# A U-Shaped Association between LDL-C/HDL-C Ratio and all-Cause Mortality in Elderly Hypertensive Patients: A Prospective Cohort Study

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**Original investigation**

**Keywords:** LDL-C/HDL-C ratio, U-shaped curve, Mortality, Hypertension

**Posted Date:** August 5th, 2020

**DOI:** https://doi.org/10.21203/rs.3.rs-52204/v1

# Abstract

**Background:** Low-density lipoprotein cholesterol/high-density lipoprotein- cholesterol (LDL-C/HDL-C) ratio is an excellent predictor of cardiovascular disease (CVD). However, previous studies linking LDL-C/HDL-C ratio to mortality have been inconsistent and limited by short follow-up. Therefore, the aim of the present study was to determine whether LDL-C/HDL-C ratio could be an effective predictor of all-cause mortality in elderly hypertensive patients.

**Methods:** We selected 6,941 hypertensive patients aged 65 years or older and untreated with lipid-lowering drugs from the Chinese Hypertension Registry for analysis. The endpoint of the study was all-cause mortality. The relationship between LDL-C/HDL-C ratio and all-cause mortality by using multivariate cox proportional hazards regression, smoothing curve fitting (penalized spline method), subgroup analysis and Kaplan–Meier survival curve to address.

**Results:** During a median follow-up of 1.72 years, 157 all-cause deaths occurred. A U-shaped association was found between LDL-C/HDL-C ratio and all-cause mortality. The LDL-C/HDL-C ratio was divided into five groups according to quintiles. Compared to the reference group (Q3: 1.67-2.10), both lower (Q1 and Q2) and higher (Q4 and Q5) LDL-C/HDL-C ratios were associated with higher all-cause mortality (<1.67: HR 1.81, 95% CI: 1.08-3.03; ≥2.10: HR 2.00, 95% CI: 1.18-3.39). Compare with lower and higher LDL-C/HDL-C ratio groups, patients with LDL-C/HDL-C ratio of 1.67-2.10 had a significant higher survival probability (log-rank $P = 0.038$).

**Conclusion:** Our results suggested that there was a U-shaped association between LDL-C/HDL-C ratio and all-cause mortality. Both lower and higher LDL-C/HDL-C ratios were associated with increased all-cause mortality in elderly hypertensive patients.


# Introduction

The leading causes of death worldwide include stroke and cardiovascular disease (CVD), both of which are associated with higher levels of low-density lipoprotein cholesterol (LDL-C) and lower levels of high-density lipoprotein cholesterol (HDL-C)[1, 2]. As a new marker, LDL-C/HDL-C ratio is calculated by dividing LDL-C by HDL-C. Some studies suggest that the predictive value of LDL-C/HDL-C ratio may be superior LDL-C or HDL-C alone and it is considered to be an excellent predictor of CVD[3, 4]. CVD and death are closely related, and LDL-C/HDL-C ratio should also be suitable for predicting death. However, previous studies on LDL-C/HDL-C ratio have inconsistent conclusions. Some studies have suggested LDL-C/HDL-C ratio was positively associated with CVD[5–8], while others have found a negative correlation between LDL-C/HDL-C ratio and all-cause mortality[9, 10]. The reasons for these inconsistencies can be attributed to differences in the study population, follow-up, and study endpoints. On the other hand, the above studies have also proposed different reference ranges for LDL-C/HDL-C ratio. Those factors hinder LDL-C/HDL-C ratio from being a valuable predictor of all-cause mortality.

In addition, there are some deficiencies in the study on the relationship between LDL-C/HDL-C ratio and all-cause mortality, including too small sample size, too short follow-up time, and the patient's condition was too serious, so the relationship between LDL-C/HDL-C ratio and all-cause mortality remains virtually unclear. Of note, elderly hypertensive patients (defined as hypertensive patients over the age of 65) have a higher mortality compared with the normal population[11]. Therefore, it is more necessary for researchers to explore a clinically valuable predictor of all-cause mortality for elderly patients with hypertension.

In an effort to address the significant gaps in knowledge, the present study aimed to investigate the prospective relationship of LDL-C/HDL-C ratio with all-cause mortality, and to examine the optimal range of LDL-C/HDL-C ratio, using data from the China Hypertension Registry Study.

## Methods

# Study population

The study data were drawn from the China Hypertension Registry Study (http://www.chictr.org.cn/, No: ChiCTR1800017274). Details of the methodology, primary objectives, inclusion and exclusion criteria for this study had been described in detail elsewhere[12]. Briefly, this project was a non-intervention, prospective, observational, and real-world study. From March 2018 to August 2018, we recruited 14,268 patients with hypertension in Wuyuan, Jiangxi Province, China to evaluate the treatment, related risk factors and prognosis of patients with hypertension. In our study, we selected 6,941 hypertensive patients aged 65 years or older and untreated with lipid-lowering drugs from the China Hypertension Registry Study. Hypertension was defined as blood pressure was 140 mmHg or above, self-report history of hypertension, or the use of antihypertensive drugs at baseline[13]. The study protocol was approved by the Ethics Committee of the Anhui Medical University Biomedical Institute, and all participants signed informed consent.

# Data Collection And Outcome Definition

All study participants were required to collect fasting, venous blood samples by trained study staff during the baseline data collection period. Total cholesterol (TC, mmol/L), triglycerides (TG, mmol/L), low-density lipoprotein cholesterol (LDL-C, mmol/L), high-density lipoprotein cholesterol (HDL-C, mmol/L), serum uric acid (SUA, μmol/L), estimated glomerular filtration rate (eGFR, ml/min/1.73 $m^2$), homocysteine (Hcy, μmol/L), fasting blood glucose (FBG, mmol/L) and albumin (g/L) were measured by an automatic clinical analyzer (Beckman Coulter, USA) in Biaojia Biotechnology Laboratory, Shenzhen, China. LDL-C/HDL-C ratio is calculated by dividing LDL-C by HDL-C. In addition to the above-mentioned laboratory indicators, other covariates of the study included age (years), sex (male or female), body mass index (BMI, kg/$m^2$), smoking status (never, former and current), alcohol consumption, history of disease (including stroke, CVD and diabetes), systolic/diastolic blood pressure (mmHg) and drug history (including antihypertensive drugs, antiplatelet drugs and glucose-lowering drugs).

The outcome of our study was all-cause mortality that occurred from 31 August 2018 to 31 March 2020. Causes of death included stroke, CVD, tumors respiratory diseases, and other reasons. All-cause mortality was ascertained from the Local Healthcare Security administration, Centers for Disease Control and Prevention, and Hospitals.

# Statistical analysis

Study population characteristics at baseline are presented according to quintiles of LDL-C/HDL-C ratio. Data are presented as mean ± SD or proportions. Multivariate cox proportional hazards regression analysis was used to analyze the relationship between LDL-C/HDL-C ratio and all-cause mortality, and the results were presented by hazard ratio (HR) and 95% confidence interval (CI). Fully adjusted smoothing curve fitting (penalized spline method) visually demonstrated the relationship between LDL-C/HDL-C ratio and all-cause mortality. Stratified analyses were conducted including sex, BMI, stroke, CVD, diabetes and eGFR, in order to identify potential subgroups that show a significant association between LDL-C/HDL-C ratio and all-cause mortality. Survival was estimated by the Kaplan-Meier method, and any differences in survival were evaluated with a stratified log-rank test.

All data analysis and form production were performed using the statistical package R (http://www.R-project.org, The R Foundation) and Empower (R) (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA). When a two-tailed *P* was < 0.05, we had enough reason to think that the analysis results were statistically significant.

# Results

A total of 6,941 hypertensive patients aged 65 or older and untreated with lipid-lowering drugs were selected for final data analysis (mean age: 71.20 ± 5.30; male: 48.18%) (Fig. 1). In our study, the distribution of baseline population characteristics according to the baseline LDL-C/HDL-C ratio quintiles is described in Table 1. Compared with lower groups (Q1 and Q2), the higher groups (Q4 and Q5) had higher values of BMI, stroke, diabetes, DBP, TC, TG, LDL-C, FBG, albumin, SUA, antihypertensive drugs and glucose-lowering drugs. In contrast, T3 group had lower values of age, male, smoking, alcohol consumption, HDL-C and eGFR (all $P < 0.05$).

Table 1
Baseline Characteristics of the Cohort Per Quintiles of LDL-C/HDL-C ratio

| Characteristics* | Quintiles of LDL-C/HDL-C ratio | | | | | *P* value |
|---|---|---|---|---|---|---|
| | Q1 (< 1.16) | Q2 (1.16–1.67) | Q3 (1.67–2.10) | Q4 (2.10–2.79) | Q5 (≥ 2.79) | |
| N | 1,387 | 1,389 | 1,389 | 1,387 | 1,389 | |
| Demographics | | | | | | |
| Age, years | 71.75 ± 5.51 | 71.67 ± 5.59 | 71.10 ± 5.36 | 70.78 ± 5.06 | 70.69 ± 4.89 | < 0.001 |
| Male, % | 836 (60.27) | 691 (49.75) | 629 (45.28) | 581 (41.89) | 607 (43.70) | < 0.001 |
| BMI, kg/m$^2$ | 20.85 ± 4.95 | 21.91 ± 3.26 | 22.77 ± 3.07 | 23.56 ± 3.25 | 24.15 ± 3.18 | < 0.001 |
| Smoking, % | | | | | | < 0.001 |
| Never | 638 (46.00) | 732 (52.74) | 778 (56.01) | 788 (56.85) | 768 (55.33) | |
| Former | 263 (18.96) | 258 (18.59) | 283 (20.37) | 260 (18.76) | 259 (18.66) | |
| Current | 486 (35.04) | 398 (28.67) | 328 (23.61) | 338 (24.39) | 361 (26.01) | |
| Alcohol consumption, % | 473 (34.10) | 297 (21.40) | 241 (17.35) | 222 (16.02) | 199 (14.34) | < 0.001 |
| History of disease, % | | | | | | |
| Stroke | 74 (5.34) | 78 (5.62) | 90 (6.48) | 90 (6.49) | 130 (9.36) | 0.001 |
| CVD | 75 (5.41) | 95 (6.84) | 86 (6.19) | 89 (6.42) | 89 (6.41) | 0.620 |
| Diabetes | 158 (11.39) | 180 (12.96) | 206 (14.83) | 274 (19.75) | 354 (25.49) | < 0.001 |
| Blood pressure | | | | | | |
| Systolic BP, mmHg | 149.30 ± 18.83 | 149.53 ± 18.69 | 150.66 ± 17.87 | 150.47 ± 18.18 | 150.33 ± 18.47 | 0.199 |

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; SUA, serum uric acid; eGFR, estimated glomerular filtration rate; Hcy, homocysteine; FBG, fasting blood glucose.

*Data are presented as number (%) or mean ± standard deviation.

| Characteristics* | Quintiles of LDL-C/HDL-C ratio | | | | | *P* value |
|---|---|---|---|---|---|---|
| | Q1 (< 1.16) | Q2 (1.16–1.67) | Q3 (1.67–2.10) | Q4 (2.10–2.79) | Q5 (≥ 2.79) | |
| Diastolic BP, mmHg | 84.88 ± 10.86 | 85.22 ± 10.71 | 85.77 ± 10.22 | 85.32 ± 10.07 | 86.04 ± 10.07 | 0.030 |
| Lipids | | | | | | |
| TC, mmol/L | 4.68 ± 0.95 | 4.95 ± 0.97 | 5.15 ± 1.03 | 5.37 ± 1.07 | 5.68 ± 1.19 | < 0.001 |
| TG, mmol/L | 0.98 ± 0.44 | 1.24 ± 0.61 | 1.47 ± 0.72 | 1.89 ± 1.03 | 2.37 ± 1.34 | < 0.001 |
| LDL-C, mmol/L | 2.21 ± 0.53 | 2.68 ± 0.55 | 2.98 ± 0.62 | 3.24 ± 0.67 | 3.64 ± 0.78 | < 0.001 |
| HDL-C, mmol/L | 2.03 ± 0.46 | 1.74 ± 0.36 | 1.59 ± 0.33 | 1.45 ± 0.30 | 1.27 ± 0.27 | < 0.001 |
| LDL-C/HDL-C ratio | 1.10 ± 0.20 | 1.54 ± 0.10 | 1.88 ± 0.10 | 2.24 ± 0.11 | 2.89 ± 0.41 | < 0.001 |
| Other plasma parameters | | | | | | |
| Hcy, μmol/L | 19.10 ± 11.19 | 19.32 ± 11.28 | 18.91 ± 11.10 | 19.18 ± 11.94 | 19.72 ± 12.54 | 0.439 |
| FBG, mmol/L | 5.90 ± 1.23 | 6.00 ± 1.35 | 6.06 ± 1.64 | 6.19 ± 1.46 | 6.43 ± 1.81 | < 0.001 |
| Albumin, g/L | 45.57 ± 4.27 | 45.83 ± 4.06 | 45.90 ± 3.98 | 46.18 ± 3.89 | 45.98 ± 3.96 | 0.002 |
| SUA, μmol/L | 413.30 ± 123.79 | 411.09 ± 114.47 | 415.57 ± 118.22 | 429.92 ± 122.14 | 450.71 ± 120.26 | < 0.001 |
| eGFR, ml/min/1.73 $m^2$ | 81.52 ± 19.56 | 81.51 ± 18.15 | 81.46 ± 19.33 | 80.44 ± 19.26 | 78.26 ± 20.21 | < 0.001 |
| Medication use, % | | | | | | |
| Antihypertensive drugs | 874 (63.01) | 897 (64.63) | 959 (69.04) | 948 (68.40) | 983 (70.82) | < 0.001 |
| Antiplatelet drugs | 34 (2.45) | 33 (2.38) | 38 (2.74) | 43 (3.10) | 39 (2.81) | 0.773 |

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; SUA, serum uric acid; eGFR, estimated glomerular filtration rate; Hcy, homocysteine; FBG, fasting blood glucose.

*Data are presented as number (%) or mean ± standard deviation.

| Characteristics* | Quintiles of LDL-C/HDL-C ratio | | | | | *P* value |
|---|---|---|---|---|---|---|
| | Q1 (< 1.16) | Q2 (1.16–1.67) | Q3 (1.67–2.10) | Q4 (2.10–2.79) | Q5 (≥ 2.79) | |
| Glucose-lowering drugs | 34 (2.45) | 47 (3.38) | 56 (4.03) | 85 (6.13) | 100 (7.20) | < 0.001 |

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; SUA, serum uric acid; eGFR, estimated glomerular filtration rate; Hcy, homocysteine; FBG, fasting blood glucose.

*Data are presented as number (%) or mean ± standard deviation.

In present study, the average follow-up duration was 1.72 years, and a total of 157 all-cause deaths (2.26%) occurred during the follow-up period. Table 2 shows the HR and 95% CI values of the relationship between the LDL-C/HDL-C ratio and all-cause mortality in the crude model, model 1 (minor adjusted) and model 2 (fully adjusted). When LDL-C/HDL-C ratio was used as a continuous variable, there was no significant difference in the relationship between LDL-C/HDL-C ratio and all-cause mortality among the three models (all $P > 0.05$). Furthermore, LDL-C/HDL-C ratio was converted from a continuous variable to a categorical variable. The LDL-C/HDL-C ratio was divided into five groups according to quintiles. Compared to the reference group (Q3: 1.67–2.10), both lower (Q1 and Q2: <1.67) and higher (Q4 and Q5: ≥2.10) LDL-C/HDL-C ratios groups had a higher mortality in all models (all $P < 0.05$). In model 2 (fully adjusted model), both the low LDL-C/HDL-C ratio and high LDL-C/HDL-C ratio were associated with higher mortality (< 1.67: HR 1.81, 95% CI: 1.08–3.03; ≥2.10: HR 2.00, 95% CI: 1.18–3.39). These results suggest that the relationship between the LDL-C/HDL-C ratio and all-cause mortality is more likely to be non-linear. The fully adjusted smooth curve fitting showed a U-shaped relationship between baseline LDL-C/HDL-C ratio and all-cause mortality (Fig. 2).

Table 2
Association between the LDL-C/HDL-C ratio and all-cause mortality during the follow-up period

| LDL-C/HDL-C ratio | Events, % | Crude model | | Model 1 | | Model 2 | |
|---|---|---|---|---|---|---|---|
| | | HR (95% CI) † | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Continuous | 157/6,947 (2.29) | 0.93 (0.73, 1.19) | 0.558 | 1.05 (0.83, 1.34) | 0.674 | 1.02 (0.76, 1.36) | 0.912 |
| Quintiles | | | | | | | |
| <1.16 | 40/1,387 (2.88) | 2.12 (1.23, 3.67) | 0.007 | 1.88 (1.09, 3.25) | 0.024 | 1.98 (1.13, 3.46) | 0.017 |
| 1.16–1.67 | 32/1,389 (2.30) | 1.69 (0.96, 2.98) | 0.070 | 1.57 (0.89, 2.78) | 0.118 | 1.64 (0.92, 2.90) | 0.091 |
| 1.67–2.10 | 19/1,389 (1.37) | Reference | | Reference | | Reference | |
| 2.10–2.79 | 30/1,387 (2.16) | 1.59 (0.89, 2.82) | 0.115 | 1.75 (0.98, 3.11) | 0.057 | 1.80 (1.01, 3.22) | 0.048 |
| ≥2.79 | 36/1,389 (2.59) | 1.91 (1.09, 3.33) | 0.023 | 2.12 (1.21, 3.70) | 0.008 | 2.24 (1.24, 4.03) | 0.008 |
| Categories | | | | | | | |
| <1.67 | 72/2,776 (2.59) | 1.91 (1.15, 3.16) | 0.012 | 1.73 (1.04, 2.87) | 0.034 | 1.81 (1.08, 3.03) | 0.024 |
| 1.67–2.10 | 19/1,389 (1.37) | Reference | | Reference | | Reference | |
| ≥2.10 | 66/2,776 (2.38) | 1.75 (1.05, 2.91) | 0.032 | 1.93 (1.16, 3.23) | 0.011 | 2.00 (1.18, 3.39) | 0.010 |
| *P* for trend | | 0.570 | | 0.598 | | 0.767 | |

†Cox proportional hazards models were used to estimate hazard ratio (HR) and 95% confidence interval (95% CI).

Abbreviations: HR, hazard ratio; CI, confidence interval; LDL-C, low density lipoprotein-cholesterol; HDL-C, high-density lipoprotein cholesterol.

Model 1: adjusted for none. Model 2: adjusted for age, sex. Model 3: adjusted for age, sex, BMI, SBP, DBP, TG, Hcy, FBG, SUA, eGFR, smoking, alcohol consumption, diabetes, stroke, CVD and anti-hypertensive drugs.

In Table 3, stratified analyses were conducted by sex, BMI, stroke, CVD, diabetes and eGFR, the U-shaped association was consistently observed in all subgroups, and there was no significant interaction between LDL-C/HDL-C ratio and all-cause mortality in all subgroups (all *P* for interaction > 0.05).

Table 3
Effect size of LDL-C/HDL-C ratio on all-cause mortality in each subgroup

| Subgroups | Categories of LDL-C/HDL-C ratio, HR (95% CI) | | | *P* for interaction |
|---|---|---|---|---|
| | Low (< 1.67) | Reference (1.67–2.10) | High (≥ 2.10) | |
| Sex | | | | 0.249 |
| male | 1.38 (0.76, 2.50) | 1 | 1.51 (0.80, 2.84) | |
| female | 3.33 (1.15, 9.69) | 1 | 3.92 (1.35, 11.36) | |
| BMI, kg/m$^2$ | | | | 0.990 |
| <24 | 1.81 (1.01, 3.26) | 1 | 2.13 (1.14, 3.98) | |
| ≥24 | 1.85 (0.62, 5.50) | 1 | 1.73 (0.64, 4.70) | |
| Stroke | | | | 0.623 |
| No | 1.71 (1.00, 2.91) | 1 | 1.81 (1.05, 3.14) | |
| Yes | 3.63 (0.40, 32.93) | 1 | 6.89 (0.79, 60.40) | |
| CVD | | | | 0.210 |
| No | 1.58 (0.93, 2.69) | 1 | 2.01 (1.17, 3.45) | |
| Yes | 4.23 (0.43, 41.60) | 1 | 1.38 (0.10, 18.38) | |
| Diabetes | | | | 0.250 |
| No | 1.63 (0.95, 2.79) | 1 | 1.68 (0.96, 2.94) | |
| Yes | 6.38 (0.80, 50.66) | 1 | 8.18 (1.04, 64.02) | |
| eGFR, ml/min/1.73 m$^2$ | | | | 0.097 |
| <60 | 5.35 (1.24, 23.09) | 1 | 8.93 (2.02, 39.51) | |

Adjusted for age, sex, BMI, SBP, DBP, TG, Hcy, FBG, SUA, eGFR, smoking, alcohol consumption, diabetes, stroke, CVD and anti-hypertensive drugs, if not be stratified.

| Subgroups | Categories of LDL-C/HDL-C ratio, HR (95% CI) | | | *P* for interaction |
|---|---|---|---|---|
| | Low (< 1.67) | Reference (1.67–2.10) | High (≥ 2.10) | |
| ≥60 | 1.45 (0.82, 2.55) | 1 | 1.44 (0.80, 2.57) | |
| Adjusted for age, sex, BMI, SBP, DBP, TG, Hcy, FBG, SUA, eGFR, smoking, alcohol consumption, diabetes, stroke, CVD and anti-hypertensive drugs, if not be stratified. | | | | |

Kaplan–Meier survival curve of all-cause mortality stratified by LDL-C/HDL-C ratio levels demonstrated (Fig. 3). Compare with lower and higher LDL-C/HDL-C ratio groups, patients with LDL-C/HDL-C ratio of 1.67–2.10 had a significantly higher survival probability (Log-rank $P < 0.05$).

# Discussion

In the current study, we found a U-shaped relationship between the LDL-C/HDL-C ratio and all-cause mortality in the elderly hypertensive population in China. Both lower and higher LDL-C/HDL-C ratios were associated with higher all-cause mortality. The optimal range of LDL-C/HDL-C ratio was 1.67–2.10. Compare with lower and higher LDL-C/HDL-C ratio groups, patients with LDL-C/HDL-C ratio of 1.67–2.10 had a significant higher survival probability.

Considering that CVD is one of the leading causes of death in elderly patients with hypertension, and studies on the relationship between LDL-C/HDL-C ratio and all-cause mortality are limited. Therefore, we also discussed the study of LDL-C/HDL-C ratio and CVD, in order to comprehensively and deeply examine the predictive value of LDL-C/HDL-C ratio. In retrospect of previous studies, there are inconsistent conclusions regarding the predictive value of the LDL-C/HDL-C ratio. Matsumoto I et al.[6] included 687 patients who underwent PCI (mean age 67.7 ± 9.9, mean follow-up years = 2.75) for analysis and found a positive association between the LDL-C/HDL-C ratio and CVD, and considered that the LDL-C/HDL-C ratio should be controlled below 1.5. Zhong et al.[7] enrolled 1,937 acute coronary syndromes (ACS) patients (mean age 64.0 ± 10.8, mean follow-up years = 1.00) for analysis, found that high LDL-C/HDL-C ratio increased the risk of CVD, and considered that LDL-C/HDL-C ratio should be controlled below 2.7. Yokokawa et al.[5] included 8,714 male patients (mean age 63.7 ± 11.5, mean follow-up years = 2.7 ± 0.9) in the analysis and found that compared with LDL-C/HDL-C ratio < 2.6, > 2.6 patients had a higher risk of CVD. The above studies suggest that there may be a positive association between LDL-C/HDL-C ratio and CVD, and different studies have proposed different reference ranges for LDL-C/HDL-C ratio. By contrast, You et al[9] included 356 patients with intracranial hemorrhage (mean age 64.1 ± 13.7, mean follow-up years = 0.22) and found that LDL-C/HDL-C ratio was negatively correlated with all-cause mortality, and considered that LDL-C/HDL-C ratio should be controlled at more than 2.96. Liu et al.[10] recruited 3,250 stroke patients (mean age 63.72 ± 11.33, mean follow-up years = 1.00) for analysis and found a negative relationship between LDL-C/HDL-C ratio and all-cause mortality, mortality was lowest as LDL-C/HDL-C ratio was between 2.23 and 2.88. The above studies suggest that the relationship between LDL-C/HDL-C

ratio and all-cause mortality may be negative, and propose an inconsistent optimal range of LDL-C/HDL-C ratio. These conflicting results can be attributed to differences in the study population, follow-up, and end-point events. Meanwhile, it also reminds us that the exact relationship between LDL-C/HDL-C ratio and all-cause mortality and the optimal level of LDL-C/HDL-C ratio are still unclear. The above factors prompted us to conduct the current study.

The mechanism driving this association is still unclear. Several possible mechanisms could explain this finding. When LDL-C/HDL-C ratio was at a low level, there was a negative correlation between LDL-C/HDL-C ratio and all-cause mortality. In Table S1, we found that all deaths caused by respiratory diseases occurred in the LDL-C/HDL-C ratio < 1.67 group. It may be that lower LDL-C/HDL-C ratio is associated with inflammation and increases energy demand for breathing, which in turn aggravates respiratory failure[14]. Of note, lower LDL-C/HDL-C ratio was caused by higher HDL-C levels[15]. Consistent with our study, Bowe et al.[16] included 1,764,986 American adults (mean follow-up years = 9.1) for analysis and found a U-shaped relationship between HDL-C and all-cause mortality, suggested that higher HDL-C was associated with increased mortality. C.M. Madsen et al.[17] included 116,508 patients (mean follow-up years = 6.0) for analysis and found that higher HDL-C levels increased all-cause mortality. It might be that higher HDL-C is associated with gene variability, including mutations in ABCA1, LIPC, and SCARB1, which in turn promote the occurrence and progression of CVD[18, 19]. On the other hand, HDL-C loses its protective effect when it is at a higher level, paradoxically enhancing senescence and impairing endothelial progenitor cell vascularization and angiogenesis[20, 21]. These mechanisms suggest that the conformational and functional properties of HDL particles may change when HDL-C is at a high level, which may lead to harmful effects. When the LDL-C/HDL-C ratio was at a high level, the LDL-C/HDL-C ratio was positively correlated with all-cause mortality. On the one hand, higher LDL-C/HDL-C ratio may promote coronary inflammation[22]. On the other hand, higher LDL-C/HDL-C ratio may also increase the vulnerability and rupture of coronary plaque[23, 24]. In addition, higher LDL-C/HDL-C ratio was associated with increased LDL-C levels[15]. Higher LDL-C was associated with increased mortality, mainly through oxidative stress and inflammatory response[25, 26]. It must be admitted that all-cause mortality contains a variety of factors, so it is difficult for us to fully explain the mechanism of the relationship between LDL-C/HDL-C ratio and all-cause mortality. Therefore, further basic experiments are needed to fully elucidate the specific biological mechanism behind this connection.

Compared with the normal population, elderly hypertensive patients have a higher mortality [27]. Therefore, for such patients, it is more important to find a valuable predictor of mortality. LDL-C/HDL-C ratio might be the useful indicators for prognosis prediction as it simultaneously evaluates the levels of both LDL-C and HDL-C. More important, the finding of U-shaped relationships has a greater clinical significance than linear relationships[28], because it suggests that LDL-C/HDL-C ratio may have an optimal range, so we can control it better.

# Limitations

Some limitations should be noted. First, in our study, the main causes of death included CVD, stroke, cancer and respiratory disease. However, because of the follow-up period was short, it was not possible to analyze cause-specific deaths due to the small number of specific deaths. It should be noted that our study is still under follow-up, so our study will be further improved in the future. Second, our study population is elderly patients with hypertension, so the generality of our conclusions is limited. Third, we only analyzed the LDL-C/HDL-C ratio at baseline and did not dynamically observe changes in LDL-C/HDL-C ratio. Finally, LDL-C/HDL-C ratio as a new predictor, the number of relevant studies is still small, so more studies are needed to confirm the predictive value of LDL-C/HDL-C ratio.

# Conclusion

The present study found a U-shaped relationship between LDL-C/HDL-C ratio and all-cause mortality in elderly hypertensive patients in China. Both lower and higher levels of LDL-C/HDL-C ratio were associated with a higher all-cause mortality. Compare with lower and higher LDL-C/HDL-C ratio groups, patients with LDL-C/HDL-C ratio of 1.67–2.10 had significant higher survival benefits. These results suggest that LDL-C/HDL-C ratio can be a valuable predictor of all-cause mortality.

# Abbreviations

BMI, body mass index; CVD, cardiovascular disease; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; SUA, serum uric acid; eGFR, estimated glomerular filtration rate; Hcy, homocysteine; FBG, fasting blood glucose; HR, hazard ratio; CI, confidence interval.

# Declarations


### Acknowledgements

All authors acknowledge the contribution the all staff who participated in this study as well as the study participants who shared their time with us.


### Authors' contributions

All authors were responsible for drafting the manuscript and revising it critically for constructive intellectual content. All authors approved the version to be published.


### Funding

This study was supported by Science and Technology Innovation Platform Project of Jiangxi Province (Grant number: 20165BCD41005); the National Natural Science Foundation of China (Grant number: 81960074 and 81500233); the Projects of the Science and Technology Department, Jiangxi (Grant

number: 20171BAB205008 and 20204237); and the Jiangxi Outstanding Person Foundation (Grant number: 20192BCBL23024).

### Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

### Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the Anhui Medical University Biomedical Institute, and all participants signed informed consent.

### Consent for publication

The authors have reviewed the manuscript and consent for publication.

### Conflicts of Interest

The authors declare no conflicts of interest in this work.

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# Figures

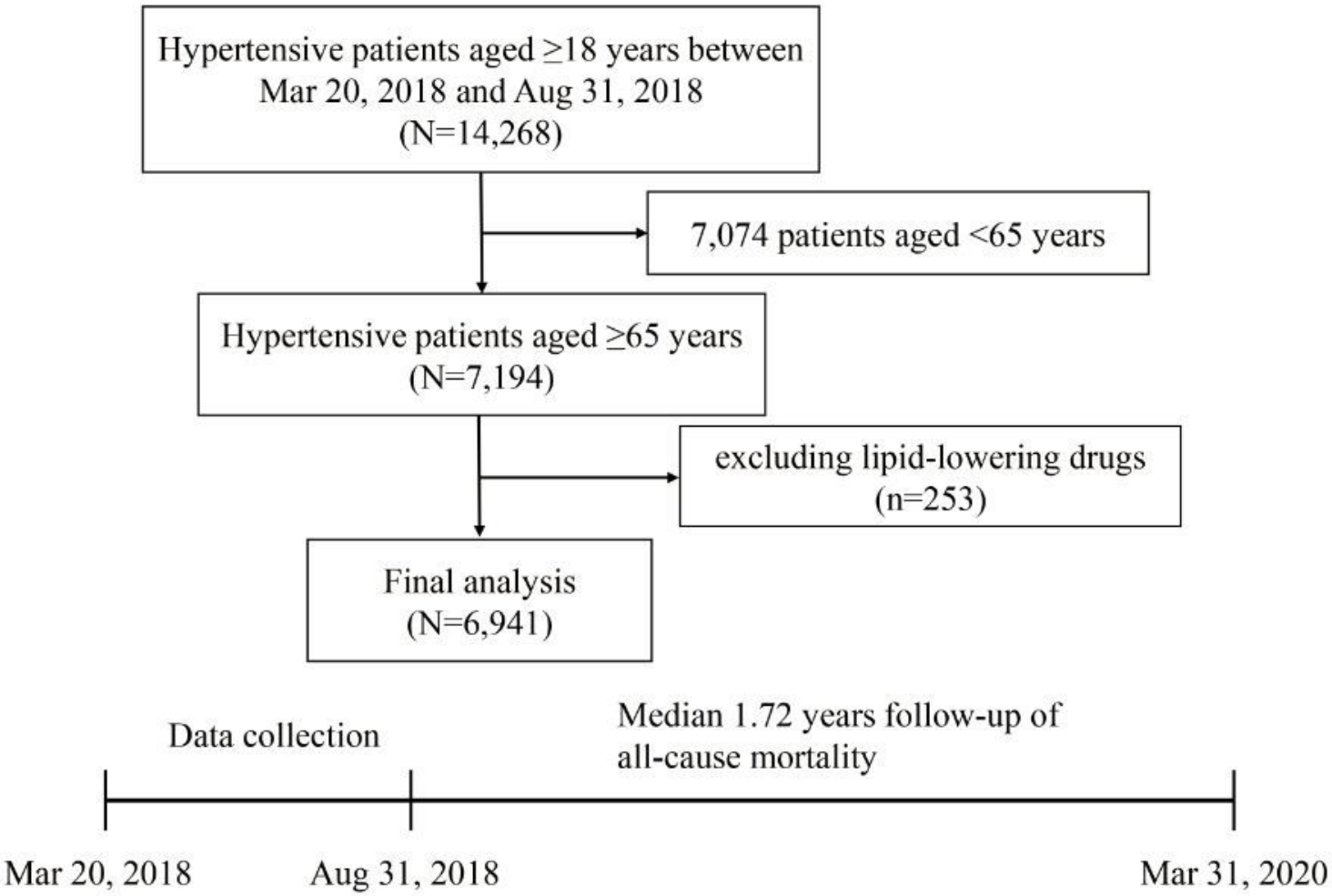
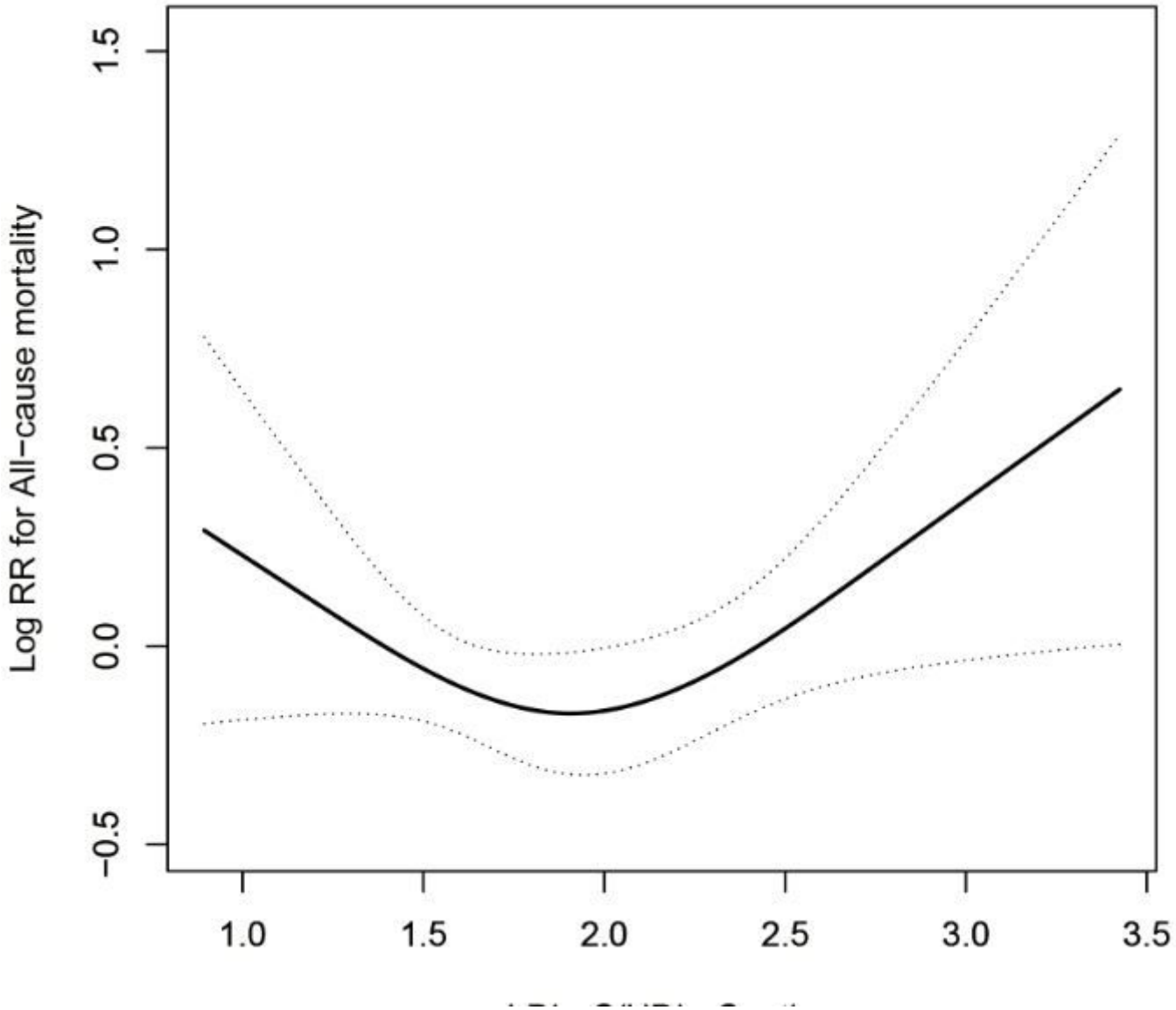



**Figure 1**

Flow chart of the study.




## Figure 2

Dose-response relationship between LDL-C/HDL-C and the probability of all-cause mortality. The smooth curve fitting presented a U-shaped relationship between LDL-C/HDL-C ratio and all-cause mortality. Adjusted for age, sex, BMI, SBP, DBP, TG, Hcy, FBG, SUA, eGFR, smoking, alcohol consumption, diabetes, stroke, CVD and anti-hypertensive drugs.

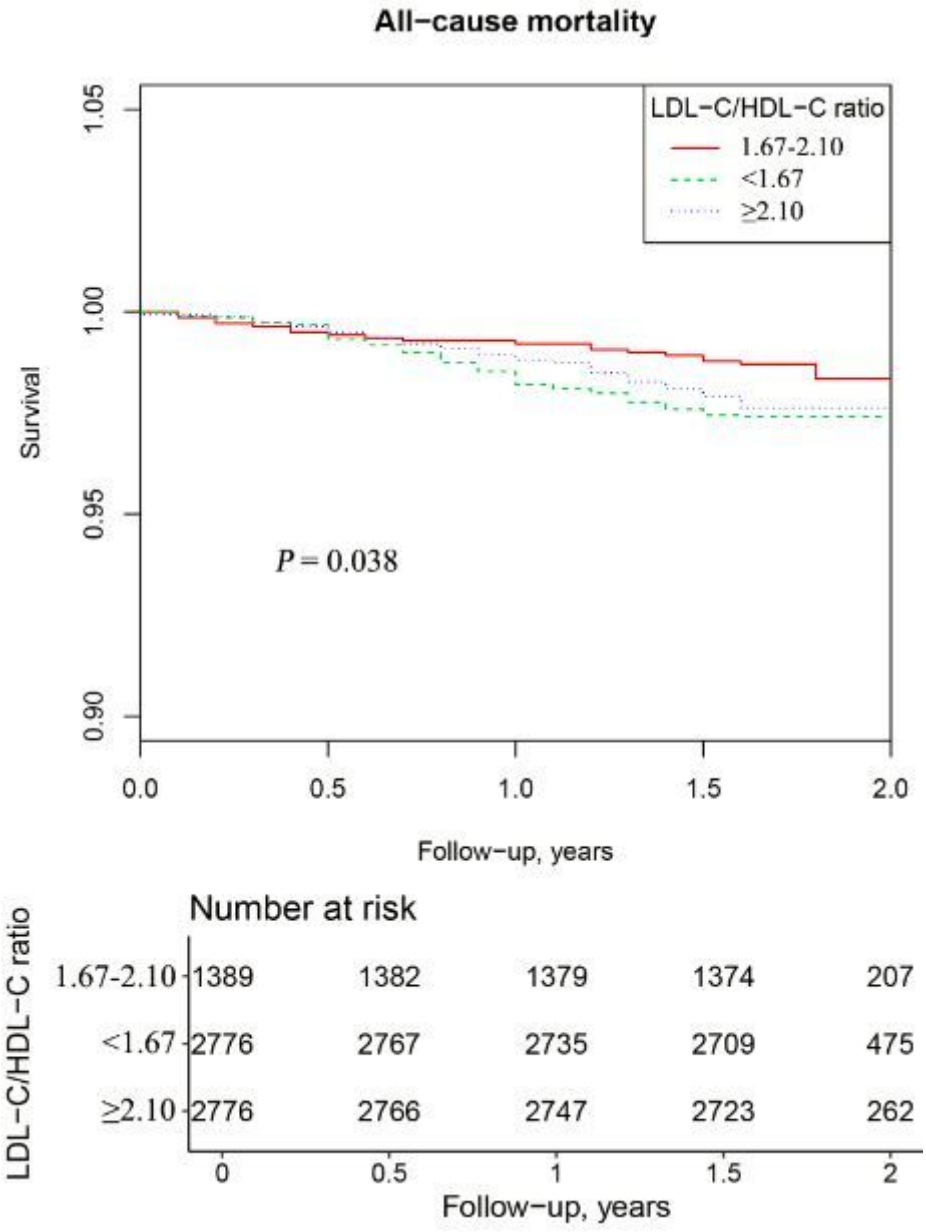



**Figure 3**

Kaplan–Meier survival curve estimates for all-cause mortality in the elderly hypertensive population.

# Supplementary Files

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