Original Article

High lactate dehydrogenase was associated with adverse outcomes in patients with acute ischemic stroke or transient ischemic attack

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Background: Previous studies found that lactate dehydrogenase (LDH) levels predicted poor outcomes in hemorrhagic stroke, but the prognostic role of LDH in ischemic stroke (IS) remains unclear. The aim of this study is to investigate the association between LDH and adverse clinical outcomes in patients with acute ischemic stroke (AIS) or transient ischemic attack (TIA).

Methods: All patients were enrolled from the Third China National Stroke Registry (CNSR-III). Adverse outcomes included all-cause death and poor functional outcomes [defined as modified Rankin Scale (mRS) score 3–6 and 2–6] at 3 months and 1 year. Multivariable Cox proportional hazards models and logistic regressions were used to evaluate the association of LDH with risk of all-cause death and poor functional outcomes, respectively.

Results: Among 9,796 included patients, the median [interquartile range (IQR)] of LDH was 175.00 (151.00–205.40) U/L. After adjustment for confounding factors, patients in the highest LDH quartile had a higher risk of all-cause death [hazard ratio (HR), 2.23; 95% confidence interval (CI), 1.27–3.90], and a higher proportion of mRS score 3–6 [odds ratio (OR), 1.54; 95% CI, 1.26–1.90] and mRS score 2–6 (OR, 1.56; 95% CI, 1.32–1.84) at 3 months. We also observed a J-shaped association between LDH and risk of each outcome. Consistent results were found at 1 year.

Conclusions: Higher LDH levels are independently associated with adverse outcomes in patients with AIS or TIA.

Keywords: Lactate dehydrogenase (LDH); all-cause death; poor functional outcomes; acute ischemic stroke (AIS); transient ischemic attack (TIA)

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Introduction

Lactate dehydrogenase (LDH), the final product of glycolysis, is a hydrogen transfer enzyme in all cell types and tissues, including muscle, liver, and brain. It is released into peripheral blood after cellular damage (1). Abnormal extracellular appearance of LDH, which is detectable in serum and used for detection of cell or tissue damage, was reported as an ominous outcome marker in a large number of clinical conditions, containing cardiac diseases such as myocardial infarction, lung diseases such as emphysema, acute viral hepatitis, cirrhosis, and metastatic carcinoma of the liver of kidneys, chronic obstructive pulmonary disease, tumors of the lung, severe infection and sepsis, malignancies, and hypoxic-ischemic encephalopathy (2-7). Although LDH has historically been considered as an indicator of various negative health outcomes, the association between LDH and outcomes of stroke has not been established.

An increase in serum LDH is demonstrated as a marker of intravascular hemolysis (8), thus the prognostic role of LDH was reported mainly in patients with hemorrhagic stroke (9,10). However, the relationship between LDH and prognosis of ischemic stroke (IS), which accounting for approximately 70% of stroke in China (11), has not been investigated up to now. Therefore, using data from the prospective cohort of the Third China National Stroke Registry (CNSR-III), we aimed to evaluate the association between LDH and adverse outcomes, consisting of all-cause death and poor functional outcomes in patients with acute ischemic stroke (AIS) or transient ischemic attack (TIA). We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2195).

Methods

Study population

The detailed design and procedure of the CNSR-III have been described previously (12). Briefly, the CNSR-III is a nationwide prospective registry for patients with AIS or TIA presented to hospitals between 2015 and March 2018 in China. Participants were consecutively enrolled if meeting the following criteria: (I) >18 years old; (II) diagnosis of IS or TIA within 7 days; (III) informed consent from participant or legally authorized representative. Finally, 15,166 patients were enrolled from 201 hospitals of 22 provinces and 4 municipalities. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Beijing Tiantan Hospital (No.: KY2015-001- 01) and all study centers gave ethical approval of the study protocol. Written consents were obtained from all participants or their legal representatives.

Baseline data collection

Trained research coordinators at each site collected baseline data prospectively via a face-to-face interview or medical records, including age, sex, body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters, kg/m^2), medical history of hypertension, diabetes, dyslipidemia, IS or TIA (stroke was defined as an acute disturbance of focal neurological function with symptoms lasting longer than 24 hours and TIA was defined as a new neurological event that lasted less than 24 hours), atrial fibrillation or flutter, peripheral vascular disease, heart failure, stroke type (IS and TIA), TOAST classification (Trial of Org 10172 in Acute Stroke Treatment) (13), current smoking, medications in hospital, National Institutes of Health Stroke Scale (NHISS) (14), time from onset to admission, serum lipid profiles, fasting blood glucose (FBG), estimated glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease Epidemiological Collaboration equation (15), high-sensitivity C-reactive protein (hs-CRP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Sample collection and measurements of LDH

Fasting blood samples were collected, preserved, and processed in a manner recommended by the clinical site laboratory's policies and procedures in every hospital within 24 hours of admission. All the blood samples were collected and then frozen in cryotube at –80 ℃ refrigerator until testing was performed. The concentration of LDH was measured by automated hematology analyzer at each research center. Laboratory technicians were blinded to the clinical outcomes of patients. All measurements were performed according to the manufacturers' recommendations.

Outcome assessment

The outcomes were obtained through clinic or telephone at 3-month and 1-year follow-up. Assessment of outcomes was completed by trained research coordinators who were

blinded to patients' baseline clinical information. Adverse outcomes in our study include all-cause death and poor functional outcomes. All-cause death was either confirmed on a death certification from the attended hospital or the local citizen registry. Modified Rankin Scale (mRS) score ranged from 0 (no symptoms) to 6 (death), and poor functional outcome was defined as mRS ranged from 3–6/2–6 at 3-month and 1-year follow-up.

Statistical analysis

Participants were divided into four categories according to quartiles of LDH. Continuous variables were described by medians and interquartile ranges (IQRs) because of skewed distribution, categorical variables were described by frequencies and percentages. The nonparametric Wilcoxon or Kruskal-Wallis test was used to compare group differences for continuous variables, and chi-square tests or Fisher exact tests were used for categorical variables. The Kaplan-Meier method and the log-rank test were used for univariate survival analysis. Ordinal logistic regression was applied to estimate the common odds ratio (OR) for a shift in the direction of a worse outcome on the mRS score, where the proportional odds assumption was not violated.

The association of LDH with all-cause death and poor functional outcomes were evaluated by Cox proportion hazard regression models and logistic regressions, respectively. Robust sandwich estimates of the variance-covariance matrix were used to account for clustering by hospital. Variables with a P<0.2 in the univariate analysis and the well-established predictors of the outcomes were selected to adjust in the multivariable analyses. Unadjusted and adjusted hazard ratios (HRs) or ORs and their 95% confidence intervals (CIs) were estimated. Model 1 was adjusted for age and gender; Model 2 was additionally adjusted for BMI, hypertension, diabetes, dyslipidemia, atrial fibrillation/flutter, stroke type, current smoking, TOAST, NIHSS, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), FBG, and eGFR; Model 3 was further adjusted for antihypertensive agents, cholesterol-lowering agents, hypoglycemic agents, antiplatelet agents, anticoagulant agents, time from onset to admission, hs-CRP, ATL and AST on admission. P for trend was calculated by treating the median LDH value of each quartile as a continuous variable in each model. In the sensitivity analysis, we excluded patients with a history of cancer or infection, given that these conditions may influence the levels of LDH. Furthermore, we used restricted cubic splines with five knots (at 5th, 25th, 50th, 75th, and 95th percentiles of LDH distribution) to examine the dose-response relationship of LDH with outcomes, with the median of the first quartile of LDH (134.00 U/L) as reference point, and HR/OR was adjusted for all potential variables described herein. Stratified analyses were performed in subgroups of age (<60 and ≥60 years), gender (female and male), stroke subtype (IS and TIA), and time from onset to admission (<24 and ≥24 h), likelihood ratio test was used to assess the significance of interaction between stratified variables and LDH.

All analyses were performed with SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided, and a P value <0.05 was deemed as statistically significant.

Results

Baseline characteristics

Patients with missing available data on LDH (n=5,057), and missing available mRS at 3-month or 1-year follow-up (n=313) were excluded. Finally, the current analysis included 9,796 patients. A comparison of baseline characteristics between the excluded and included patients are showed in Table S1. There was no significant clinical difference between excluded and included participants in terms of all the baseline characteristics.

Table 1 shows the baseline characteristics of included patients stratified by quartiles of LDH. Of all the patients, the median (IQR) age was 63.00 (55.00–70.00) years, 6,696 (68.35%) patients were men, and the median (IQR) level of LDH was 175.00 (151.00–205.40) U/L. Compared with patients in the first quartile group, patients with higher LDH were older, had less men, lower BMI, a higher proportion of hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation/flutter, IS, large-artery atherosclerosis subtype, less current smokers, take less cholesterol-lowering, agents and antiplatelet agents but more antihypertensive and anticoagulant agents, higher NIHSS score, shorten time from onset to admission, higher TC, LDL-C, HDL-C, FBG, hs-CRP, ALT and AST levels but lower TG and eGFR levels.

Association between LDH and all-cause death

One hundred and fifty-four (1.57%) and 329 (3.36%) patients died at 3-month and 1-year assessment. The

Table 1 Baseline characteristics of included patients according to quartiles of LDH

Variables	Overall	Quartiles of LDH				P value
		Q1	Q2	Q3	Q4	
No. of the patients	9,796	2,468	2,422	2,458	2,448	
LDH, U/L	175.00 (151.00–205.40)	138.00 (127.00–145.00)	164.00 (158.00–169.00)	188.00 (181.00–196.00)	235.00 (218.00–279.00)	<0.0001
Age, y	63.00 (55.00–70.00)	61.00 (53.00–68.00)	63.00 (55.00–71.00)	63.00 (55.00–70.00)	64.00 (56.00–72.00)	<0.0001
Men, n (%)	6,696 (68.35)	1,872 (75.85)	1,663 (68.66)	1,624 (66.07)	1,537 (62.79)	<0.0001
BMI, kg/m^2	24.49 (22.59–26.57)	24.51 (22.86–26.57)	24.61 (22.60–26.61)	24.49 (22.60–26.71)	24.22 (22.32–26.40)	0.0026
Medical history, n (%)						
Hypertension	6,090 (62.17)	1,461 (59.20)	1,530 (63.17)	1,563 (63.59)	1,536 (62.75)	0.0052
Diabetes mellitus	2,293 (23.41)	680 (27.55)	573 (23.66)	536 (21.81)	504 (20.59)	<0.0001
Dyslipidemia	760 (7.76)	188 (7.62)	208 (8.59)	204 (8.30)	160 (6.54)	0.0365
Stroke or TIA	2,072 (21.15)	511 (20.71)	515 (21.26)	537 (21.85)	509 (20.79)	0.7493
Atrial fibrillation/flutter	703 (7.18)	94 (3.81)	137 (5.66)	168 (6.83)	304 (12.42)	<0.0001
Peripheral vascular disease	67 (0.68)	20 (0.81)	15 (0.62)	17 (0.69)	15 (0.61)	0.8219
Heart failure	63 (4.47)	15 (4.98)	11 (3.41)	16 (4.55)	21 (4.85)	0.7546
Stroke type/subtype, n (%)						
IS	9,128 (93.18)	2,284 (92.54)	2,256 (93.15)	2,278 (92.68)	2,310 (94.36)	0.0472
TIA	668 (6.82)	184 (7.46)	166 (6.85)	180 (7.32)	138 (5.64)	
TOAST, n (%)						
Large-artery atherosclerosis	2,455 (25.06)	626 (25.36)	593 (24.48)	609 (24.78)	627 (25.61)	<0.0001
Cardioembolism	610 (6.23)	90 (3.65)	121 (5.00)	139 (5.66)	260 (10.62)	
Small-vessel occlusion	1,976 (20.17)	536 (21.72)	514 (21.22)	512 (20.83)	414 (16.91)	
Other determined etiology	131 (1.34)	30 (1.22)	36 (1.49)	23 (0.94)	42 (1.72)	
Undetermined etiology	4,624 (47.2)	1,186 (48.06)	1,158 (47.81)	1,175 (47.80)	1,105 (45.14)	
Current smoker, n (%)	3,043 (31.06)	922 (37.36)	777 (32.08)	709 (28.84)	635 (25.94)	<0.0001
Medication in hospital, n (%)						
Cholesterol-lowering agents	9,328 (95.94)	2,346 (96.03)	2,286 (94.93)	2,358 (96.80)	2,338 (95.98)	0.0122
Antihypertensive agents	4,458 (45.85)	972 (39.79)	1,131 (46.97)	1,146 (47.04)	1,209 (49.63)	<0.0001
Hypoglycemic agents	2,482 (25.53)	707 (28.94)	614 (25.50)	599 (24.59)	562 (23.07)	<0.0001

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Overall	Quartiles of LDH				P value
		Q1	Q2	Q3	Q4	
Antiplatelet agents	9,443 (97.12)	2,402 (98.32)	2,340 (97.18)	2,373 (97.41)	2,328 (95.57)	<0.0001
Anticoagulant agents	1,105 (11.36)	218 (8.92)	237 (9.84)	265 (10.88)	385 (15.80)	<0.0001
NIHSS score on admission	3 [1–6]	3 [1–5]	3 [1–5]	3 [1–6]	4 [2–7]	<0.0001
Time from onset to admission, h	14.00 (3.00–46.00)	17.00 (3.00–47.00)	16.00 (3.00–47.00)	15.00 (3.00–46.00)	11.00 (3.00–38.00)	0.0004
Lipid level						
TC, mmol/L	4.02 (3.33–4.77)	3.86 (3.25–4.61)	4.01 (3.32–4.78)	4.08 (3.38–4.78)	4.12 (3.40–4.91)	<0.0001
LDL-C, mmol/L	2.35 (1.74–3.02)	2.22 (1.68–2.92)	2.36 (1.72–3.00)	2.39 (1.78–3.08)	2.41 (1.78–3.10)	<0.0001
HDL-C, mmol/L	0.94 (0.78–1.13)	0.89 (0.76–1.08)	0.93 (0.77–1.12)	0.96 (0.79–1.15)	0.98 (0.80–1.17)	<0.0001
TG, mmol/L	1.37 (1.03–1.88)	1.40 (1.04–1.95)	1.41 (1.05–1.91)	1.35 (1.01–1.88)	1.31 (1.00–1.8)	0.0007
FBG, mmol/L	5.59 (4.92–6.95)	5.62 (4.97–7.14)	5.54 (4.91–6.94)	5.50 (4.90–6.77)	5.65 (4.90–7.00)	0.0226
eGFR, mL/min/1.73 m^2	92.90 (81.31–101.66)	95.01 (84.7–103.43)	92.83 (81.39–101.71)	92.19 (80.40–101.17)	90.62 (77.84–99.78)	<0.0001
hs-CRP, mg/L	1.78 (0.82–4.66)	1.46 (0.74–3.43)	1.58 (0.78–4.34)	1.81 (0.85–4.78)	2.36 (0.97–6.39)	<0.0001
ALT, U/L	18.00 (13.00–16.00)	16.40 (12.00–22.90)	17.18 (13.00–24.00)	18.00 (13.00–26.00)	20.00 (15.00–30.00)	<0.0001
AST, U/L	19.00 (16.00–24.00)	17.00 (14.00–20.65)	18.60 (15.00–23.00)	20.00 (17.00–24.000)	22.80 (18.10–29.00)	<0.0001

Continuous variables are expressed as median with IQR; categorical variables are expressed as frequency with percentage. LDH, lactate dehydrogenase; BMI, body mass index; TIA, transient ischemic attack; IS, ischemic stroke; NIHSS, The National Institutes of Health Stroke Scale; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range.

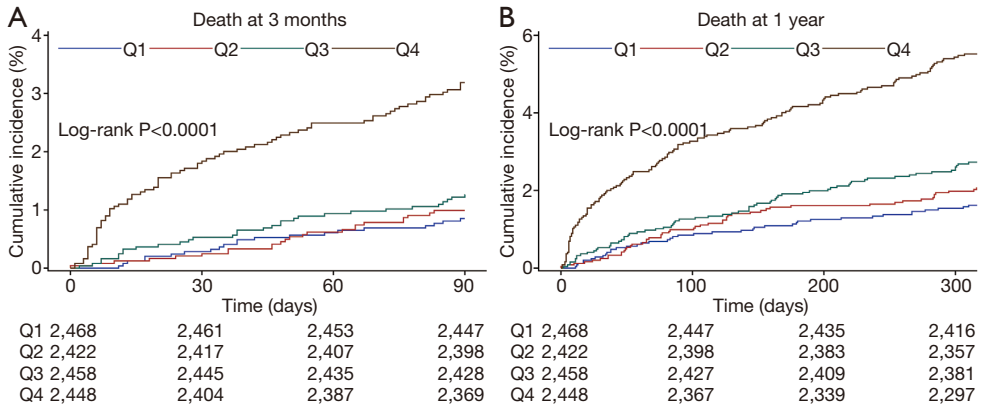

Figure 1 Kaplan-Meier curves of the incidence rate of all-cause death by quartiles of LDH. (A) Death at 3 months; (B) death at 1 year. LDH, lactate dehydrogenase.

Kaplan-Meier curves by quartiles of LDH appeared to separately early and to continue to diverge throughout the follow-up period (*Figure 1A,1B*). Patients with higher LDH quartile showed a higher cumulative incidence of all-cause at 3 months and 1 year (log-rank test P<0.0001 for all).

The associations between LDH and risk of all-cause death are presented in *Table 2*. After adjustment for potential confounding factors, patients with higher LDH level were associated with increased risk of all-cause death at 3 months, the adjusted HR for the highest versus the lowest quartile of LDH was 2.23 (95% CI, 1.27–3.90; P for trend =0.0015). The association remained significant at 1 year. Furthermore, there were J-shaped associations between LDH levels and the risk of all-cause death at 3 months and 1 year (*Figure 2A,2B*).

Association between LDH and poor functional outcomes

1404 (14.33%) and 1,363 (13.91%) patients had mRS score 3–6, 2,593 (26.47%) and 2,381 (24.31%) patients had mRS score 2–6 at 3 months and 1 year. J-shaped associations also exist in the relationship between LDH levels and the risk of poor functional outcomes at both 3 months and 1 year (*Figure 2C-2F*). There were significant shifts in the distributions of the mRS scores according to the quartiles of LDH, the common OR for the highest quartile was 1.29 (95% CI, 1.16–1.44) at 3 months and 1.34 (95% CI, 1.20–1.49) at 1 year (*Figure 3*). In the fully adjusted model, when comparing the highest quartile to the lowest quartile of LDH, LDH was significantly associated with a higher proportion of mRS score 3–6 (OR, 1.54; 95% CI, 1.26–1.90; P for trend <0.0001), and mRS score 2–6 (OR, 1.56; 95% CI, 1.32–1.84; P for trend <0.0001) at 3 months. Consistent associations were observed at 1 year (*Table 2*).

Sensitivity and subgroup analysis

Results of sensitivity analysis by excluding patients with a history of cancer (n=85) or infection (n=295) were similar with the main analysis (Table S2). Results of subgroup analysis are presented in Table S3. There was no significant interaction between LDH and stratified variables, including age, gender, stroke subtypes and time from onset to admission (P for interaction >0.05 for all), indicating the associations of LDH with all-cause death and poor functional outcomes were consistent across these subgroups.

Discussion

The main finding of the current study conducted in the CNSR-III was that the level of LDH was positively associated with the risk of all-cause death and poor functional outcomes in patients with AIS or TIA at 3-month and 1-year follow-up. These associations persisted after multivariable adjustment for important potential confounders.

Prior studies reported that serum LDH may be considered as a distinguishing clinical prognostic indicator for survival and predictor of response for management in patients with specific diseases. A community-based cohort study demonstrated that abnormal high levels of serum LDH was correlated with cardiovascular mortality in patients with long-term arsenic exposure (4). Results from the NHANES III study (National Health and Nutrition

Table 2 Association of all-cause death and poor functional outcomes with quartiles of LDH

Outcomes	Quartiles of LDH				P for trend
	Q1	Q2	Q3	Q4	
Within 3 months					
Death	21 (0.85)	24 (0.99)	31 (1.26)	78 (3.19)	
Unadjusted	Reference	1.24 (0.68–2.26)	1.75 (0.99–3.10)	4.69 (2.80–7.86)	<0.0001
Model 1	Reference	1.09 (0.60–2.00)	1.54 (0.86–2.74)	3.74 (2.20–6.34)	<0.0001
Model 2	Reference	1.07 (0.57–1.99)	1.41 (0.77–2.57)	2.65 (1.52–4.61)	<0.0001
Model 3	Reference	0.98 (0.52–1.83)	1.24 (0.67–2.27)	2.23 (1.27–3.90)	0.0015
mRS 3–6	258 (10.45)	268 (11.07)	367 (14.93)	511 (20.87)	
Unadjusted	Reference	1.09 (0.90–1.32)	1.58 (1.32–1.89)	2.34 (1.95–2.80)	<0.0001
Model 1	Reference	1.00 (0.83–1.22)	1.44 (1.20–1.73)	2.06 (1.71–2.47)	<0.0001
Model 2	Reference	0.97 (0.79–1.19)	1.36 (1.12–1.67)	1.62 (1.32–1.98)	<0.0001
Model 3	Reference	0.96 (0.78–1.18)	1.34 (1.10–1.64)	1.54 (1.26–1.90)	<0.0001
mRS 2–6	524 (21.23)	556 (22.96)	673 (27.38)	840 (34.31)	
Unadjusted	Reference	1.16 (1.01–1.34)	1.48 (1.29–1.71)	2.05 (1.77–2.36)	<0.0001
Model 1	Reference	1.09 (0.94–1.26)	1.38 (1.20–1.60)	1.85 (1.60–2.14)	<0.0001
Model 2	Reference	1.12 (0.95–1.31)	1.37 (1.17–1.60)	1.61 (1.36–1.89)	<0.0001
Model 3	Reference	1.11 (0.95–1.30)	1.36 (1.16–1.59)	1.56 (1.32–1.84)	<0.0001
Within 1 year					
Death	48 (1.94)	60 (2.48)	71 (2.89)	150 (6.13)	
Unadjusted	Reference	1.38 (0.94–2.04)	1.76 (1.21–2.58)	3.95 (2.78–5.60)	<0.0001
Model 1	Reference	1.22 (0.83–1.80)	1.53 (1.04–2.24)	3.21 (2.25–4.58)	<0.0001
Model 2	Reference	1.20 (0.81–1.78)	1.42 (0.96–2.09)	2.33 (1.61–3.36)	<0.0001
Model 3	Reference	1.12 (0.75–1.66)	1.34 (0.90–1.98)	2.10 (1.45–3.03)	<0.0001
mRS 3–6	239 (9.68)	287 (11.85)	337 (13.71)	500 (20.42)	
Unadjusted	Reference	1.32 (1.09–1.59)	1.59 (1.32–1.92)	2.47 (2.06–2.97)	<0.0001
Model 1	Reference	1.19 (0.98–1.45)	1.41 (1.16–1.71)	2.12 (1.75–2.56)	<0.0001
Model 2	Reference	1.19 (0.97–1.47)	1.34 (1.09–1.65)	1.68 (1.37–2.07)	<0.0001
Model 3	Reference	1.17 (0.95–1.44)	1.32 (1.08–1.62)	1.60 (1.30–1.97)	<0.0001
mRS 2–6	470 (19.04)	523 (21.59)	605 (24.61)	783 (31.99)	
Unadjusted	Reference	1.24 (1.07–1.44)	1.48 (1.28–1.71)	2.06 (1.77–2.38)	<0.0001
Model 1	Reference	1.15 (0.99–1.34)	1.36 (1.17–1.57)	1.83 (1.58–2.13)	<0.0001
Model 2	Reference	1.17 (1.00–1.37)	1.33 (1.13–1.56)	1.56 (1.32–1.84)	<0.0001
Model 3	Reference	1.16 (0.98–1.36)	1.31 (1.12–1.54)	1.50 (1.27–1.77)	<0.0001

Model 1: adjusted for age and gender; Model 2: further adjusted for BMI, history of hypertension, diabetes, dyslipidemia, atrial fibrillation/flutter, stroke type, current smoke, TOAST, NHISS, blood glucose, TC, LDL-C, HDL-C, TG, eGFR on admission; Model 3: further adjusted for antihypertensive agents, cholesterol-lowering agents, hypoglycemic agents, antiplatelet agents, anticoagulant agents, time from onset to admission, hs-CRP, ALT, and AST on admission. LDH, lactate dehydrogenase; mRS, modified Rankin Scale; BMI, body mass index; NHISS, The National Institutes of Health Stroke Scale; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

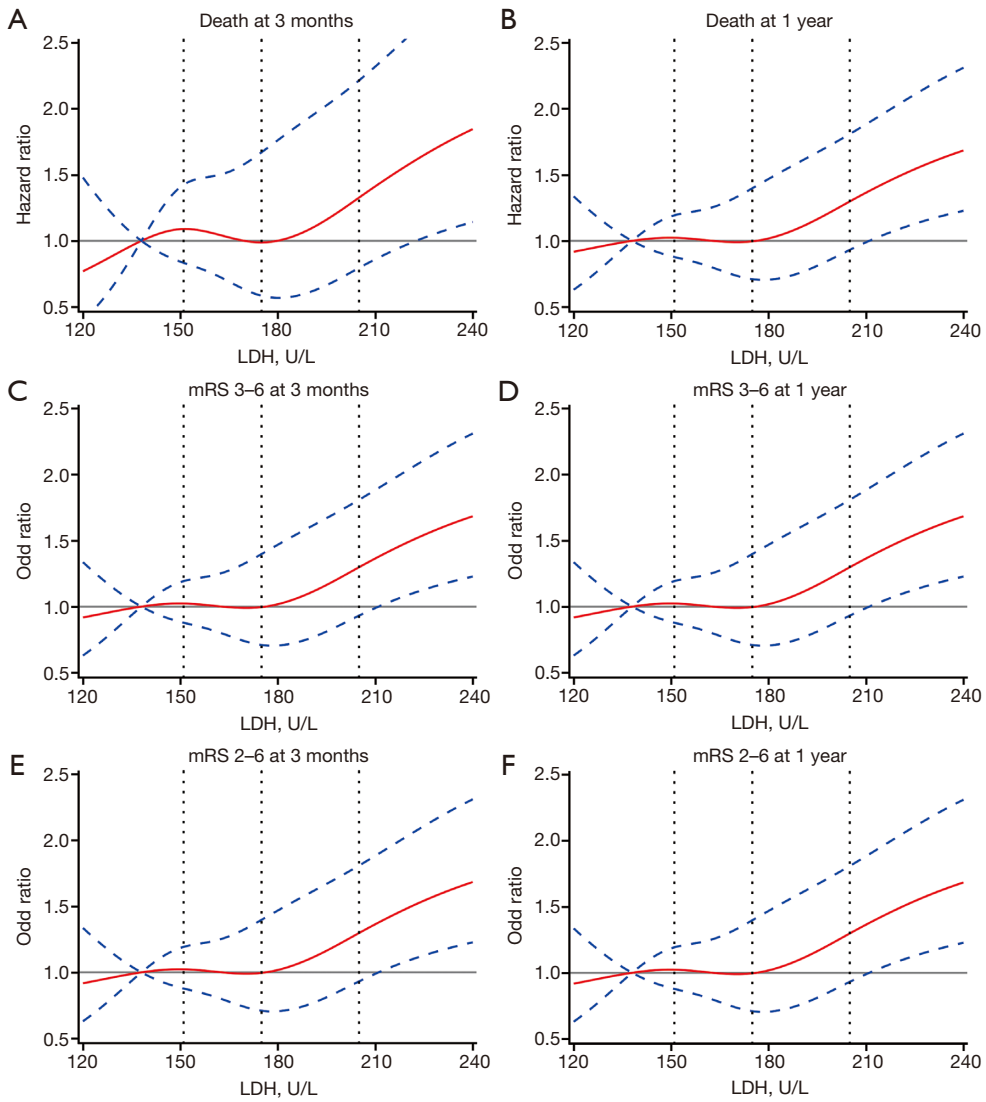

Figure 2 Association of LDH levels with risk of all-cause death and poor functional outcome at 3 months and 1 year. (A,B) All-cause death at 3 months and 1 year. (C-F) mRS score 3–6 and mRS score 2–6 at 3 months and 1 year. Adjusted for age, gender, BMI, history of hypertension, diabetes, dyslipidemia, atrial fibrillation/flutter, stroke type, current smoke, TOAST, NHISS, antihypertensive agents, cholesterol-lowering agents, hypoglycemic agents, antiplatelet agents, anticoagulant agents, FBG, TC, LDL-C, HDL-C, TG, eGFR and hs-CRP. LDH, lactate dehydrogenase; mRS, modified Rankin Scale; BMI, body mass index; NHISS, The National Institutes of Health Stroke Scale; FBG, fasting blood glucose; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein.

Examination Survey III) suggested that a higher level of serum LDH was significantly related to mortality from all causes in patients with metabolic syndrome (16). The AMORIS study (Apolipoprotein Mortality RISk) found that higher pre-diagnostic LDH was corresponded to lower overall and cancer-specific survival following cancer diagnosis (17). In addition, similar interrelations between elevated LDH and mortality were also observed in patients with post infarction myocardial rupture, peritonitis-induced sepsis, and acute respiratory distress syndrome (18-20).

The findings of above studies tend to demonstrate that serum LDH has significant prognostic value in various diseases in clinical practice. Nevertheless, there are limited evidence regarding on the association between LDH and

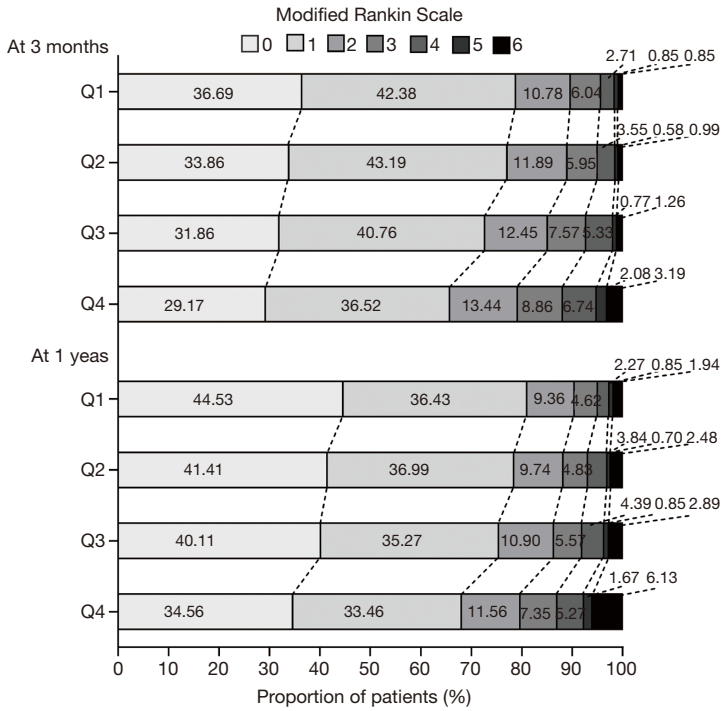

Figure 3 mRS Scores Stratified by quartiles of LDH. The figure is shown the distribution of scores on the mRS. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability and 6 death. mRS, modified Rankin Scale; LDH, lactate dehydrogenase.

the prognosis of stroke, and mainly related to hemorrhagic stroke. Chu et.al demonstrated that high LDH levels (≥220 U/L) independently predicted hematoma expansion and poor outcomes (defined as mRS score >3) in patients with intracerebral hemorrhage (10). According to Muiz's *et al.* study, a high LDH levels was also a predictor of mortality in intracerebral hemorrhagic patients (21). Furthermore, Anan *et al.* found that LDH concentrations in carotid cisternal cerebrospinal fluid may vividly reflect the early brain injury and may thus represent predictive biomarkers of delayed cerebral ischemia of subarachnoid hemorrhage (9).

As for IS, previous study demonstrated that LDH levels were increased in patients with central nervous system disorders such as cerebral infarction and hypoxic-ischemic encephalopathy (7). However, the link between LDH and prognostic outcomes of stroke has not been comprehensively evaluated up to now. To fill this knowledge gap, we performed the current study, the results of our study showed that higher LDH was independently associated with elevated all-cause death risk and poor functional outcomes risk in patients with AIS or TIA, indicating the prognostic role of LDH could also be extended to IS. LDH may be a good predictor due to the applicability and simplification for routine use based on common clinical practice, and patients with higher LDH levels warrant particular vigilance and should be follow-up closely for the prevention of adverse outcomes of stroke.

Although the precise mechanism underlying the association between LDH and adverse outcomes of stroke, several plausible explanations have been proposed. First, LDH has been considered to be a promising biomarker for inflammatory burdens, and its inhibitors can be used for anti-inflammation (22,23). Inflammation is linked to the dysfunction of endothelial cells and is directly related to the development atherosclerosis and instability of atheroma, which may contribute to the pathological progression of death and poor functional outcomes (24-26). Second, LDH is an enzyme presented in essentially all organ systems, and its serum level increased in the condition of many disorders (2-7). This could mean that the LDH level, a proxy for the extent of the harm to multiple organs systems, can serve as a useful predictor of the adverse outcomes of stroke. The clear mechanisms need further investigations.

The strengths of our study include the multicenter prospective registry design and a large sample size. However, there were still several limitations to our study. First, this study only monitored baseline LDH and did not examine the effect of LDH changes, which may provide more valuable information towards the mechanism. Second, we did not collected data on the isoforms of LDH, we thus failed to draw conclusions on whether the diversity of LDH was associated with increased the risk of adverse outcomes. Third, the etiology of mortality in our study was classified into three categories: cardiovascular death, non-vascular death and other undetermined causes, other detailed information was not available in the present database, thus we could not assess the association between LDH and detailed cause-specific death, which needed further investigations. Finally, because all the patients were from China, the findings should be extrapolated cautiously to other populations. Further prospective studies conducted among different populations are needed to replicate our findings.

Conclusions

In conclusion, the results of this study suggested that higher LDH levels substantially increased all-cause death risk and the occurrence of poor functional outcomes in patients with AIS or TIA at 3-month and 1-year follow-up. The finding highlighted the role of LDH in the prognosis of stroke due to its feasibility and convenience for clinical practice.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2195). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Beijing Tiantan Hospital (No.: KY2015-001- 01) and all study centers gave ethical approval of the study protocol. Written consents were obtained from all participants or their legal representatives.

References

1. Yum SK, Moon CJ, Youn YA, et al. Changes in lactate dehydrogenase are associated with central gray matter lesions in newborns with hypoxic-ischemic encephalopathy. J Matern Fetal Neonatal Med 2017;30:1177-81.
2. Chu WW, Dieter RS, Stone CK. A review of clinically relevant cardiac biochemical markers. WMJ 2002;101:40-8.
3. Lee TH, Goldman L. Serum enzyme assays in the diagnosis of acute myocardial infarction. Recommendations based on a quantitative analysis. Ann Intern Med 1986;105:221-33.
4. Liao YT, Chen CJ, Li WF, et al. Elevated lactate dehydrogenase activity and increased cardiovascular mortality in the arsenic-endemic areas of southwestern Taiwan. Toxicol Appl Pharmacol 2012;262:232-7.

5. Buckner SL, Loenneke JP, Loprinzi PD. Cross-Sectional Association Between Normal-Range Lactate Dehydrogenase, Physical Activity and Cardiovascular Disease Risk Score. Sports Med 2016;46:467-72.
6. Drent M, Cobben NA, Henderson RF, et al. Usefulness of lactate dehydrogenase and its isoenzymes as indicators of lung damage or inflammation. Eur Respir J 1996;9:1736-42.
7. Thoresen M, Liu X, Jary S, et al. Lactate dehydrogenase in hypothermia-treated newborn infants with hypoxic-ischaemic encephalopathy. Acta Paediatr 2012;101:1038-44.
8. Thenappan T, Stulak JM, Agarwal R, et al. Early intervention for lactate dehydrogenase elevation improves clinical outcomes in patients with the HeartMate II left ventricular assist device: Insights from the PREVENT study. J Heart Lung Transplant 2018;37:25-32.
9. Anan M, Nagai Y, Fudaba H, et al. Lactate and Lactate Dehydrogenase in Cistern as Biomarkers of Early Brain Injury and Delayed Cerebral Ischemia of Subarachnoid Hemorrhage. J Stroke Cerebrovasc Dis 2020;29:104765.
10. Chu H, Huang C, Dong J, et al. Lactate Dehydrogenase Predicts Early Hematoma Expansion and Poor Outcomes in Intracerebral Hemorrhage Patients. Transl Stroke Res 2019;10:620-9.
11. Wang Y, Liu M, Pu C. 2014 Chinese guidelines for secondary prevention of ischemic stroke and transient ischemic attack. Int J Stroke 2017;12:302-20.
12. Wang Y, Jing J, Meng X, et al. The Third China National Stroke Registry (CNSR-III) for patients with acute ischaemic stroke or transient ischaemic attack: design, rationale and baseline patient characteristics. Stroke Vasc Neurol 2019;4:158-64.
13. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.
14. Thompson MP, Luo Z, Gardiner J, et al. Impact of Missing Stroke Severity Data on the Accuracy of Hospital Ischemic Stroke Mortality Profiling. Circ Cardiovasc Qual Outcomes 2018;11:e004951.
15. Pottel H, Delanaye P, Schaeffner E, et al. Estimating glomerular filtration rate for the full age spectrum from serum creatinine and cystatin C. Nephrol Dial Transplant 2017;32:497-507.
16. Wu LW, Kao TW, Lin CM, et al. Examining the association between serum lactic dehydrogenase and all-cause mortality in patients with metabolic syndrome: a retrospective observational study. BMJ Open 2016;6:e011186.
17. Wulaningsih W, Holmberg L, Garmo H, et al. Serum lactate dehydrogenase and survival following cancer diagnosis. Br J Cancer 2015;113:1389-96.
18. Yuan SM, Jing H, Lavee J. The implications of serum enzymes and coagulation activities in postinfarction myocardial rupture. Rev Bras Cir Cardiovasc 2011;26:7-14.
19. Liao MH, Chen SJ, Tsao CM, et al. Possible biomarkers of early mortality in peritonitis-induced sepsis rats. J Surg Res 2013;183:362-70.
20. van der Zee P, Rietdijk W, Somhorst P, et al. A systematic review of biomarkers multivariately associated with acute respiratory distress syndrome development and mortality. Crit Care 2020;24:243.
21. Muiz AJ, Abdullah J, Naing NN, et al. Spontaneous intracerebral hemorrhage in northeast Malaysian patients: a four-year study. Neuroepidemiology 2003;22:184-95.
22. Miyoshi N, Tanigawa T, Nishioka S, et al. Association of salivary lactate dehydrogenase level with systemic inflammation in a Japanese population. J Periodontal Res 2018;53:487-94.
23. Manerba M, Di Ianni L, Govoni M, et al. Lactate dehydrogenase inhibitors can reverse inflammation induced changes in colon cancer cells. Eur J Pharm Sci 2017;96:37-44.
24. Wang G, Jing J, Li J, et al. Association of elevated hs-CRP and multiple infarctions with outcomes of minor stroke or TIA: subgroup analysis of CHANCE randomised clinical trial. Stroke Vasc Neurol 2021;6:80-6.
25. Dhanesha N, Chorawala MR, Jain M, et al. Fn-EDA (Fibronectin Containing Extra Domain A) in the Plasma, but Not Endothelial Cells, Exacerbates Stroke Outcome by Promoting Thrombo-Inflammation. Stroke 2019;50:1201-9.
26. Mengel A, Ulm L, Hotter B, et al. Biomarkers of immune capacity, infection and inflammation are associated with poor outcome and mortality after stroke - the PREDICT study. BMC Neurol 2019;19:148.

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Supplementary

Table S1 Baseline characteristics of the excluded and included patients

Characteristics	Excluded (n=5,370)	Included (n=9,796)	P value	ASD/HL estimator, %
Age, y	62.00 (54.00–70.00)	63.00 (55.00–70.00)	<0.0001	7.04
Men, n (%)	3,668 (68.31)	6,696 (68.35)	0.9505	0.11
BMI, kg/m^2	24.47 (22.66–26.37)	24.49 (22.59–26.57)	0.3623	0.62
Medical history, n (%)				
Hypertension	3,404 (63.39)	6,090 (62.17)	0.1372	2.53
Diabetes mellitus	1,217 (22.66)	2,293 (23.41)	0.2985	1.77
Dyslipidemia	431 (8.03)	760 (7.76)	0.5577	0.10
Stroke or TIA	1,283 (23.89)	2,072 (21.15)	0.0001	5.23
Atrial fibrillation/flutter	316 (5.88)	703 (7.18)	0.0024	5.23
Peripheral vascular disease	51 (0.95)	67 (0.68)	0.0748	2.95
Heart failure	31 (4.32)	63 (4.47)	0.8704	0.75
Stroke type/subtype, n (%)				
IS	5,018 (93.45)	9,128 (93.18)	0.5345	1.06
TIA	352 (6.55)	668 (6.82)		
TOAST, n (%)				
Large-artery atherosclerosis	1,401 (26.09)	2,455 (25.06)	0.0019	6.51
Cardioembolism	307 (5.72)	610 (6.23)		
Small-vessel occlusion	1,189 (22.14)	1,976 (20.17)		
Other determined etiology	51 (0.95)	131 (1.34)		
Undetermined etiology	2,422 (45.10)	4,624 (47.20)		
Current smoker, n (%)	1,709 (31.82)	3,043 (31.06)	0.0003	7.14
Medication in hospital, n (%)				
Cholesterol-lowering agents	5,178 (97.15)	9,328 (95.94)	0.0001	6.51
Antihypertensive agents	2,542 (47.69)	4,458 (45.85)	0.0302	3.69
Hypoglycemic agents	1,310 (24.58)	2,482 (25.53)	0.1995	2.19
Antiplatelet agents	5,170 (97.00)	9,443 (97.12)	0.6706	0.72
Anticoagulant agents	441 (8.27)	1,105 (11.36)	<0.0001	9.40
NIHSS score on admission	3 [1–6]	3 [1–6]	0.0657	2.05
Time from onset to admission, h	13.00 (3.00–40.00)	14.00 (3.00–46.00)	0.0616	4.37
Lipid level				
TC, mmol/L	3.89 (3.28–4.63)	4.02 (3.33–4.77)	<0.0001	9.48
LDL-C, mmol/L	2.24 (1.69–2.89)	2.35 (1.74–3.02)	<0.0001	9.44
HDL-C, mmol/L	0.93 (0.77–1.10)	0.94 (0.78–1.13)	0.0064	7.22
TG, mmol/L	1.36 (1.04–1.86)	1.37 (1.03–1.88)	0.7680	0.79
FBG, mmol/L	5.43 (4.84–6.75)	5.59 (4.92–6.95)	<0.0001	5.91
eGFR, mL/min/1.73 m^2	93.49 (82.24–102.45)	92.90 (81.31–101.66)	0.0108	3.64
hs-CRP, mg/L	1.78 (0.83–4.84)	1.78 (0.82–4.66)	0.5579	1.55
ALT, U/L	18.00 (13.00–25.80)	18.00 (13.00–26.00)	0.1239	1.41
AST, U/L	19.00 (16.00–24.00)	19.00 (16.00–24.00)	0.0644	4.10

Continuous variables were presented as medians along with IQR; categorical variables were presented as percentages. Given the extensive data set, comparison using P<0.05 indicated statistical significance but might not have any clinical significance. Therefore, baseline characteristics were compared using absolute standardized differences (for percentages) or HL estimator (for median), with indicator ≥10% considered to be clinically significant. BMI, body mass index; TIA, transient ischemic attack; IS, ischemic stroke; NIHSS, The National Institutes of Health Stroke Scale; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ASD, absolute standardized difference; HL, Hodges-Lehmann; IQR, interquartile range.

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Table S2 Sensitivity analysis for the association between LDH and outcomes by excluding patients with cancer of infection

Outcomes	Quartiles of LDH				P for trend
	Q1	Q2	Q3	Q4	
Within 3 months					
Death	Reference	1.19 (0.60–2.33)	1.52 (0.79–2.95)	2.40 (1.30–4.46)	0.0013
mRS 3–6	Reference	0.92 (0.74–1.14)	1.33 (1.08–1.63)	1.57 (1.27–1.94)	<0.0001
mRS 2–6	Reference	1.11 (0.94–1.30)	1.35 (1.15–1.59)	1.61 (1.36–1.90)	<0.0001
Within 1 year					
Death	Reference	1.12 (0.74–1.70)	1.43 (0.95–2.16)	2.26 (1.53–3.33)	<0.0001
mRS 3–6	Reference	1.12 (0.90–1.38)	1.28 (1.04–1.59)	1.61 (1.30–2.00)	<0.0001
mRS 2–6	Reference	1.11 (0.94–1.30)	1.27 (1.08–1.50)	1.51 (1.27–1.79)	<0.0001

Adjusted for age, gender, BMI, history of hypertension, diabetes, dyslipidemia, atrial fibrillation/flutter, stroke type, current smoke, TOAST, NHISS, antihypertensive agents, cholesterol-lowering agents, hypoglycemic agents, antiplatelet agents, anticoagulant agents, FBG, TC, LDL-C, HDL-C, TG, eGFR and hs-CRP. LDH, lactate dehydrogenase; mRS, modified Rankin Scale; BMI, body mass index; NHISS, The National Institutes of Health Stroke Scale; FBG, fasting blood glucose; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein.

Table S3 Subgroup analysis for the association of high LDH (Q4) with all-cause death and poor functional outcomes

Subgroups	All cause death		mRS 3–6		mRS 2–6	
	At 3 months	At 1 year	At 3 months	At 1 year	At 3 months	At 1 year
Age						
<60	2.57 (0.74–9.03)	2.56 (1.64–3.98)	2.06 (1.55–2.74)	2.35 (1.72–3.22)	1.74 (1.40–2.16)	1.85 (1.48–2.33)
≥60	2.84 (1.49–5.42)	2.72 (1.34–5.52)	1.69 (1.30–2.19)	1.64 (1.26–2.12)	1.74 (1.39–2.17)	1.52 (1.22–1.91)
$P_{interaction}$	0.3850		0.8264	0.3250	0.8682	0.1726
Gender						
Female	3.28 (1.63–6.57)	2.63 (1.69–4.10)	1.95 (1.54–2.48)	2.04 (1.60–2.60)	1.80 (1.50–2.17)	1.97 (1.62–2.38)
Male	3.54 (1.14–10.95)	3.09 (1.43–6.68)	1.57 (1.12–2.22)	1.56 (1.09–2.24)	1.67 (1.25–2.22)	1.22 (0.91–1.64)
$P_{interaction}$	0.7456	0.5744	0.1293	0.2999	0.8904	0.1586
Stroke subtypes						
IS	2.67 (1.56–4.68)	2.51 (1.73–3.68)	1.8291.50–2.20)	1.91 (1.56–2.33)	1.77 (1.52–2.06)	1.72 (1.46–2.02)
TIA	–	–	1.40 (1.16–1.70)	0.51 (0.05–5.12)	1.34 (0.34–5.21)	0.73 (0.17–3.22)
$P_{interaction}$	–	0.9401	0.7442	0.3489	0.5584	0.3030
Time from onset to admission						
<24 h	3.39 (1.64–7.03)	2.98 (1.79–4.99)	1.84 (1.44–2.36)	1.81 (1.41–2.34)	1.77 (1.44–2.16)	1.70 (1.39–2.09)
≥24 h	3.42 (1.28–9.14)	2.46 (1.38–4.36)	1.49 (1.16–1.90)	1.91 (1.37–2.64)	1.64 (1.28–2.09)	1.68 (1.30–2.17)
$P_{interaction}$	0.7408	0.9367	0.7439	0.7924	0.4005	0.9419

Adjusted for BMI, history of hypertension, diabetes, dyslipidemia, atrial fibrillation/flutter, stroke type, current smoke, TOAST, NHISS, FBG, TC, LDL-C, HDL-C, TG, eGFR on admission, antihypertensive agents, cholesterol-lowering agents, hypoglycemic agents, antiplatelet agents, anticoagulant agents, and hs-CRP on admission other than variables for stratification. LDH, lactate dehydrogenase; mRS, modified Rankin Scale; IS, ischemic stroke; TIA, transient ischemic attack; BMI, body mass index; NHISS, The National Institutes of Health Stroke Scale; FBG, fasting blood glucose; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein.

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