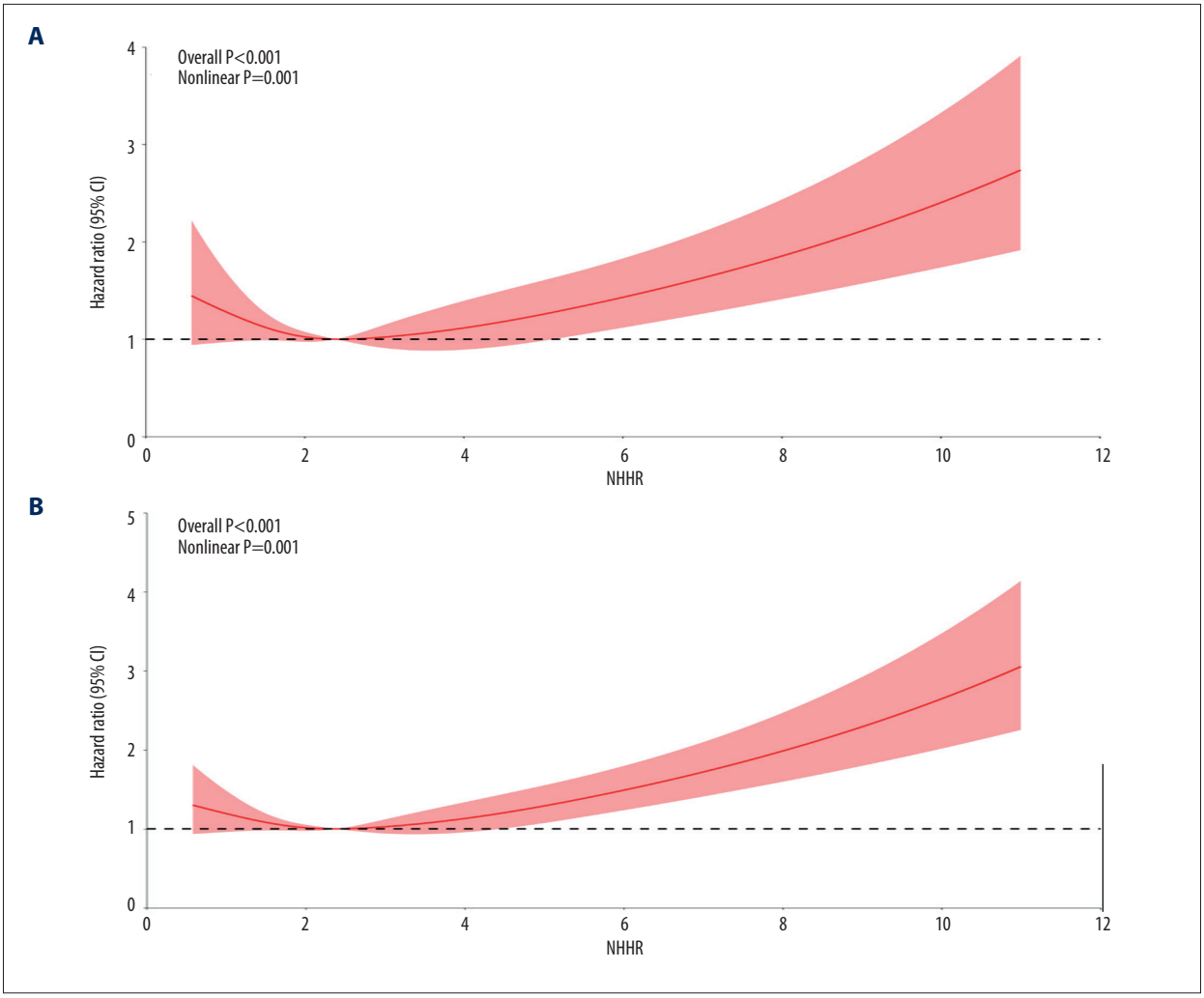

Figure 2. Restricted cubic spline analyses of the associations of NHHR with 28-day and 365-day mortality in patients with ischemic stroke. (**A**) Restricted cubic spline curve showing the adjusted association between NHHR and 28-day mortality. (**B**) Restricted cubic spline curve showing the adjusted association between NHHR and 365-day mortality. Both models were adjusted for potential confounders. Overall P-values indicated significant associations between NHHR and mortality; nonlinear P-values demonstrated evidence of nonlinear relationships. Abbreviations: CI, confidence interval; NHHR, non-high-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio.

was associated with a greater mortality risk (HR = 1.10, 95% CI: 1.06-1.15, $P < 0.001$). When analyzed categorically using the second quartile (Q2) as the reference, patients in the lowest NHHR quartile (Q1) had a significantly elevated risk of 365-day mortality (HR = 1.26, 95% CI: 1.03-1.53, $P = 0.022$). The third quartile (Q3) showed a nonsignificant trend toward increased risk (HR = 1.19, 95% CI: 0.97-1.46, $P = 0.103$). In contrast, patients in the highest quartile (Q4) had a significantly increased risk of mortality (HR = 1.30, 95% CI: 1.05-1.62, $P = 0.017$). These findings suggest that the lowest risk was observed in Q2. Both lower and higher NHHR levels were associated with increased mortality risk.

Nonlinear analyses revealed a significant association between NHHR and 365-day mortality (**Table 5**). The standard linear regression model demonstrated a positive association between NHHR and mortality risk (effect size = 1.103, 95% CI: 1.060-1.148, $P < 0.001$). A 2-piecewise linear regression model identified an inflection point at NHHR = 2.111. Below this threshold, NHHR was inversely associated with 365-day mortality (effect size = 0.791, 95% CI: 0.658-0.951, $P = 0.013$). In contrast, NHHR values at or above 2.111 were strongly associated with an increased risk of death (effect size = 1.141, 95% CI: 1.099-1.186, $P < 0.001$). The likelihood ratio test indicated that the piecewise model provided a significantly better fit than the standard linear model ($P < 0.001$).

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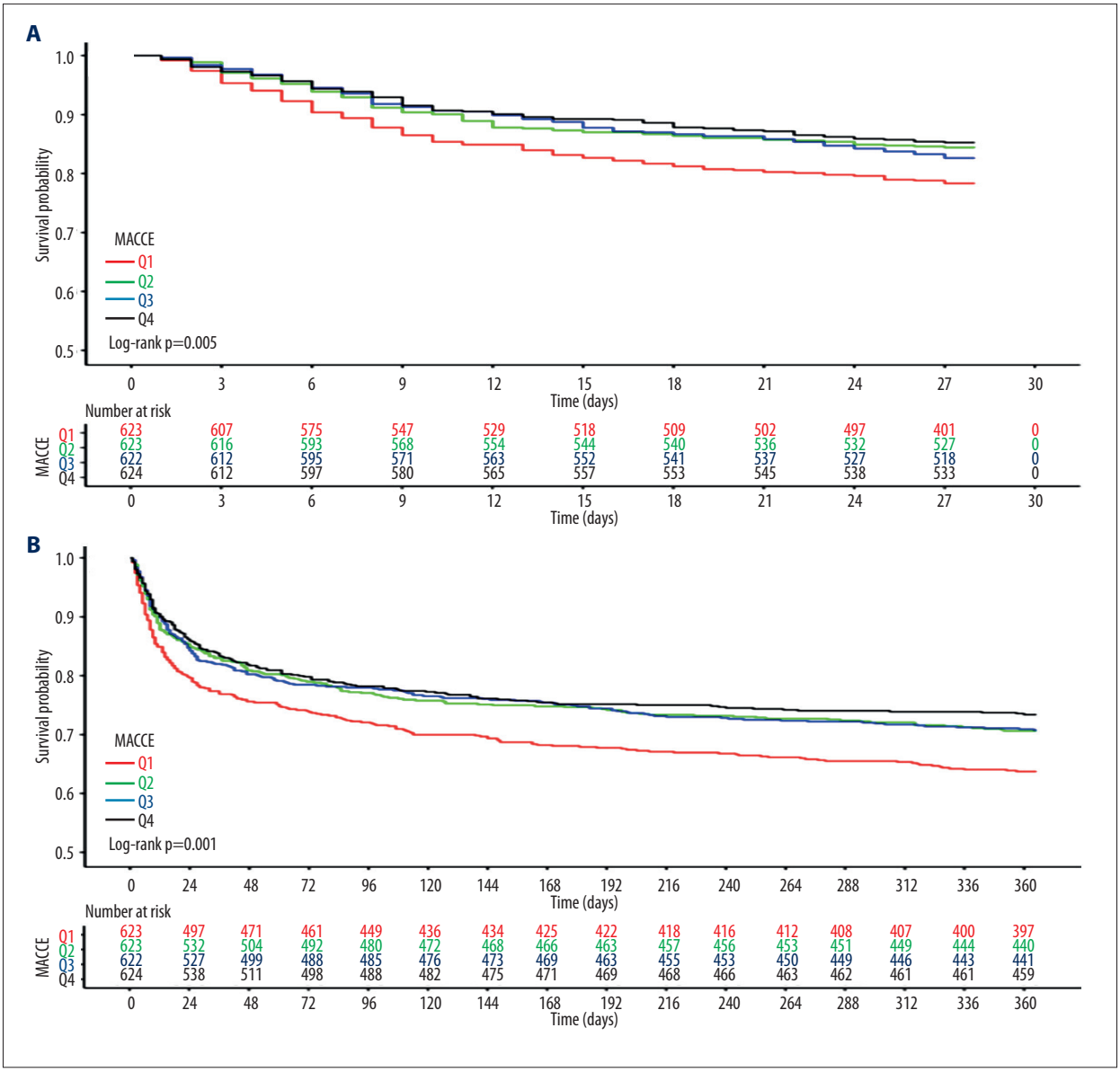

Figure 3. Kaplan-Meier survival curves for 28-day and 365-day mortality across NHHR quartiles. (**A**) Twenty-eight-day survival curves and (**B**) 365-day survival curves for patients stratified by NHHR quartiles (Q1-Q4). Survival probabilities significantly differed across NHHR categories, as indicated by the log-rank test. Higher NHHR levels were consistently associated with increased mortality risk. Abbreviations: MACCE, major adverse cardiovascular and cerebrovascular events; NHHR, non-high-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio.

For 365-day mortality (**Figure 2**), a similar pattern was observed, with greater separation among NHHR quartiles during long-term follow-up relative to the 28-day curves. The overall association remained highly significant ($P < 0.001$), and the nonlinear test confirmed a pronounced nonlinear dose-response relationship ($P = 0.001$). Consistent with the short-term findings, mortality risk increased as NHHR values rose, suggesting a nonlinear upward-curving pattern across the NHHR spectrum. Kaplan-Meier survival analyses showed a pattern for 365-day mortality similar to that observed for 28-day mortality, but with more distinct and sustained separation among NHHR quartiles during long-term follow-up (**Figure 3**). Long-term survival rates significantly differed across quartiles (log-rank $P = 0.001$); higher NHHR levels were consistently associated with increased mortality risk, whereas lower NHHR quartiles were associated with more favorable long-term survival outcomes.

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Table 4. Association between NHHR and 365-day mortality in critically ill patients with ischemic stroke.

Characteristic	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
NHHR (continuous)	1.00 (0.96-1.05)	0.956	1.10 (1.06-1.14)	< 0.001	1.10 (1.06-1.15)	< 0.001
NHHR quartile						
Q2	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q1	1.30 (1.07-1.59)	0.008	1.25 (1.03-1.53)	0.023	1.26 (1.03-1.53)	0.022
Q3	0.99 (0.81-1.22)	0.957	1.17 (0.95-1.43)	0.143	1.19 (0.97-1.46)	0.103
Q4	0.90 (0.73-1.10)	0.302	1.28 (1.03-1.59)	0.024	1.30 (1.05-1.62)	0.017

Abbreviations: CI, confidence interval; HR, hazard ratio; NHHR, non-high-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio. Model 1: Crude model; Model 2: Adjusted for age, sex, race, language, marital status, insurance status, admission type (emergency, urgent, surgical, observation, and elective), heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, respiratory rate, temperature, and SpO_2; Model 3: Adjusted for variables in Model 2 plus glucose, hematocrit, hemoglobin, platelet count, white blood cell count, anion gap, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, sodium, potassium, international normalized ratio, prothrombin time, partial thromboplastin time, total bilirubin, hypertension, myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, diabetes, paraplegia, renal disease, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, severe liver disease, malignant cancer, metastatic solid tumor, and sepsis.

Table 5. Nonlinear association between NHHR and 365-day mortality in critically ill patients with ischemic stroke.

Outcome	Effect size (95% CI)	*P*
Fitted by standard linear regression	1.103 (1.060-1.148)	< 0.001
Fitted by 2-piecewise linear regression		
Inflection point	2.111	
< 2.111	0.791 (0.658-0.951)	0.013
≥ 2.111	1.141 (1.099-1.186)	< 0.001
P for likelihood ratio test	< 0.001	

Abbreviations: CI, confidence interval; HR, hazard ratio; NHHR, non-high-density lipoprotein cholesterol-to-high-density lipoprotein cholesterol ratio.

Establishment and Validation of Predictive Models

Using LASSO regression with 10-fold cross-validation, we identified the optimal penalty parameter (**Figure 4A**), after which coefficient profiles gradually decreased to 0 as λ increased (**Figure 4B**). Sixteen predictors with non-zero coefficients were retained from the training cohort, including age, kidney disease, malignancy, congestive heart failure, NHHR, respiratory rate, prothrombin time, calcium, sodium, heart rate, glucose, temperature, blood urea nitrogen, white blood cell count, SpO_2, and the Charlson Comorbidity Index. These variables were subsequently combined with recursive feature elimination to refine the feature set for the random forest model. Cross-validation was performed to assess model robustness; receiver operating characteristic curves and decision curve analysis were utilized to evaluate discrimination and clinical utility. Six machine learning algorithms were compared: Cox proportional hazards model, conditional inference tree, elastic net regularization, neural network, RSF, and XGBoost. Decision curve analyses further supported the clinical utility of RSF. For both 28-day (training set in **Figure 5A**) and 365-day (validation set in **Figure 5B**) mortality, RSF consistently provided greater net benefit across a broad range of threshold probabilities relative to the other algorithms, indicating stronger potential clinical value. For 28-day mortality, RSF achieved the highest predictive accuracy (AUC = 0.8056), followed by XGBoost (AUC = 0.7963), as demonstrated by receiver operating characteristic curves (training set in **Figure 5C**). Similarly, for 365-day mortality, RSF showed superior discriminatory performance (AUC = 0.7638), and XGBoost displayed comparable performance (AUC = 0.7531) (validation set in **Figure 5D**).

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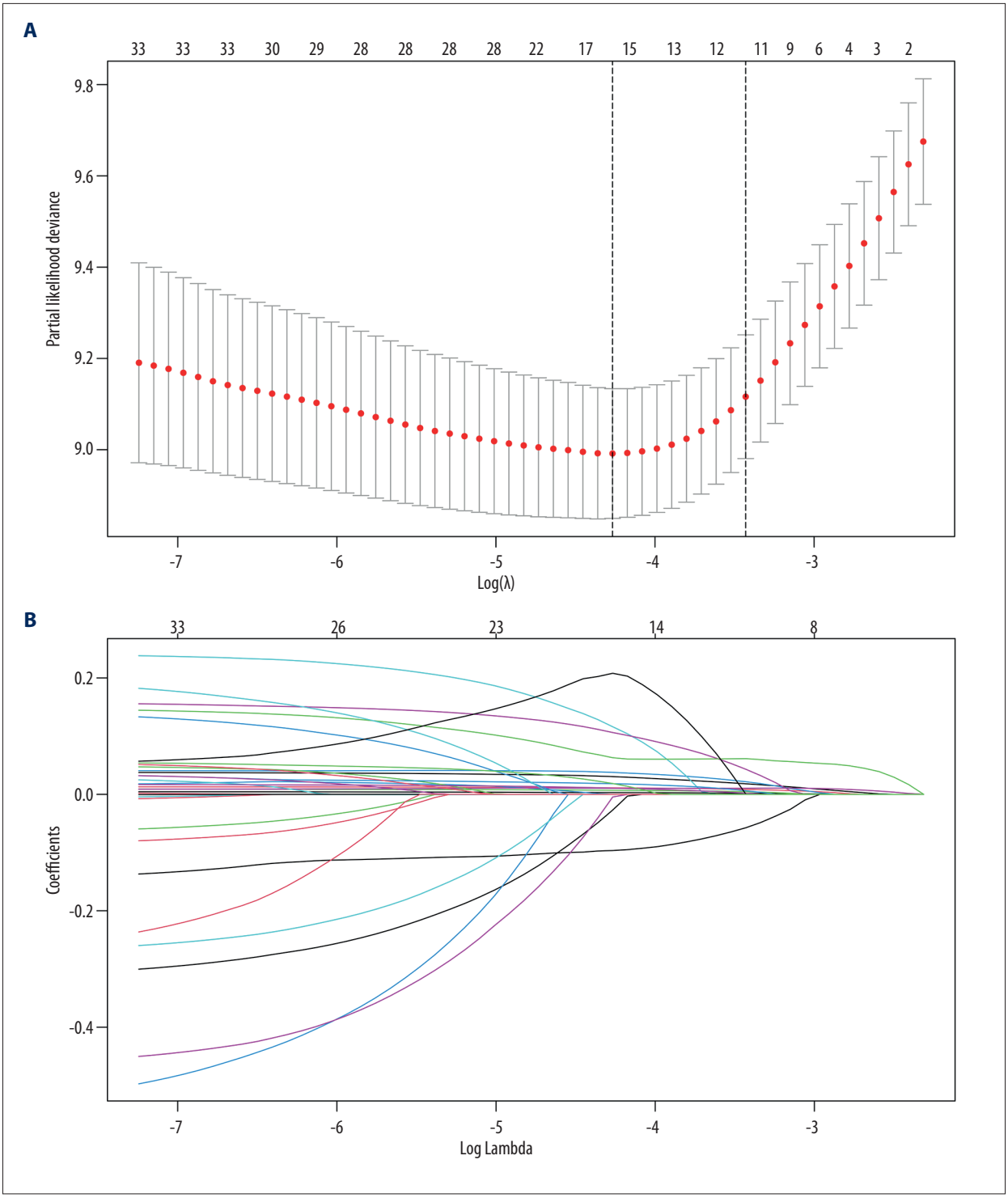

Figure 4. Selection of the optimal λ value and trajectories of LASSO coefficients. (**A**) The optimal penalty parameter λ was determined using 10-fold cross-validation. Vertical dashed lines indicate the λ value that minimized the partial likelihood deviance and the λ value within 1 standard error of the minimum. (**B**) Coefficient profiles for all candidate predictors are plotted against the log(λ) sequence, illustrating how variable coefficients progressively shrink toward 0 as the penalty increases. Abbreviation: LASSO, least absolute shrinkage and selection operator.

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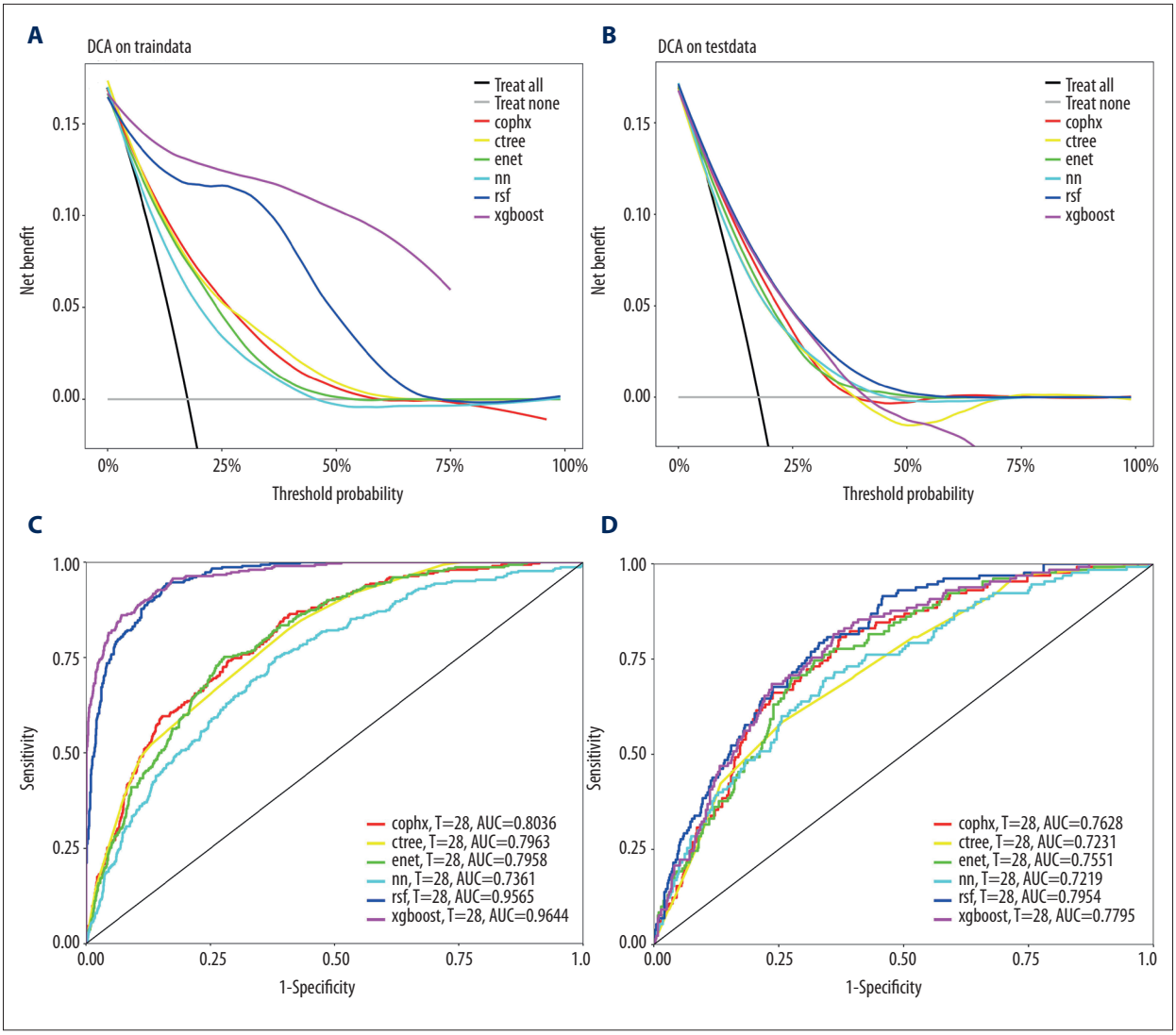

Figure 5. Evaluation of the predictive performance of machine learning models. Decision curve analysis was used to assess the net clinical benefit of each model in the training set (**A**) and validation set (**B**). Receiver operating characteristic curves were subsequently used to evaluate model discrimination in the training set (**C**) and validation set (**D**). Abbreviations: AUC, area under the curve; coxph, Cox proportional hazards model; ctree, conditional inference tree; enet, elastic net regularization; nn, neural network; rsf, random survival forest; xgboost, Cox gradient boosting.

Discussion

This retrospective cohort study examined the association between NHHR and mortality risk in critically ill patients with ischemic stroke. We identified a distinct nonlinear, J-shaped relationship between NHHR levels and mortality risk, whereby both elevated and reduced NHHR values were associated with increased mortality. Accurate prognostic biomarkers are essential to optimize the management of ischemic stroke in intensive care settings [16]. Our analysis provides evidence that NHHR offers important biological insights into dysregulated lipid metabolism and mortality risk.

NHHR integrates multiple atherogenic lipoproteins, including very-low-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), intermediate-density lipoprotein cholesterol, and lipoprotein(a), relative to anti-atherosclerotic high-density lipoprotein cholesterol (HDL-C); thus, it reflects the dynamic balance of circulating lipids [17]. Emerging evidence suggests that NHHR is a superior predictor of disease risk compared with individual lipid indices. For example, Wang et al [7] reported a nonlinear inverted U-shaped association between NHHR and hyperuricemia risk in Chinese adults. Qing et al [5] found that elevated NHHR levels were associated with an increased risk of suicidal ideation. Liu et al [18] identified a U-shaped relationship between baseline NHHR levels and the

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occurrence of major adverse cardiovascular and cerebrovascular events in patients with coronary artery disease undergoing percutaneous coronary intervention. Additional studies have supported the prognostic value of NHHR across diverse conditions, including a U-shaped association with all-cause mortality among individuals with diabetes or prediabetes [19] and a dual-risk relationship in hypertensive populations [20]. Li et al [9] identified an L-shaped relationship between NHHR and cardiovascular mortality in patients with type 2 diabetes mellitus and diabetic kidney disease. Previous ischemic stroke research has predominantly focused on LDL-C and HDL-C individually, revealing that elevated LDL-C is associated with increased risk and elevated HDL-C is generally considered protective [21]. In contrast, our findings emphasize the clinical relevance of lipid ratios such as NHHR. Our results demonstrated a strong J-shaped relationship between NHHR and mortality, providing further insight into lipid dynamics with respect to stroke prognosis. Additionally, by incorporating NHHR into machine learning models, including LASSO regression and 6 predictive algorithms, we identified NHHR as an important predictor of mortality. However, caution is warranted because multicollinearity among predictors may influence model performance and interpretation.

The biological mechanisms underlying the observed J-shaped relationship between NHHR and mortality remain incompletely understood. Elevated NHHR likely reflects an increased atherosclerotic burden [8,22]. LDL-C promotes foam cell formation within atherosclerotic plaques through oxidative processes that impair endothelial integrity and amplify inflammatory responses [23,24]. Conversely, HDL-C mitigates atherosclerosis by facilitating reverse cholesterol transport, enhancing endothelial function, and suppressing oxidative stress and inflammatory cytokine production [25,26]. Lipoprotein(a) further contributes to atherosclerosis by increasing plasminogen activator inhibitor-1 levels, thus impairing fibrinolysis and increasing thrombosis risk [27]. Histological evidence suggests that smooth muscle cell proliferation and extracellular matrix synthesis represent early stages of atherosclerotic plaque development, followed by macrophage-mediated cholesterol deposition, a key pathogenic event in atherogenesis [28,29]. Both HDL and LDL play critical roles in this process. The accelerated progression of atherosclerosis associated with low HDL-C or substantially elevated non-HDL-C levels may contribute to the increased mortality observed among individuals with excessively high NHHR values. Conversely, extremely low NHHR values may indicate systemic malnutrition or frailty because they are associated with low total cholesterol levels, poor nutritional status, cachexia, and heightened systemic inflammation, all of which can contribute to adverse outcomes [30-32]. Another possible explanation involves genetic abnormalities, whereby individuals with extremely high HDL-C levels may develop dysfunctional HDL particles that lose their protective properties and instead exert pro-inflammatory effects [33,34]. Further mechanistic studies are needed to clarify the underlying biological pathways.

To our knowledge, this study is the first to identify a J-shaped relationship between NHHR and mortality among critically ill patients with ischemic stroke using a large-scale dataset and integrating multivariable Cox regression, restricted cubic spline analysis, subgroup stratification, and machine learning approaches. Although LDL-C remains the primary lipid biomarker in current guidelines, our findings suggest that NHHR can provide additional prognostic value beyond conventional lipid measures. Nevertheless, some limitations should be acknowledged. First, the cross-sectional study design limits causal inference. Future longitudinal studies with serial NHHR measurements are needed to establish temporal relationships. Second, despite extensive adjustment for confounding factors, residual confounding from unmeasured variables (eg, medication use and lifestyle changes) cannot be excluded. Future randomized controlled trials and prospective longitudinal cohort studies are warranted to validate and extend these findings.

Conclusions

NHHR is a promising prognostic indicator of all-cause mortality in critically ill patients with ischemic stroke, demonstrating distinct J-shaped relationships with short- and long-term outcomes. Routine monitoring of NHHR may provide valuable insights for mortality risk stratification and prognostic assessment in this vulnerable population.

Availability of Data and Materials

Data supporting the findings of this study are available from the corresponding author upon reasonable request. Registered users may access the publicly available MIMIC-IV database (https://mimic.physionet.org/), which supports the present findings.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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References:

1. Fan J, Li X, Yu X, et al. Global burden, risk factor analysis, and prediction study of ischemic stroke, 1990-2030. Neurology. 2023;101(2):e137-50
2. Hou S, Zhang Y, Xia Y, et al. Global, regional, and national epidemiology of ischemic stroke from 1990 to 2021. Eur J Neurol. 2024;31(12):e16481
3. Zhu L, Lu Z, Zhu L, et al. Lipoprotein ratios are better than conventional lipid parameters in predicting coronary heart disease in Chinese Han people. Kardiol Pol. 2015;73(10):931-38
4. Yan C, Wang H, Liu C, et al. Association between non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) with depressive symptoms: Recent findings from NHANES 2005-2018. Front Psychiatry. 2024;15:1467142
5. Qing G, Deng W, Zhou Y, et al. The association between non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and suicidal ideation in adults: A population-based study in the United States. Lipids Health Dis. 2024;23(1):17
6. Ma HX, Chen HQ, Wang PC. Association between non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and stroke among adults in the USA: A cross-sectional NHANES study. Biomed Environ Sci. 2025;38(1):37-46
7. Wang Z, Wu M, Du R, et al. The relationship between non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and hyperuricaemia. Lipids Health Dis. 2024;23(1):187
8. Sheng G, Liu D, Kuang M, et al. Utility of non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio in evaluating incident diabetes risk. Diabetes Metab Syndr Obes. 2022;15:1677-86
9. Li Z, Xu H. Association between non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio and cardiovascular disease mortality in patients with type 2 diabetes mellitus and diabetic kidney disease. Front Endocrinol (Lausanne). 2025;16:1509752
10. Sajda P. Machine learning for detection and diagnosis of disease. Annu Rev Biomed Eng. 2006;8:537-65
11. Devaux A, Genuer R, Peres K, et al. Individual dynamic prediction of clinical endpoint from large dimensional longitudinal biomarker history: A landmark approach. BMC Med Res Methodol. 2022;22(1):188
12. Senders JT, Staples P, Mehrtash A, et al. An online calculator for the prediction of survival in glioblastoma patients using classical statistics and machine learning. Neurosurgery. 2020;86(2):E184-92
13. Nopour R. Prediction of five-year survival among esophageal cancer patients using machine learning. Heliyon. 2023;9(12):e22654
14. Rahimi M, Akbari A, Asadi F, et al. Cervical cancer survival prediction by machine learning algorithms: A systematic review. BMC Cancer. 2023;23(1):341
15. Alhamzawi R, Ali HTM. The Bayesian adaptive lasso regression. Math Biosci. 2018;303:75-82
16. Wu S, Wu B, Liu M, et al. Stroke in China: Advances and challenges in epidemiology, prevention, and management. Lancet Neurol. 2019;18(4):394-405
17. Blaha MJ, Blumenthal RS, Brinton EA, et al. The importance of non-HDL cholesterol reporting in lipid management. J Clin Lipidol. 2008;2(4):267-73
18. Liu J, Oorloff MD, Nadella A, et al. Association between the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and cardiovascular outcomes in patients undergoing percutaneous coronary intervention: A retrospective study. Lipids Health Dis. 2024;23(1):324
19. Yu B, Li M, Yu Z, et al. The non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) as a predictor of all-cause and cardiovascular mortality in US adults with diabetes or prediabetes: NHANES 1999-2018. BMC Med. 2024;22(1):317
20. Su X, Rao H, Zhao C, et al. Association between the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio and mortality among hypertension patients. Sci Rep. 2025;15(1):6012
21. Gong X, Chen L, Song B, et al. Associations of lipid profiles with the risk of ischemic and hemorrhagic stroke: A systematic review and meta-analysis of prospective cohort studies. Front Cardiovasc Med. 2022;9:893248
22. Kim SW, Jee JH, Kim HJ, et al. Non-HDL-cholesterol/HDL-cholesterol is a better predictor of metabolic syndrome and insulin resistance than apolipoprotein B/apolipoprotein A1. Int J Cardiol. 2013;168(3):2678-83
23. Yamada Y, Doi T, Hamakubo T, et al. Scavenger receptor family proteins: roles for atherosclerosis, host defence and disorders of the central nervous system. Cell Mol Life Sci. 1998;54:628-40
24. Tabas I. Macrophage death and defective inflammation resolution in atherosclerosis. Nat Rev Immunol. 2010;10(1):36-46
25. O'Neill F, Charakida M, Topham E, et al. Anti-inflammatory treatment improves high-density lipoprotein function in rheumatoid arthritis. Heart. 2017;103(10):766-73
26. Feig JE, Hewing B, Smith JD, et al. High-density lipoprotein and atherosclerosis regression: Evidence from preclinical and clinical studies. Circ Res. 2014;114(1):205-13
27. Jung RG, Motazedian P, Ramirez FD, et al. Association between plasminogen activator inhibitor-1 and cardiovascular events: A systematic review and meta-analysis. Thromb J. 2018;16:12
28. Finney AC, Funk SD, Green JM, et al. EphA2 expression regulates inflammation and fibroproliferative remodeling in atherosclerosis. Circulation. 2017;136(6):566-82
29. Adiguzel E, Ahmad PJ, Franco C, et al. Collagens in the progression and complications of atherosclerosis. Vasc Med. 2009;14(1):73-89
30. Tuikkala P, Hartikainen S, Korhonen MJ, et al. Serum total cholesterol levels and all-cause mortality in a home-dwelling elderly population: A six-year follow-up. Scand J Prim Health Care. 2010;28(2):121-27
31. Johannesen CDL, Langsted A, Mortensen MB, et al. Association between low density lipoprotein and all cause and cause specific mortality in Denmark: Prospective cohort study. BMJ. 2020;371:m4266
32. Jacobs D, Blackburn H, Higgins M, et al. Report of the Conference on Low Blood Cholesterol: Mortality associations. Circulation. 1992;86(3):1046-60
33. Zeng RX, Xu JP, Kong YJ, et al. U-shaped relationship of non-HDL cholesterol with all-cause and cardiovascular mortality in men without statin therapy. Front Cardiovasc Med. 2022;9:903481
34. Madsen CM, Varbo A, Nordestgaard BG. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: Two prospective cohort studies. Eur Heart J. 2017;38(32):2478-86

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