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ORIGINAL RESEARCH

Relationship Between Cumulative Exposure of Lactate Dehydrogenase Concentrations and Major Adverse Cardiac and Cerebrovascular Events in Hypertensive Patients: A Retrospective Cohort Study from Northwest China

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Background: As of 2023, cardiovascular disease (CVD) affects 626 million people globally, imposing a heavy burden on both society and families. Despite advances in antihypertensive therapy, residual risk persists, underscoring the need for potential biomarkers to optimize risk stratification. Lactate dehydrogenase (LDH), traditionally a marker of tissue injury, may reflect metabolic or inflammatory stress associated with vascular damage. This study investigates the association between annual cumulative LDH exposure and incident major adverse cardiac and cerebrovascular events (MACCE) in hypertensive patients, providing insights for prevention strategies.

Methods: In this retrospective cohort study, we included hypertensive patients treated at a large tertiary hospital in Urumqi, China, from January 2011 to April 2025. Kaplan-Meier curves visualized survival differences, and Cox proportional hazards models assessed the association between annual LDH_AUC and MACCE risk. Stratified and sensitivity analyses evaluated robustness, while C-statistics compared the predictive performance of annual LDH_AUC versus single-timepoint LDH.

Results: During a median follow-up period of 47 months, a total of 879 new MACCE were recorded. The research results showed that whether the annual LDH_AUC was used as a continuous variable or a categorical variable, an increase in annual LDH_AUC would increase the risk of MACCE (HR=1.012, 95% CI, 1.007–1.017; HR=1.431, 95% CI, 1.185–1.727). Moreover, the predictive value of annual LDH_AUC for MACCE is superior to that of a single LDH measurement.

Conclusion: In hypertensive patients, elevated annual LDH_AUC levels is associated with an elevated risk MACCE.

Keywords: hypertension, lactate dehydrogenase, major adverse cardiac and cerebrovascular events

Introduction

Cardiovascular disease (CVD) remains the leading global cause of disability-adjusted life years (DALYs) lost and mortality, according to the Global Burden of Disease (GBD) Study.[1] Among them, ischemic heart disease, hemorrhagic and ischemic stroke are the most common types of CVD that lead to DALYs.[1,2] CVD often progresses asymptomatically

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during its early stages, frequently delaying diagnosis and timely intervention, thereby posing a significant threat to human health and representing a major public health challenge.[3]

Previous studies have demonstrated that traditional modifiable risk factors (such as hypertension, hyperhomocysteinemia, elevated LDL-C, and smoking) and emerging environmental factors (including air pollution and temperature fluctuations) can increase the risk of CVD.[4–6] In recent years, studies have found that elevated lactate dehydrogenase (LDH) levels can participate in the development and progression of CVD.[7] LDH is a cytoplasmic enzyme that is widely distributed throughout bodily tissues. When cellular damage occurs, LDH is released into the extracellular space, thus serving as an indicator of cardiac injury and acute myocardial infarction.[8–10] Recent studies indicate that LDH contributes to chronic cardiovascular damage and CVD development through both inflammatory and non-inflammatory mechanisms.[11–14] Elevated levels of LDH are often observed in pathological conditions characterized by tissue hypoxia,[15] metabolic disorders,[16] cellular injury,[17,18] inflammation,[19] and oxidative stress,[20,21] all of which are critical drivers of CVD occurrence and progression. Mechanistically, excessive LDH induces oxidative stress.[19,20] Additionally, LDH influences the generation of various inflammatory mediators, including TNF-α, IL-6, and nitric oxide (NO), through the overproduction of lactate.[18,19,22] Furthermore, LDH contributes to the occurrence and progression of CVD, including atherosclerosis, myocardial infarction, cardiomyopathy, pulmonary arterial hypertension, and heart failure, by modulating lactate levels to alter protein lactylation.[23,24]

Despite these mechanistic insights, current epidemiological evidence is limited. Although previous studies have investigated the association between LDH and CVD, their findings may have limited generalizability due to the small sample size and the focus on a specific population.[11,13,15] Moreover, most prior studies have focused on single baseline LDH measurements, failing to capture the dynamic nature of metabolic risk over time. In contrast, cumulative exposure metrics—integrating both magnitude and duration of risk factor elevation—may better capture the chronic, progressive nature of cardiovascular damage. Therefore, leveraging real-world longitudinal data, the primary objective of this retrospective cohort study was to investigate whether cumulative exposure to elevated LDH is independently associated with an increased risk of MACCE among patients with hypertension.

Material and Methods

Study Design and Participants

We conducted a retrospective cohort study to investigate the association between cumulative exposure to LDH and MACCE. The data utilized in this study is sourced from UHDATA, with further details pertaining to this data set documented in the preceding article.[25] The population under consideration comprised hypertensive patients who received treatment in our department during the period from January 2011 to April 2025 and who underwent at least twice LDH detection. The present study further excluded: (1) patients with a time interval between two LDH tests of less than 1 year; (2) patients with CVD at baseline; (3) patients with hepatitis and cirrhosis or decompensated renal failure; (4) patients with connective tissue diseases or haematological diseases (such as leukaemia and lymphoma); (5) patients with acute and chronic infection or inflammatory state; (6) patients who were pregnant; (7) patients with follow-up of less than 3 months. Finally, 13089 patients were included in the study.

Data Collection and Definition

The initial data set was retrieved from the medical electronic system, encompassing the following information, demographic: sex, age, smoking, drinking, waist circumference, body mass index (BMI), systolic and diastolic blood pressure (SBP, DBP); biochemical indicators: blood urea nitrogen (BUN), creatinine (Cr), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), total cholesterol (TC), uric acid (UA), serum potassium, serum sodium, fasting plasma glucose (FPG), aspartate transaminase (AST), alanine transaminase (ALT), white blood cell (WBC) and LDH; medical history: hypertension and course, dyslipidemia, diabetes mellitus (DM); medication history: antihypertensive drugs, hypoglycemic drugs, hypolipidemic drugs and antiplatelet drugs. For a more detailed exposition of the specific measurement details, please refer to the Supplementary Documentation.

The diagnosis of hypertension, diabetes and dyslipidaemia is made in accordance with the relevant guidelines, and further details can be found in the Supplementary Material.

This study followed the RECORD (Reporting of studies Conducted using Observational Routinely-collected Data) guidelines for reporting observational studies, and the completed RECORD checklist is provided as Supplementary Material.

Cumulative Exposure Assessment to LDH

The cumulative LDH exposure magnitude was quantified via area under the (AUC) reflecting the relationship between age and LDH, termed total cumulative LDH burden (LDH_AUC). To mitigate inter-individual variability in sampling intervals, we implemented time-standardized normalization (annualized by dividing LDH_AUC by follow-up duration in years), ensuring robustness against temporal measurement heterogeneity while preserving biological interpretability.

Follow Up and Outcome

The present study established the deadline for the follow-up period as April 2025, or the occurrence of the first major adverse cardiovascular and cerebrovascular events (MACCE) during the follow-up period, whichever occurred first. The MACCE event is defined as the primary endpoint, which specifically includes the following: all-cause death; non-fatal myocardial infarction; cardiac revascularisation (including coronary artery bypass grafting and percutaneous coronary intervention); non-fatal haemorrhagic or ischaemic stroke; and transient ischaemic attack (TIA). In addition, we divided MACCE into cardiovascular disease and cerebrovascular disease for further analysis.

Statistical Analysis

We used the missforest program in R language for nonparametric interpolation to solve the problem of missing data. Continuous variables underwent normality testing and were described as mean ± standard deviation or median (interquartile range). Group comparisons were performed using independent samples *t*-tests/analysis of variance (ANOVA) or Mann–Whitney *U*-tests. Categorical variables were summarized as frequencies and proportions, with intergroup differences assessed via chi-squared tests. Survival analysis calculated the cumulative incidence of the primary endpoint using the Kaplan-Meier method, with group differences evaluated by Log rank tests. In this study, LASSO regression was employed to conduct feature screening on potential predictors (Supplementary Figure 1). Based on the optimal penalty parameter (λ value), the variables were divided into a high - correlation group (a few key factors) and a medium - correlation group (most potential factors). A simplified model (Model 1) and a comprehensive model (Model 2) were constructed respectively. The robustness of the models was verified through multivariate Cox regression analysis. Statistical analyses were conducted using IBM SPSS Statistics version 31.0 and R version 4.4.2.

Results

Baseline Characteristics

Based on the inclusion and exclusion criteria, a total of 13089 patients met the criteria and were included in the analysis (Figure 1). The mean age of the subjects is 52.34 years, with 7234 subjects are men, accounting for 55.27%. Among them, 4327 individuals were identified as smokers, accounting for 33.15%, 3890 individuals were classified as drinkers, accounting for 29.85% (Table 1). Baseline population is grouped according to quartiles of annual LDH_AUC. Participants with higher annual LDH_AUC tended to have higher BMI, SBP, DBP, waist, Cr, LDL-C, TG, TC, UA, Serum potassium, Serum sodium, AST, ALT, WBC and duration of hypertension. Meanwhile, the use of antihypertensive drugs, lipid-lowering drugs, and antiplatelet drugs also has a higher proportion in the higher annual LDH_AUC group (Table 1). We also provided baseline features grouped according to the quartiles of LDH, as detailed in Supplementary Table 1.

Relationship between Annual LDH Cumulative Exposure and MACCE and its Subtypes

During a median follow-up period of 47 months, a total of 879 new MACCE were recorded in the study. Preliminary statistical analysis indicates an incidence rate of 17.1 cases per 1,000 person-years for MACCE. From Q1 to Q4 groups,

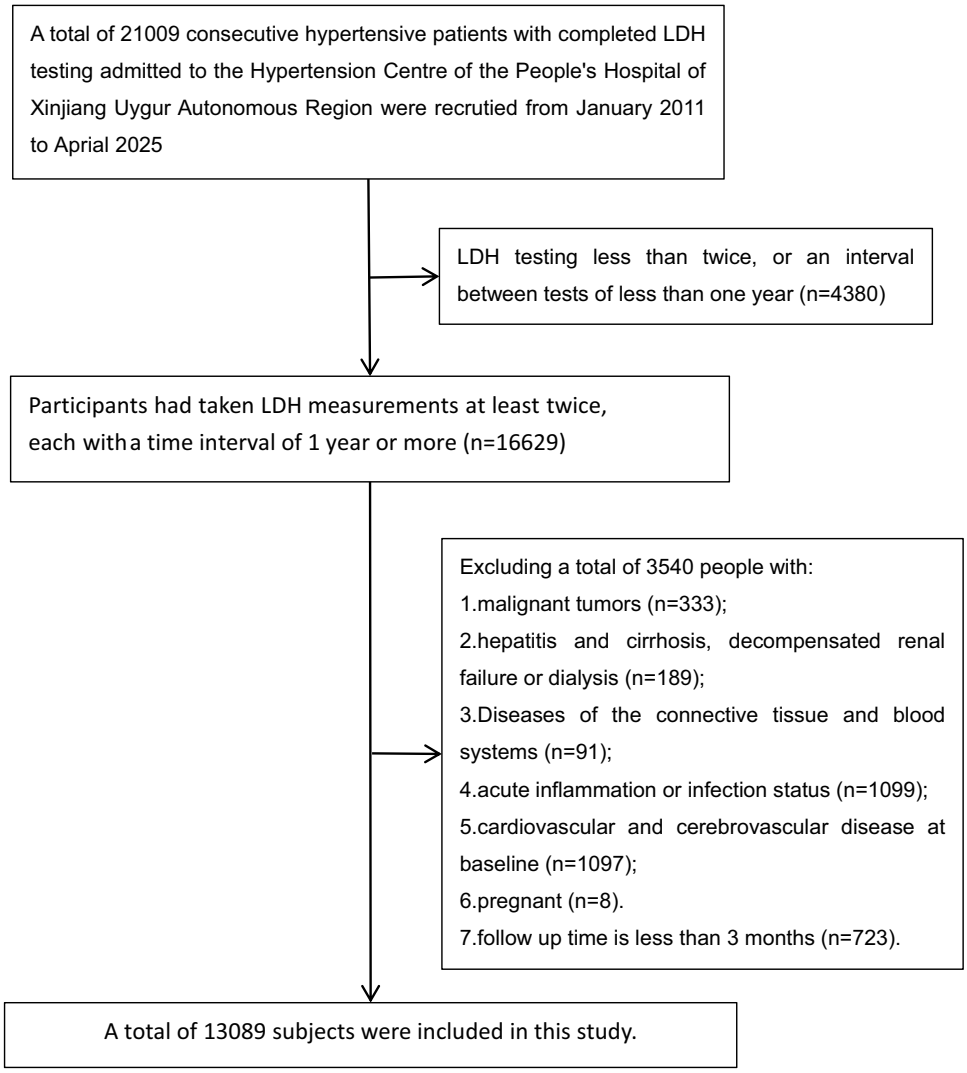

Figure 1 Flow chart of participants selection.

the incidence of MACCE increased from 6.3% to 8.7%. The incidence of MACCE, which includes cerebrovascular events, cardiovascular events, and all-cause mortality, has exhibited a consistent trend. Indicating that an increase in annual LDH_AUC was associated with elevated incidence rates of MACCE and its subtypes (Table 2). Kaplan-Meier

Table 1 Baseline Characteristics of the Study Population Based on Annual LDH_AUC Exposure

	Total	Q1	Q2	Q3	Q4	P
N	13089	3246	3281	3283	3279	
Age (years)	52.34 ± 12.12	50.82 ± 11.42	52.17 ± 11.90	53.01 ± 12.06	53.35 ± 12.90	<0.001
Men (n, %)	7234 (55.27)	2037 (62.75)	1846 (56.26)	1721 (52.42)	1630 (49.71)	<0.001
Women (n, %)	5855 (44.73)	1209 (37.25)	1435 (43.74)	1562 (47.58)	1649 (50.29)	<0.001
Smoke (n, %)	4327 (33.15)	1283 (39.67)	1053 (32.16)	1020 (31.15)	971 (29.70)	<0.001
Alcohol (n, %)	3890 (29.85)	1147 (35.53)	999 (30.55)	902 (27.58)	842 (25.79)	<0.001
Abdominal obesity (n, %)	11,104 (85.17)	2658 (82.29)	2766 (84.59)	2803 (85.69)	2877 (88.06)	<0.001
BMI (kg/m2)	27.23 ± 3.92	26.61 ± 3.50	27.03 ± 3.78	27.34 ± 3.89	27.93 ± 4.34	<0.001

(*Continued*)

Table 1 (Continued).

	Total	Q1	Q2	Q3	Q4	P
DBP (mmHg)	88.49 ± 14.53	87.87 ± 13.50	88.25 ± 14.32	88.24 ± 14.35	89.59 ± 15.80	<0.001
SBP (mmHg)	145.41 ± 20.13	142.42 ± 18.89	144.80 ± 19.95	145.36 ± 19.86	149.05 ± 21.19	<0.001
Waist (cm)	98.05 ± 11.61	96.84 ± 11.06	97.48 ± 11.37	98.20 ± 11.64	99.64 ± 12.14	<0.001
BUN (mmol/L)	5.27 ± 1.75	5.16 ± 1.48	5.18 ± 1.56	5.25 ± 1.65	5.51 ± 2.19	<0.001
Cr (umol/L)	69.78 ± 28.43	69.24 ± 20.75	68.82 ± 30.94	68.53 ± 21.48	72.56 ± 37.02	<0.001
HDL-C (mmol/L)	1.07 ± 0.28	1.03 ± 0.26	1.06 ± 0.27	1.08 ± 0.28	1.10 ± 0.29	<0.001
LDL-C (mmol/L)	2.72 ± 0.84	2.62 ± 0.79	2.71 ± 0.83	2.75 ± 0.84	2.82 ± 0.90	<0.001
TG (mmol/L)	1.89 ± 1.50	1.97 ± 1.54	1.92 ± 1.47	1.82 ± 1.38	1.88 ± 1.60	<0.001
TC (mmol/L)	4.51 ± 1.00	4.40 ± 0.95	4.50 ± 0.98	4.52 ± 0.96	4.63 ± 1.07	<0.001
UA (umol/L)	342.12 ± 94.00	344.49 ± 93.37	339.39 ± 92.42	338.91 ± 94.16	345.71 ± 95.86	0.004
Serum potassium (mmol/L)	3.85 ± 0.37	3.86 ± 0.35	3.85 ± 0.36	3.84 ± 0.38	3.86 ± 0.41	0.031
Serum sodium (mmol/L)	141.07 ± 2.53	140.97 ± 2.53	141.04 ± 2.50	141.12 ± 2.52	141.14 ± 2.57	0.026
FPG (mmol/L)	5.16 ± 1.70	5.20 ± 1.74	5.16 ± 1.75	5.09 ± 1.57	5.17 ± 1.73	0.068
AST (U/l)	20.94 ± 13.03	18.57 ± 6.77	20.23 ± 8.48	21.05 ± 9.72	23.88 ± 21.26	<0.001
ALT (U/l)	26.52 ± 22.59	23.79 ± 16.09	25.72 ± 18.76	26.69 ± 21.86	29.87 ± 30.52	<0.001
WBC ($\times 10^9$/L)	6.34 ± 1.70	6.16 ± 1.53	6.25 ± 1.61	6.36 ± 1.69	6.60 ± 1.90	<0.001
LDH (U/L)	192.27 ± 43.71	157.90 ± 22.72	181.23 ± 27.00	197.86 ± 27.44	231.74 ± 52.48	<0.001
Annual LDH_AUC (U/L×years)	198.03 ± 50.19	158.07 ± 11.95	183.12 ± 5.44	202.54 ± 6.29	247.98 ± 74.34	<0.001
Duration of hypertension (years)	6.82+7.73	6.17+6.96	6.67+7.38	7.04+8.07	7.41+8.36	<0.001
MACCE (n, %)	879 (6.72)	206 (6.35)	187 (5.70)	202 (6.15)	284 (8.66)	<0.001
Dyslipidemia (n, %)	7497 (57.28)	1911 (58.87)	1893 (57.70)	1849 (56.32)	1844 (56.24)	0.098
DM (n, %)	2401 (18.34)	659 (20.30)	589 (17.95)	564 (17.18)	589 (17.96)	0.008
ACEIs/ARBs (n, %)	5637 (43.07)	1353 (41.68)	1420 (43.28)	1407 (42.86)	1457 (44.43)	0.161
Beta-blockers (n, %)	2198 (16.79)	455 (14.02)	538 (16.40)	547 (16.66)	658 (20.07)	<0.001
Calcium channel blockers (n, %)	8527 (65.15)	1973 (60.78)	2092 (63.76)	2130 (64.88)	2332 (71.12)	<0.001
Diuretics (n, %)	3358 (25.66)	688 (21.20)	830 (25.30)	846 (25.77)	994 (30.31)	<0.001
Hypoglycemic agents (n, %)	1748 (13.35)	467 (14.39)	423 (12.89)	415 (12.64)	443 (13.51)	0.164
Hypolipidemic drugs (n, %)	5060 (38.66)	1097 (33.80)	1233 (37.58)	1355 (41.27)	1375 (41.93)	<0.001
Antiplatelet medication (n, %)	6662 (50.90)	1588 (48.92)	1669 (50.87)	1724 (52.51)	1681 (51.27)	0.034

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; BUN, blood urea nitrogen; Cr, creatinine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; UA, uric acid; FPG, fasting plasma glucose; AST, aspartate transaminase; ALT, alanine transaminase; WBC, white blood cell; LDH, lactate dehydrogenase; AUC, area under the curve; MACCE, major adverse cardiovascular and cerebrovascular events; DM, diabetes mellitus; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

Table 2 Incidence of Events Among Groups

	Total	Q1	Q2	Q3	Q4
N	13089	3246	3281	3283	3279
Median follow-up (months)	47.0 (23.0,81.0)	49.5 (24.0,83.0)	49.0 (24.0,84.0)	47.0 (23.0,81.0)	43.0 (21.0,16.0)
Person-years followed	51265.3	13,389.8	13,397.4	12,858.4	11,749.8
MACCE	879	206	187	202	284
Per 1000 person-year incidence	17.1	15.4	14	15.7	24.2
Incidence rate (%)	6.7	6.3	5.7	6.2	8.7
Cerebrovascular events	351	82	80	80	109
Per 1000 person-year incidence	6.8	6.1	6.0	6.2	9.3
Incidence rate (%)	2.7	2.5	2.4	2.4	3.3
Cardiac events	491	120	100	114	157
Per 1000 person-year incidence	9.6	9.0	7.5	8.9	13.4
Incidence rate (%)	3.8	3.7	3	3.5	4.1
All-cause death	37	4	7	8	18
Per 1000 person-year incidence	0.7	0.3	0.5	0.6	1.5
Incidence rate (%)	0.3	0.1	0.2	0.2	0.5

Abbreviation: MACCE, major adverse cardiovascular and cerebrovascular events.

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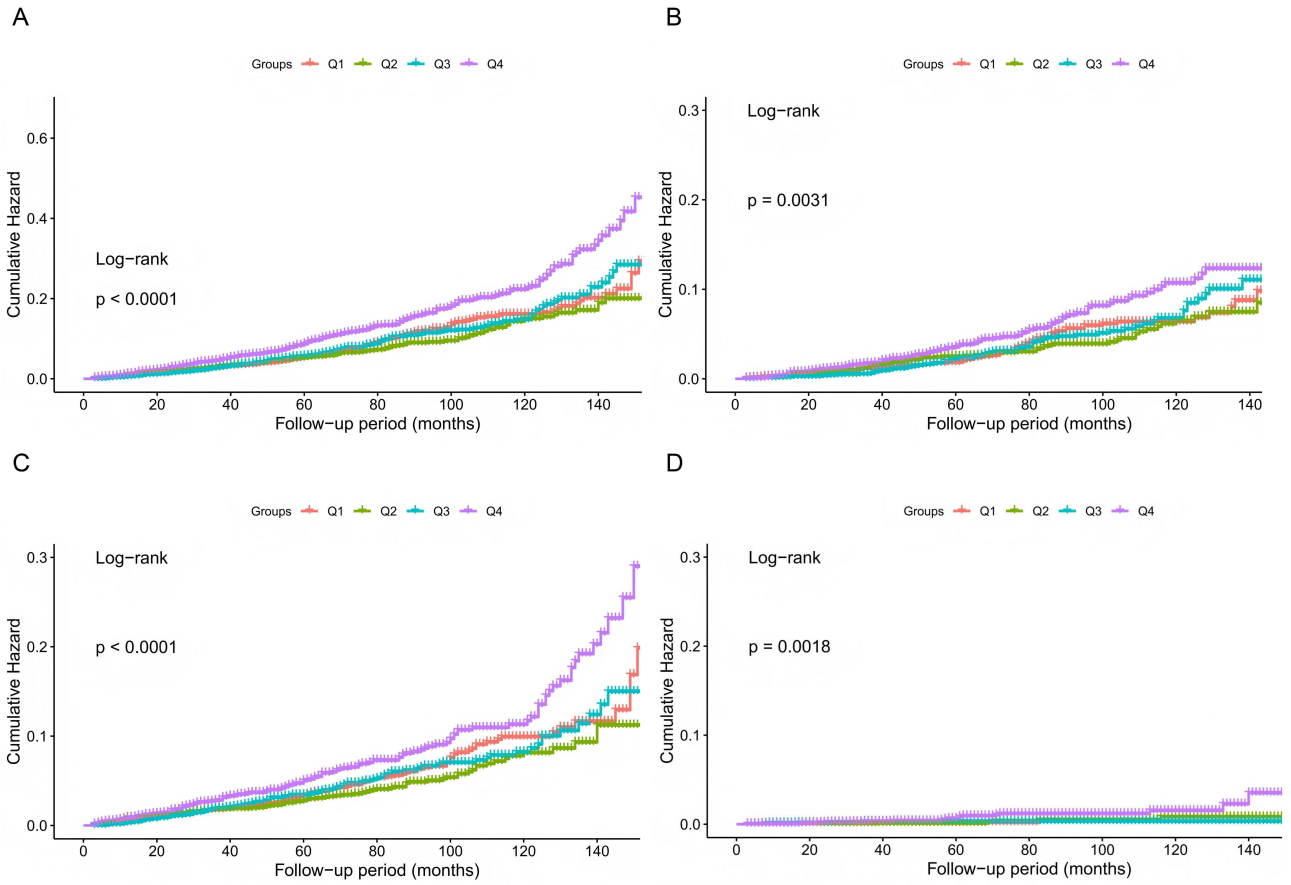

Figure 2 Kaplan-Meier cumulative morbidity risk curves for MACCE and its subtypes based on annual LDH_AUC quartiles. (**A**) MACCE. (**B**) Cerebrovascular events. (**C**) Cardiac events. (**D**) All-causer death.

survival curves were constructed. As shown in Figure 2, patients in the highest LDH_AUC quartile (Q4) exhibited significantly higher cumulative hazard rates of MACCE and its subtypes compared with those in Q1–Q3 groups ($P < 0.05$). Analysis stratified by single-timepoint LDH levels demonstrated consistent trends, with elevated LDH levels predicting higher risks of MACCE and its subtypes ($P < 0.05$), except for all-cause mortality (Supplementary Figure 2). To investigate the predictive efficacy of annual LDH_AUC and single LDH measurement for MACCE event risk, a multivariate Cox regression analysis was conducted. The inclusion of single LDH detection data in the fully calibrated model (Model A) showed a significant correlation between LDH and the risk of MACCE and cerebrovascular events ($P<0.05$), but no statistical association with cardiovascular events and all-cause mortality (Table 3). After adding the

Table 3 Cox Regression of Multifactor-Adjusted Annual LDH_AUC to LDH

MACCE	Model A	P	Model B	P
	HR (95% CI)		HR (95% CI)	
LDH (per 10U/L increase)	1.025 (1.011,1.040)	<0.001	1.011 (1.007,1.036)	0.004
Annual LDH_AUC (per 10-U/L×years increase)	-		1.006 (1.006,1.016)	<0.001
C-index	0.741		0.744	
Cerebrovascular events				
LDH (per 10U/L increase)	1.032 (1.010,1.054)	<0.001	1.031 (1.008,1.053)	0.008
Annual LDH_AUC (per 10-U/L×years increase)	-		1.005 (0.994,1.016)	0.416

(*Continued*)

Table 3 (Continued).

MACCE	Model A	P	Model B	P
	HR (95% CI)		HR (95% CI)	
C-index	0.744		0.745	
Cardiac events				
LDH (per 10U/L increase)	1.019 (1.000,1.040)	0.056	1.014 (0.994,1.034)	0.179
LDH_AUC (per 10-U/L×years increase)	-		1.014 (1.008,1.020)	<0.001
C-index	0.757		0.760	
All-cause death				
LDH (per 10U/L increase)	1.022 (0.944,1.106)	0.589	1.011 (0.931,1.096)	0.801
LDH_AUC (per 10-U/L×years increase)	-		1.023 (1.004,1.042)	0.019
C-index	0.757		0.760	

Notes: Adjusted indicators: age, sex, smoke, Cr, FPG, WBC, DM, duration of hypertension, ACEIs/ARBs, beta-blockers, hypoglycemic drugs, hypolipidemic drugs, antiplatelet medication, alcohol, BMI, DBP, waist, BUN, HDL-C, TC, UA, potassium, sodium, AST. Model A: adjusted indicators plus adjustment for LDH (per 10U/L increase). Model B: adjusted indicators plus adjustment for LDH (per 10U/L increase) and annual LDH_AUC (per 10-U/L×years increase).
Abbreviations: MACCE, major adverse cardiovascular and cerebrovascular events; HR, hazard ratio; CI, Confidence Interval. Other abbreviations, see Table 1.

annual LDH_AUC (Model B), the results remained consistent. The annual LDH_AUC has significant predictive value for MACCE and its subtypes (excluding cerebrovascular events), with hazard ratios of 1.006 (95% CI: 1.006–1.016), 1.014 (95% CI: 1.008–1.020), and 1.023 (95% CI: 1.004–1.042), respectively. The C-index also indicates that LDH_AUC has high predictive value for MACCE and its subtypes. (C-index=0.744, P<0.001). These findings suggest that time-dependent cumulative LDH exposure demonstrates superior predictive efficacy for MACCE and their subtypes compared to single-timepoint measurements. To evaluate the incremental predictive value of annual LDH_AUC exposure, we compared models with and without the annual LDH_AUC metric. As shown in Supplementary Table 2, adding cumulative LDH to the fully adjusted model resulted in an improvement in the C-index across all outcomes.

Table 4 shows the cox regression of annual LDH_AUC and MACCE and their subtypes. Research has shown that elevated levels of LDH are significantly correlated with the risk of MACCE (P<0.001) and cerebrovascular events (P=0.004), while elevated LDH_AUC is significantly positively correlated with the risk of MACCE (HR=1.012, 95% CI: 1.007–1.017), cardiovascular events (HR=1.014, 95% CI: 1.009–1.020), and all-cause mortality (HR=1.023, 95% CI: 1.004–1.042). Further analysis shows that when grouped by the annual LDH_AUC third quartile, the MACCE event and

Table 4 Analysis of the Relationship Between LDH, LDH_AUC and Different End Point Events

	Crude Model	P	Model 1	P	Model 2	P
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
MACCE						
LDH (per 10U/L increase)	1.034 (1.022,1.047)	<0.001	1.031 (1.018,1.044)	<0.001	1.025 (1.011,1.040)	<0.001
Annual LDH_AUC (per 10-U/L×years increase)	1.018 (1.013,1.022)	<0.001	1.013 (1.009,1.018)	<0.001	1.012 (1.007,1.017)	<0.001
Q1	Reference		Reference		Reference	
Q2	0.979 (0.825,1.160)	0.804	1.014 (0.855,1.204)	0.872	0.984 (0.828,1.169)	0.852
Q3	1.417 (1.209,1.661)	<0.001	1.420 (1.206,1.670)	<0.001	1.341 (1.135,1.585)	<0.001
P for trend	0.001		0.001		0.001	
Q1	Reference		Reference		Reference	
Q2	0.890 (0.730,1.085)	0.251	0.927 (0.760, 1.131)	0.454	0.909 (0.745,1.110)	0.350
Q3	1.013 (0.834,1.230)	0.895	1.069 (0.879,1.300)	0.507	1.015 (0.833,1.237)	0.879
Q4	1.523 (1.273,1.822)	<0.001	1.520 (1.265,1.827)	<0.001	1.431 (1.185,1.727)	<0.001
P for trend	<0.001		<0.001		<0.001	

(*Continued*)

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Table 4 (Continued).

	Crude Model	P	Model 1	P	Model 2	P
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
Cerebrovascular events						
LDH (per 10U/L increase)	1.039 (1.020,1.057)	<0.001	1.038 (1.019,1.057)	<0.001	1.032 (1.010,1.054)	0.004
Annual LDH_AUC (per 10-U/L×years increase)	1.016 (1.007,1.026)	<0.001	1.011 (1.002,1.021)	0.016	1.007 (0.998,1.017)	0.148
Q1	Reference		Reference		Reference	
Q2	0.956 (0.732,1.250)	0.744	0.993 (0.758,1.299)	0.957	0.947 (0.723,1.242)	0.695
Q3	1.376 (1.071,1.769)	0.013	1.383 (1.069,1.790)	0.013	1.267 (0.973,1.649)	0.079
P for trend	0.090		0.090		0.090	
Q1	Reference		Reference		Reference	
Q2	0.946 (0.695,1.287)	0.723	0.974 (0.715,7.327)	0.868	0.953 (0.699,1.300)	0.762
Q3	1.009 (0.742,1.373)	0.953	1.072 (0.785,1.463)	0.663	0.991 (0.724,1.357)	0.956
Q4	1.503 (1.129,2.002)	0.005	1.502 (1.120,2.014)	0.007	1.381 (1.022,1.865)	0.035
P for trend	0.044		0.044		0.044	
Cardiac events						
LDH (per 10U/L increase)	1.032 (1.015,1.049)	<0.001	1.026 (1.008,1.043)	0.004	1.019 (1.000,1.040)	0.056
Annual LDH_AUC (per 10-U/L×years increase)	1.019 (1.014,1.026)	<0.001	1.015 (1.009,1.020)	<0.001	1.014 (1.009,1.020)	<0.001
Q1	Reference		Reference		Reference	
Q2	0.957 (0.762,1.202)	0.705	1.020 (0.811,1.283)	0.866	0.985 (0.782,1.241)	0.899
Q3	1.414 91.144,1.748)	0.001	1.455 (1.171,1.283)	<0.001	1.353 (1.082,1.692)	0.008
P for trend	0.017		0.017		0.017	
Q1	Reference		Reference		Reference	
Q2	0.821 (0.629,1.070)	0.144	0.864 (0.662,1.127)	0.280	0.841 (0.644,1.098)	0.203
Q3	0.989 (0.765,1.178)	0.932	1.076 (0.831,1.394)	0.578	1.019 (0.785,1.323)	0.887
Q4	1.464 (1.154,1.856)	0.002	1.495 (1.172,1.909)	0.001	1.380 (1.074,1.773)	0.012
P for trend	0.009		0.009		0.009	
All-cause death						
LDH (per 10U/L increase)	1.036 (0.981,1.095)	0.203	1.018 (0.945,1.096)	0.639	1.022 (0.944,1.106)	0.590
Annual LDH_AUC (per 10-U/L×years increase)	1.026 (1.011,1.042)	<0.001	1.018 (1.001,1.035)	0.034	1.023 (1.004,1.042)	0.016
Q1	Reference		Reference		Reference	
Q2	1.778 (0.699,4.523)	0.227	1.469 (0.576,3.748)	0.421	1.709 (0.663,4.406)	0.267
Q3	2.923 (1.219,7.008)	0.016	1.938 (0.800,4.694)	0.143	2.160 (0.882,5.290)	0.092
P for trend	0.025		0.025		0.025	
Q1	Reference		Reference		Reference	
Q2	1.659 (0.485,5.670)	0.420	1.474 (0.429,5.066)	0.538	1.431 (0.412,4.971)	0.573
Q3	2.071 (0.623,6.877)	0.235	1.584 (0.472,5.312)	0.456	1.742 (0.518,5.860)	0.370
Q4	5.057 (1.711,14.945)	0.003	3.117 (1.036,9.379)	0.043	3.468 (1.131,10.630)	0.030
P for trend	0.001		0.001		0.001	

Notes: Model 1: age, sex, smoke, Cr, FPG, WBC, DM. Model 2: Model 1 plus duration of hypertension, ACEIs/ARBs, beta-blockers, hypoglycemic drugs, hypolipidemic drugs, antiplatelet medication, alcohol, BMI, DBP, waist, BUN, HDL-C, TC, UA, serum potassium, serum sodium, AST. Other abbreviations, see Table 1.
Abbreviations: MACCE, major adverse cardiovascular and cerebrovascular events; HR, hazard ratio; CI, CONFIDENCE Interval.

its subtype risk in the third quartile group show an increasing trend; quartile grouping analysis further confirms that elevated LDH_AUC is significantly associated with increased risk of MACCE and their subtypes (trend test P<0.05). Research has shown that elevated levels of LDH are significantly correlated with the risk of MACCE (P<0.05) and cerebrovascular events (P<0.01), while elevated LDH_AUC is significantly positively correlated with the risk of MACCE (HR=1.012, 95% CI: 1.006–1.018), cardiovascular events (HR=1.014, 95% CI: 1.008–1.020), and all-cause mortality (HR=1.023, 95% CI: 1.004–1.042). Further analysis shows that when grouped by the annual LDH_AUC third quartile, the MACCE event and its subtype risk in the third quartile group show an increasing trend; Quartile grouping analysis further confirms that elevated LDH_AUC is significantly associated with increased risk of MACCE and their subtypes (trend test P<0.05). Supplementary Table 3 provides Cox regression analysis before data interpolation, which is

consistent with the results after data interpolation. Supplementary Figure 3 provide the nomogram for predicting MACCE.

Dose Response Relationship Between Annual Cumulative LDH Exposure and MACCE and Their Subtypes

Restricted cubic spline (RCS) analysis demonstrated that annual LDH_AUC levels exhibited a significant nonlinear dose-response relationship with MACCE and its subtypes. When annual LDH_AUC > 192.88 U/L, the risks of MACCE, cerebrovascular events, cardiovascular events, and all-cause mortality were significantly elevated (Figure 3). Supplementary Table 4 revealed that participants with annual LDH_AUC > 192.88 U/L had 1.286-fold (95% CI: 1.120–1.476, P<0.001), 1.203-fold (95% CI: 0.968–1.497, P=0.096), 1.307-fold (95% CI: 1.086–1.572, P=0.005), and 2.22-fold (95% CI: 1.076–4.581, P=0.031) higher risks of MACCE, cerebrovascular events, cardiovascular events, and all-cause mortality, respectively, compared to those with annual LDH_AUC ≤192.88.

Subgroup Analysis

A stratified analysis was further conducted to evaluate the impact of gender (men, women), BMI (<24, ≥24), smoking status (yes, no), alcohol consumption (yes, no), dyslipidemia (yes, no), diabetes mellitus (yes, no), hypertension duration (<5 years, ≥5 years), and antihypertensive medication types (<2 vs ≥2 types) on the study outcomes. Stratified analysis demonstrated that annual LDH_AUC levels were significantly associated with MACCE across subgroups of smoking status, alcohol consumption, dyslipidemia, and hypertension duration (P<0.05). Further analysis revealed that this association persisted in male participants, those with BMI ≥24 kg/m^2, non-diabetic individuals, and patients receiving ≥2 types of antihypertensive medications (P<0.05), indicating robustness of the findings. Importantly, no significant interaction effects were observed between these variables and the primary association (P-values >0.05). See Supplementary Table 5 for details.

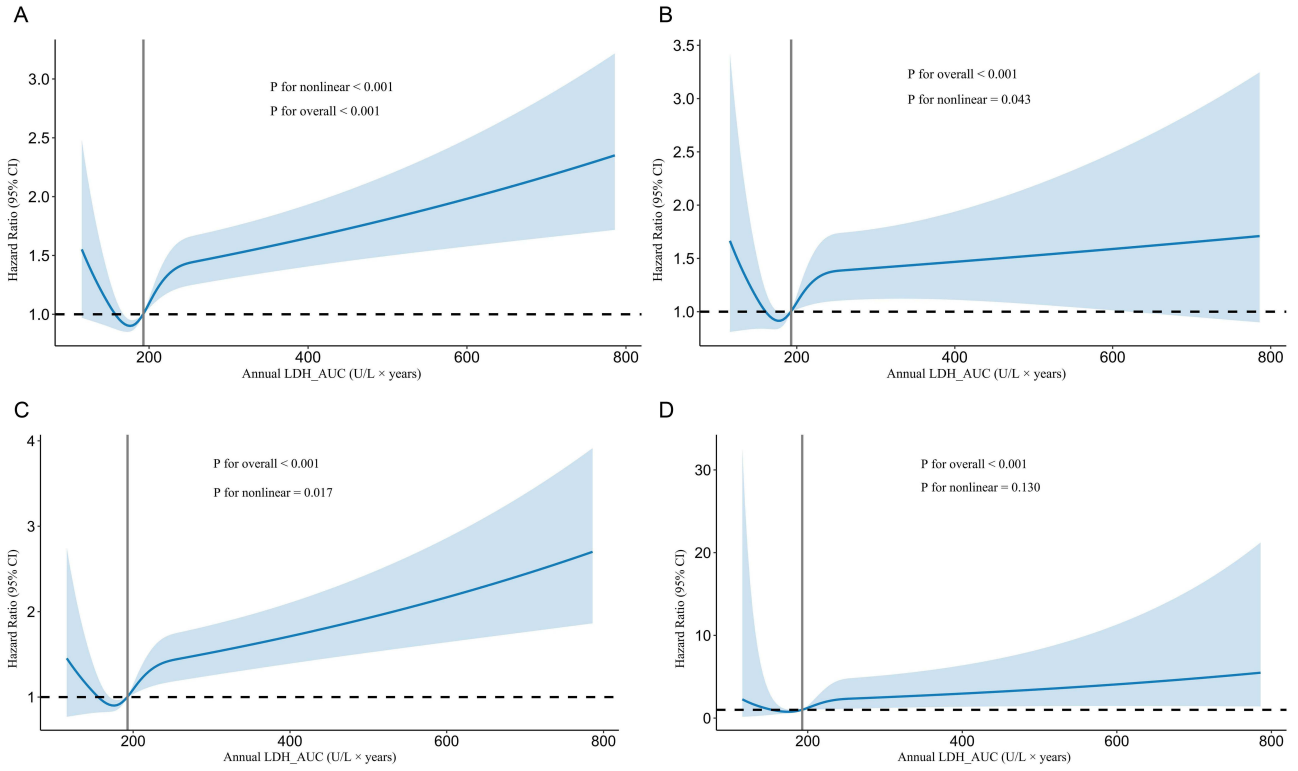

Figure 3 Dose-response association between annual LDH_AUC and the risk of MACCE and its subtypes. (**A**) MACCE. (**B**) Cerebrovascular events. (**C**) Cardiac events. (**D**) All-causer death.

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Sensitivity Analysis

Sensitivity analyses were further performed by excluding diabetic patients (Supplementary Table 6) and those with follow-up duration <2 years (Supplementary Table 7). The results were consistent with primary findings, demonstrating that elevated annual LDH_AUC levels remained significantly associated with increased risks of MACCE and its subtypes.

Discussion

This study employed a retrospective cohort design to investigate the relationship between annual LDH_AUC levels and MACCE in patients with hypertension. The results suggest that higher annual LDH_AUC levels are associated with an increased risk of MACCE and their subtypes, including cardiovascular and cerebrovascular events, as well as all-cause mortality. The results of the subgroup and sensitivity analyses indicate that this relationship remains significant, suggesting that the results are robust. Furthermore, compared with single-timepoint LDH measurements, annual LDH_AUC demonstrated superior predictive value for MACCE and its subtypes. These findings suggest that clinicians should pay attention to LDH test results, especially annual LDH_AUC levels.

Previous studies have also demonstrated a correlation between serum LDH levels and CVD, and the results of this study were consistent with these findings. Zhu et al conducted a cross-sectional study to investigate the relationship between LDH levels and 10-year cardiovascular risk (CVD10). Their findings revealed a significant association between elevated LDH levels and increased arterial stiffness, as well as heightened CVD10 risk. However, the observational design of this study may limit the establishment of causal relationships.[11] A cohort study comparing populations from arsenic-endemic and non-endemic regions demonstrated that LDH levels exhibited a dose-dependent elevation in arsenic-exposed individuals, correlating with increased cardiovascular mortality rates. However, the relatively small sample size may limit the external validity of these findings.[12] A cohort study in elderly populations demonstrated that elevated serum LDH levels were significantly associated with pronounced cardiac remodeling compared to normal LDH groups, suggesting its potential role as a predictive biomarker for post-myocardial infarction cardiac dysfunction.[13] While the majority of existing studies have focused on elevated LDH levels beyond physiological ranges as indicators of adverse health outcomes, Buckner et al's investigation utilizing NHANES database demonstrated that serum LDH elevation within normal reference intervals exhibited an inverse association with atherosclerotic cardiovascular disease risk scores.[26] Our research results showed a consistent trend with this study. This suggests that clinical doctors should pay attention to LDH detection in patients. The lack of statistical significance following adjustment for LDH and annualized LDH_AUC may be attributed to the following factors. First, the limited number of cerebrovascular events might mask underlying trends in this subgroup analysis. In addition, LDH is mainly used as a biomarker for myocardial cell injury.[9,27,28] In the context of cerebrovascular events, LDH levels are often associated with the prognosis of cerebrovascular events, especially serving as a predictor of poor prognosis.[29,30] The specific underlying mechanisms require further in - depth research.

It has been suggested that LDH are involved in CVD through the following suggested mechanisms. LDH, a key glycolytic enzyme, catalyzes the conversion of pyruvate to lactate under anaerobic conditions.[31] Accumulated lactate has been demonstrated to modulate inflammatory mediator production, including interleukin-6 (IL-6) and nitric oxide (NO), thereby mediating inflammatory responses through multiple pathways.[19,32] Furthermore, elevated lactate levels may contribute to cardiovascular pathogenesis via lactylation modification mechanisms.[33,34] In addition, excessive LDH can increase oxidative stress and damage the cardiovascular system.[35] Furthermore, elevated LDH levels may serve as a biomarker for impaired tissue perfusion, reflecting underlying cellular damage or hypoxic stress that exacerbates cardiovascular pathogenesis through multiple mechanistic pathways.[16,36]

To our knowledge, this is the first study to investigate the impact of cumulative LDH exposure on the risk of MACCE. The present study has several strengths. It features a relatively large sample size and a longitudinal design, coupled with an innovative methodological approach that systematically employs the annual LDH_AUC to capture dynamic longitudinal exposure, thereby integrating both the magnitude and duration of LDH elevation. Furthermore, stratified and sensitivity analyses confirmed the robustness and reliability of the findings, underscoring their potential

clinical importance for the prevention and management of MACCE in this population. Furthermore, this study employed an exclusion criterion by excluding patients who had already experienced MACCE at baseline. The analytical cohort was restricted to patients without prior MACCE to investigate the annual LDH-AUC in relation to subsequent MACCE incidence. This methodological approach effectively eliminates potential confounding factors from pre-existing conditions, thereby enhancing the credibility of the findings regarding LDH's prognostic value in MACCE prediction. However, several limitations should be acknowledged. First, despite extensive adjustment for confounders, residual confounding from unmeasured factors, such as socioeconomic status and physical activity, cannot be excluded. Second, as all enrolled participants were recruited from tertiary hospitals, the study is subject to inherent selection biases associated with non-randomized designs. Future studies incorporating multi-center or community-based populations are warranted to enhance the generalizability of the results. Third, this study is the relatively low incidence of mortality events, which may be attributable to the single-center origin of our clinical database, potentially resulting in incomplete capture of death outcomes due to institutional reporting constraints. Besides, since LDH consists of multiple isoenzymes with distinct tissue distributions, our measurement of total LDH may lack specificity. Future research should aim to clarify the role of specific LDH isoenzymes in the context of MACCE, and establish causality.

Conclusions

In conclusion, our study confirms that the cumulative LDH exposure in hypertensive patients is significantly correlated with an increased risk of MACCE. Clinicians should serial LDH monitoring to optimize risk stratification in this population.

Data Sharing Statement

The data that support the findings of this study are available upon reasonable request from the corresponding author.

Ethics Approval and Consent to Participate

The Ethics Board of the People's Hospital of the Xinjiang Uygur Autonomous Region (KY2022080903) approved this retrospective study. The study procedures were carried out by the Declaration of Helsinki. All data were de-identified before analysis, and strict confidentiality protocols were followed to protect patient privacy throughout the research process. As the study was retrospective, informed consent was waived.

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Author Contributions

H W: Methodology, Project administration, Data curation, Writing- Original draft. N L: Conceptualization, Supervision, Project administration. M H, Q Z: Data curation, Validation. L Y, H M, Q W, X L, B N and J H: Data curation. All authors have approved the manuscript for publication in its current form. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors have no relevant financial or non-financial interests to disclose.

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