Journal of Inflammation Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

HDL Levels as a Novel Predictor of Long-Term Adverse Outcomes in Patients with Heart Failure: A Retrospective Cohort Study

Aihaidan Abudouwayiti, Sureya Yisimayili, Ruzeguli Tuersun, Salamaiti Aimaier, Didaer Yisha, Xing Yan Zhang, Ying-Ying Zheng*, Ailiman Mahemuti*

The First Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Ying-Ying Zheng; Ailiman Mahemuti, Cardiovascular Department of The First Affiliated Hospital of Xinjiang Medical University, 137 Carp Road, Xinshi District, Urumqi, 830054, Xinjiang, People's Republic of China, Tel +86-15214804944; +86-13639970300, Email zhengying527@163.com; xinjiangailiman@163.com

Background: The role of high-density lipoprotein cholesterol (HDL-C) in heart failure (HF) outcomes is contentious. We aimed to assess HDL-C's prognostic value in HF patients.

Methods: In this retrospective cohort study (2012–2022) at the First Affiliated Hospital of Xinjiang Medical University, we analyzed 4442 patients, categorized by HDL-C quartiles. We applied the Cox proportional hazards model to assess survival and report hazard ratios (HR) with 95% confidence intervals (CI).

Results: Over a decade, we recorded 1354 fatalities (42.3%) and 820 readmissions. The third HDL-C quartile (0.93–1.14 mmol/L) showed the lowest mortality rates, with reduced risks in the second and third quartiles compared to the first (Q2 HR=0.809, 95% CI 0.590–1.109; Q3 HR=0.794, 95% CI 0.564–1.118). The fourth quartile presented a lower mortality risk compared to the first (Q4 HR=0.887, 95% CI 0.693–1.134). A significant correlation existed between HDL-C levels and cardiovascular risk (HR=0.85, 95% CI 0.75–0.96, $p<0.01$).

Conclusion: HDL-C levels exhibit a complex association with mortality in HF, indicating the importance of HDL-C in HF prognosis and the need for tailored management strategies.

Keywords: high-density lipoprotein cholesterol, heart failure, death, readmission, cardiovascular disease

Introduction

Cardiovascular disease (CVD) is the leading cause of death globally, with Heart Failure (HF) emerging as a significant terminal event within this spectrum.[1] HF is a complex and treacherous syndrome, marked by elevated illness and mortality rates, diminished daily functioning and life satisfaction, and imposing a considerable economic burden on healthcare systems.

Geographical differences shape the epidemiology of HF. While it seems to have plateaued or may be declining in developed countries, an aging population, advancements in coronary artery disease interventions, and the use of life-extending treatments have contributed to a global increase in HF cases.[2] An analysis of medical insurance data from 50 million urban workers in China suggests a substantial HF patient population of 12.05 million, with an annual rise of approximately 2.97 million new patients.[3] The Chinese Heart Failure Patient Registration Study (China-HF) reports a 4.1% mortality rate among hospitalized HF patients,[4] highlighting the strain HF places on China's public health system and the urgent need for prevention strategies.

Effective strategies include the early identification of at-risk populations and timely interventions for modifiable risk factors, which are crucial for slowing HF progression, improving patient longevity, and reducing the incidence, severity, and mortality rates associated with HF.

Received: 26 July 2024
Accepted: 31 August 2024
Published: 10 September 2024

A well-established body of evidence links blood lipoproteins to HF onset. High-density lipoprotein particles (HDL-P) in the bloodstream are known to influence processes such as atherosclerosis, inflammation, and endothelial health, all of which are integral to HF pathogenesis. HDL cholesterol (HDL-C) has long been recognized for its cardioprotective potential, with numerous epidemiological studies showing that each 1 mg/dL increase in HDL-C levels corresponds to a 2 to 3 percentage point decrease in cardiovascular mortality rates.[5–10]

However, recent research in epidemiology and genetics indicates that HDL-C levels may not uniformly predict heart-related health issues in every case.[11–13] The precise mechanisms by which HDL-C is associated with different cardiovascular events remain incompletely understood, particularly for high-risk individuals such as HF patients. Our review focuses on a cohort of 4442 individuals diagnosed with HF, with long-term monitoring to understand how HDL-C levels are related to disease progression and treatment outcomes.

Methods

Methodological Approach and Participant Selection

We conducted a comprehensive review of medical records from 4442 individuals hospitalized for HF at the First Affiliated Hospital of Xinjiang Medical University, covering a period of ten years from July 2012. Our study, a substantial retrospective cohort analysis, included patients who met the established HF diagnostic criteria[14] and had complete clinical records. The study adhered to the Declaration of Helsinki, and the research protocol was approved by the hospital's Ethics Committee (ethics number 202207–019). Given the study's retrospective nature, informed consent from participants was waived, as per the Ethics Committee's approval. Additional study design details can be found under the identifier NCT06092658 on the ClinicalTrials.gov registry. Participants were included if they were 18 years or older and fulfilled the HF diagnostic standards outlined in the 2018 Chinese Guidelines for the Diagnosis and Treatment of Heart Failure.[14] Participants had to have a minimum HF diagnosis duration of 3 months to be eligible for the study. Informed consent was required for participant enrollment. We excluded individuals with late-stage cancers, significant organ impairment, immune system disorders, and blood-related conditions, as well as those with a familial predisposition to psychiatric disorders or a history of recent (within three months) surgical intervention or severe injury. After applying these criteria, the study enrolled 3203 individuals with available HDL-C measurements. The standard flow chart for discharge is depicted in Figure 1.

Gathering Clinical Information and Establishing Outcome Measures

We compiled a comprehensive dataset encompassing demographic details, cardiovascular risk factors, and laboratory values from all enrolled patients, including hematologic and chemical blood tests. Noted risk factors included sex, age, chronic conditions such as hypertension and diabetes, and details of pharmaceutical interventions. Coronary heart disease (CHD) was classified according to the American Heart Association criteria, based on a confirmed diagnosis through prior angiographic evidence. Hypertension was identified in participants with a recorded medical history and ongoing anti-hypertensive therapy or consistent elevated blood pressure recordings (≥140/90 mmHg) on multiple visits.[15] Diabetes was defined by a documented diagnosis and therapy with blood sugar-lowering medications, confirmed by elevated blood glucose thresholds: a fasting measurement >7.1 mmol/L and a postprandial level ≥11.1 mmol/L two hours after meals.[16]

For HDL-C level measurement, participants were required to fast for 6 to 9 hours prior to the procedure. Venous blood was then drawn and analyzed using enzymatic assays with magnesium phosphodiesterase and a method combining rapid centrifugation with targeted precipitation.

For HDL-C Level Measurement

To ensure accurate measurement of high-density lipoprotein cholesterol (HDL-C) levels, participants were required to fast for 6 to 9 hours prior to the blood draw. Venous blood samples were collected in a standardized procedure and processed using the phosphodiesterase magnesium enzyme method, which facilitates the separation of HDL particles through a combination of rapid centrifugation and targeted precipitation techniques.The HDL-C levels were measured using the I2000 automated chemiluminescence immunoassay analyzer (Abbott Laboratories, USA), a device known for

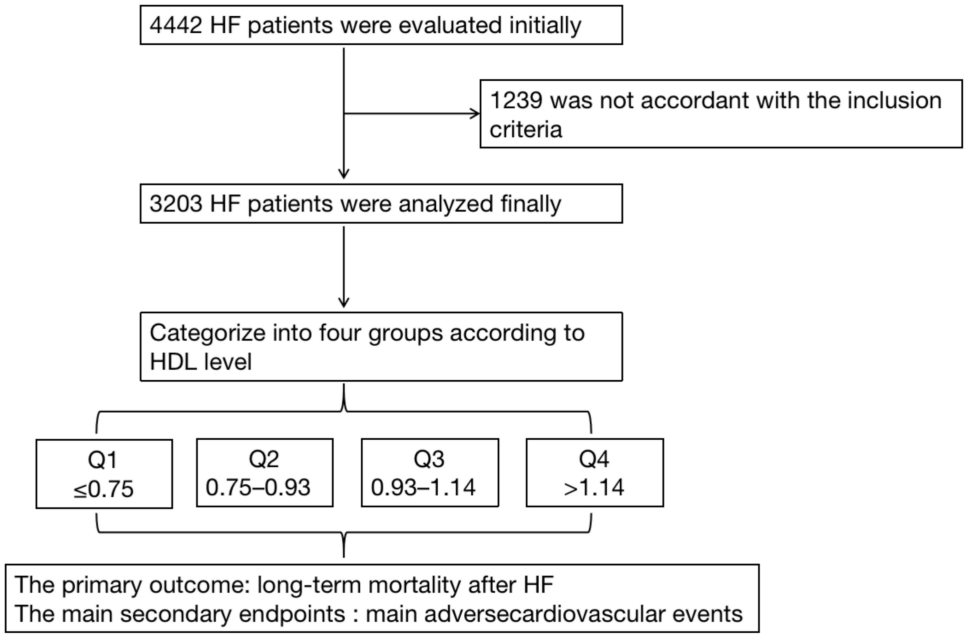

Figure 1 Flowchart depicting the patient selection process for the study on long-term mortality and main adverse cardiovascular events in heart failure (HF) patients categorized by high-density lipoprotein cholesterol (HDL-C) levels.

its precision and reliability in clinical chemistry testing. The detection kit, procured from Fujian New Continent Biotechnology Co., Ltd., was utilized according to the manufacturer's instructions to ensure the accuracy of the results.It is important to note that the specific testing procedure should adhere strictly to the guidelines provided in the reagent kit's instruction manual. The reagent kit, which includes quality control serum or standards, was used to perform quality control measures throughout the testing process, ensuring the reliability and consistency of our measurements.

Follow-Up

This retrospective cohort study tracked individuals diagnosed with HF, initiating contact at the study's outset and maintaining it at 6-month intervals up to 36 months, with additional assessments as required. The study aimed to monitor patients for at least one year, focusing on the incidence of significant cardiovascular and cerebrovascular events and the likelihood of hospital readmission. Data collected during these intervals were systematically submitted for analysis, essential for ongoing patient surveillance post-discharge and for identifying and monitoring adverse medical events. Comprehensive follow-up was ensured using outpatient consultations, telecommunication, and alternative contact methods until a critical event occurred or the study concluded. The study duration ranged from a median of 22.75 months, with an interquartile range of 12.37 to 47.11 months, and was designed to assess all-cause mortality (ACM).

Statistical Analysis

Data analyses were performed using SPSS 26.0. Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are expressed as numbers (percentages). The normality of continuous variable distributions was assessed with the Kolmogorov–Smirnov test. Parametric attributes were analyzed using one-way ANOVA, and non-parametric attributes were evaluated with the Kruskal–Wallis test. Categorical data were analyzed using the chi-square (χ^2) test. Statistical significance was set at $P < 0.05$. For continuous variables, the specific statistical test applied—either one-way ANOVA or the non-parametric equivalent—is indicated by the χ^2/F/H value column. The rank sum test was used for non-parametric data. The term "n" refers to the number of participants in each quartile group.

The Cox proportional hazards model was applied in both univariate and multivariate settings to identify determinants associated with ACM. In the univariate analysis, potential predictors were assessed, and variables found to be statistically significant ($P < 0.05$) were included in the multivariate model for further analysis. Hazard ratios (HR) and 95%

confidence intervals (CI) were calculated to quantify the associations. The Kaplan-Meier method was used to estimate survival probabilities for ACM, and the Log rank test was applied to compare survival curves between groups. Significance was set at $P < 0.05$.

Results

Baseline Characteristics Across Four HDL-C Categories

Enrolling a total of 3203 HF patients, our study comprised 2071 males (64.7%) and 1132 females (35.5%), with an average age of 64.18 ± 13.69 years. The follow-up duration for participants ranged from 1 to 10 years. Patients were categorized into quartiles based on plasma HDL-C levels: Q1 ≤ 0.75 mmol/L, Q2 from 0.76 to 0.93 mmol/L, Q3 from 0.94 to 1.14 mmol/L, and Q4 > 1.14 mmol/L.Comprehensive data encompassing clinical, echocardiographic, and laboratory findings for these participants are detailed in Table 1.

Table 2 presents the participants' baseline characteristics, laboratory parameters, and diagnostic indicators in a clear and logical manner. One-way ANOVA was used to identify significant inter-quartile differences among variables. There were statistically significant differences in age, HDL-C, Low-Density Lipoprotein Cholesterol (LDL-C), total cholesterol, triglycerides, hemoglobin, apolipoprotein AI (Apo AI), apolipoprotein B (Apo B), C-reactive protein (CRP), total bilirubin, albumin/globulin ratio (A/G ratio), and left ventricular ejection fraction (LVEF) (all $P < 0.05$). Significant differences were also found in the medical histories of gender, coronary heart disease, hypertension, diabetes, and chronic obstructive pulmonary disease (COPD) by chi-square tests (all $P < 0.001$). The rank sum test revealed statistically significant differences for creatinine and N-terminal pro-brain natriuretic peptide (NT-proBNP) ($P < 0.05$).

Table 1 Clinical and Laboratory Characteristics

Parameters	Total(N = 3203)
Age, y	64.18 ± 13.69
Male Sex, n (%)	2,071 (64.7%)
HDL-cholesterol, mmol/L	3.67±1.13
LDL-cholesterol, mmol/L	2.36±0.92
TC, mmol/L	3.67±1.13
Triglycerides, mmol/L	1.75±2.35
Hb,g/L	130.47±24.49
CRP, mg/L	30.19±27.68
Creatinine, μmol/L	69.84(68.42,75.25)
Total Bilirubin, μmol/L	21.53±26.00
A/G ratio	1.34±0.39
Apo AI, g/L	0.73±0.19
Apo B, g/L	0.73±0.26
CHD[n (%)]	329(48.0%)
Hypertension[n (%)]	276(40.2%)
DM[n (%)]	186(27.1%)
COPD[n (%)]	55(8.0%)
LVEF%	46.69±12.69

(*Continued*)

Table 1 (Continued).

Parameters	Total(N = 3203)
NT-proBNP, ng/L	1366.06(1274.95,1457.17)
HDL quartiles (mmol/L)	
Q1 (≤ 0.75)	686(21.42%)
Q2 (0.76–0.93)	860(26.85%)
Q3 (0.94 −1.14)	853(26.63%)
Q4 (> 1.14)	804(25.10%)

Notes: Data are presented as mean ± standard deviation (SD) for continuous variables and number (percentage) for categorical variables.n, number of participants in each quartile group.Statistical tests used: One-way ANOVA for continuous variables, chi-square tests for categorical variables, and rank sum tests for non-parametric data.

Abbreviations: HDL-Cholesterol: High-Density Lipoprotein Cholesterol; LDL-Cholesterol: Low-Density Lipoprotein Cholesterol; TC:total cholesterol; Hb:hemoglobin; CRP:C-reactive protein, A/G ratio, albumin/globulin ratio; Apo AI, apolipoprotein AI; po B, apolipoprotein B; CHD, coronary heart disease; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction;NT-proBNP:N-terminal pro-brain natriuretic peptide.

Table 2 Baseline Characteristics and Laboratory Parameters by HDL-Cholesterol Quartiles

Parameter	Q1 n=686	Q2 n=860	Q3 n=853	Q4 n=804	F/χ^2/H value	*P* value
Baseline Characteristics						
Age, y	62.05±14.02	63.02±13.87	64.38±13.40	67.04±13.02	19.75	**<0.001**
Male Sex, n (%)	479(69.8%)	610(70.9%)	550(64.5%)	432(53.7%)	64.84	**<0.001**
Biochemical Parameters						
HDL-cholesterol,mmol/L	0.58±0.12	0.82±0.05	1.02±0.06	1.40±0.31	21.56	**<0.001**
LDL-cholesterol, mmol/L	1.91±0.74	2.33±0.84	2.47±0.90	2.68±0.99	99.85	**<0.001**
TC, mmol/L	2.97±0.94	3.58±1.02	3.81±1.04	4.22±1.15	182.68	**<0.001**
Triglycerides, mmol/L	1.96 ±3.09	1.92±2.63	1.67±1.99	1.49±1.44	6.79	**<0.001**
Uric acid, μmol/L	503.38 (481.26, 525.49)	501.03 (464.66, 537.39)	490.48 (452.73, 528.24)	478.01 (437.24, 518.78)	0.39	0.760
Hematological Parameters						
WBC, $*10^9$/L	9.55±8.65	8.81±8.03	8.94±9.69	8.57±7.73	1.65	0.176
Hb,g/L	124.87±28.66	132.83±26.10	133.64±25.59	130.47±24.49	16.37	**<0.001**
PLT,$*10^9$/L	229.52±116.33	233.73±90.47	228.80±87.43	229.02±92.62	0.475	0.700
CRP, mg/L	38.98±36.86	24.31±29.79	16.88±22.73	22.56±42.88	25.1	**<0.001**
Renal Function Parameters						
eGFR	74.50±29.47	77.82±25.88	77.51±24.18	75.24±25.99	1.27	0.285
Creatinine, μmol/L	72.59(62.31,82.87)	57.60(43.56,71.64)	63.57(62.09,65.05)	68.84(58.42,75.25)	38.84	**<0.001**
Liver Function Parameters						
Total Bilirubin, μmol/L	31.42±40.69	20.09±20.35	18.14±13.72	18.23±23.05	44.67	**<0.001**
Total protein, g/L	67.00±7.84	67.06±7.26	67.37±6.61	67.80±7.33	2.00	0.111
A/G ratio	1.34±0.39	1.46±0.42	1.51±0.38	1.50±0.35	31.52	**<0.001**
Apo AI, g/L	0.73±0.19	0.96±0.16	1.10±0.18	1.30±0.25	830.64	**<0.001**
Apo B, g/L	0.73±0.26	0.82±0.27	0.86±0.30	0.89±0.29	29.14	**<0.001**

(*Continued*)

Table 2 (Continued).

Parameter	Q1 n=686	Q2 n=860	Q3 n=853	Q4 n=804	F/χ^2/H value	*P* value
Cardiovascular Risk Factors						
CHD[n (%)]	329(48.0%)	345(40.1%)	361(42.3%)	375(46.6%)	12.88	**0.005**
Hypertension [n (%)]	276(40.2%)	475(55.2%)	481(56.4%)	451(56.1%)	53.31	**<0.001**
DM[n (%)]	186(27.1%)	255(29.7%)	228(26.7%)	166(20.6%)	18.57	**<0.001**
COPD [n (%)]	55(8.0%)	66(7.7%)	64(7.5%)	113(14.1%)	28.84	**<0.001**
Cardiac Function Parameters						
LVEF%	46.69±12.69	47.19±13.20	48.80±12.94	50.37±12.17	9.99	**<0.001**
NT-proBNP, ng/L	1366.06 (1274.95,1457.17)	1120.06 (1028.6,1211.46)	1029.47 (939.37,1119.59)	1038.23 (951.41,1125.05)	92.427	**<0.001**
Other Diagnostic Indicators						
Congenital heart disease [n (%)]	19(2.8%)	13(1.5%)	18(2.1%)	17(2.1%)	2.96	0.398
Valvular heart disease [n (%)]	147 (21.4%)	169 (19.7%)	190 (22.3%)	190 (23.6%)	4.08	0.253
Cardiomyopathies [n (%)]	115(16.8%)	119(13.8%)	134(15.7%)	106(13.2%)	4.96	0.175
Arrhythmia [n (%)]	281(41.0%)	379(44.1%)	396(46.4%)	389(48.4%)	9.22	0.027

Notes:*P*-value < 0.05 is considered statistically significant. Data are presented as mean ± standard deviation (SD) for continuous variables and number (percentage) for categorical variables.n, number of participants in each quartile group.Statistical tests used: One-way ANOVA for continuous variables, chi-square tests for categorical variables, and rank sum tests for non-parametric data. The specific test used for each variable is indicated by the χ^2/F/H value column.Covariates highlighted in bold indicate statistically significant differences across the HDL-Cholesterol quartiles.

Abbreviations: HDL-Cholesterol: High-Density Lipoprotein Cholesterol; LDL-Cholesterol: Low-Density Lipoprotein Cholesterol; TC:total cholesterol; WBC:white blood cell; Hb:hemoglobin; PLT:platelet; CRP:C-reactive protein, eGFR, estimated glomerular filtration rate; A/G ratio, albumin/globulin ratio; Apo AI, apolipoprotein AI; Apo B, apolipoprotein B; CHD, coronary heart disease; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction;NT-proBNP: N-terminal pro-brain natriuretic peptide.

The gender distribution across HDL-C quartiles showed an inverted U-shaped pattern for males and an ascending trend for females. Notably, individuals in higher HDL-C quartiles more frequently exhibited elevated levels in age, LDL-C, total cholesterol (TC), Apo AI, Apo B, A/G ratio, and LVEF.

Our cohort had a notably higher prevalence of male HF patients. However, no statistically significant differences were observed across the quartiles for uric acid, white blood cell and platelet counts, estimated glomerular filtration rate (eGFR), total protein, or the prevalence of certain health conditions such as congenital heart disease, valvular disease, myocardial disease, and arrhythmia ($P > 0.05$).

Drug therapy analysis revealed notable differences in medication usage among heart failure patients categorized by HDL cholesterol levels. β-blockers, Sodium-Glucose Transporter 2 (SGLT-2) inhibitors, Angiotensin-Converting Enzyme (ACE) inhibitors or Angiotensin Receptor Neprilysin Inhibitors (ARNI), and Mineralocorticoid Receptor Antagonist (MRA) each demonstrated significant prevalence, with all *P*-values < 0.001, indicating their importance in treatment protocols. In contrast, the prevalence of other drugs did not reach statistical relevance and is detailed in Table 3.

Comparison of Different Clinical Outcomes

In an extended follow-up spanning over a decade, there were 1354 all-cause fatalities, accounting for 42.3% of the cases, and readmission occurred in 820 instances, representing 28.7% of the cases. Table 4 presents a comparative analysis of the unfavorable outcomes across patient groups, with statistically significant differences observed in both all-cause mortality and readmission rates for each of the four groups (P < 0.05).

The ACM rate decreased from 55.4% in Group 1 to 36.5% in Group 2, and then rose to 39.6% in Group 4, with a significant difference between the two (*P*=0.000). Conversely, the readmission rate slightly increased from 24.3% in Group 1 to 31.0% in Group 2, with the last group at 30.6%, which also indicated significance (*P*=0.030). Analysis using spline functions revealed the continuous risk ratio of HDL-C in relation to mortality and readmission. The all-cause

Table 3 Distribution of Medications in Our Population

Parameter	Q1 n=686	Q2 n=860	Q3 n=853	Q4 n=804	χ^2or F value	*P* value
ACE inhibitor, n (%)	29(5.7%)	59(8.7%)	83(11.6%)	82(12.2%)	17.46	**0.001**
ARNI, n (%)	119(23.5%)	212(31.2%)	231(32.3%)	173(25.7%)	16.25	**0.001**
Diuretics, n (%)	61(12.0%)	84(12.4%)	80(11.2%)	72(10.7%)	1.08	0.783
MRA, n (%)	85(16.8%)	121(17.8%)	169(23.7%)	139(20.7%)	11.60	**0.009**
β-Blockers, n (%)	152(30.0%)	284(41.8%)	317(44.3%)	261(38.8%)	27.67	**<0.0001**
SGLT2 inhibitor, n (%)	26(5.1%)	73(10.8%)	52(7.3%)	30(4.5%)	23.95	**<0.0001**

Notes: The *P*-values were meticulously determined through chi-square tests, which scrutinized the distribution patterns of categorical variables. Notably, the covariates that are emboldened signify the presence of statistically significant disparities as they manifest across the stratified quartiles of HDL-Cholesterol.
Abbreviations: ACE: Angiotensin-Converting Enzyme; ARNI: Angiotensin Receptor Neprilysin Inhibitors; MRA: Mineralocorticoid Receptor Antagonist; SGLT-2: Sodium-Glucose Transporter 2; HDL: High-Density Lipoprotein.

Table 4 Clinical Outcomes Distribution Across HDL Cholesterol Levels

Parameter	Low HDL cholesterol, n=686	Medium1HDL cholesterol, n=860	Medium2 HDL cholesterol, n=853	High HDL cholesterol, n=804	χ^2 value	*P* value
Death[n (%)]	380(55.4%)	345(40.1%)	311(36.5%)	318(39.6%)	64.29	0.000
Readmission[n (%)]	143(24.3%)	216(28.1%)	241(31.0%)	220(30.6%)	8.97	0.030

Notes: "Parameter" indicates the type of clinical outcome being measured."Low HDL cholesterol" through "High HDL cholesterol" denote the respective groups based on HDL cholesterol levels."χ^2 value" and "*P* value" reflect the results of the chi-square test used to assess statistical differences between groups"n" represents the count of cases for each outcome within the group."%" signifies the percentage of cases relative to the group total.

mortality rate exhibited a U-shaped relationship with plasma HDL levels, whereas the readmission rate showed an inverted U-shaped correlation with plasma HDL concentration, as depicted in Figure 2A and B.

At the Q3 quartile of plasma HDL-C levels, all-cause mortality rates reach their nadir, while readmission rates peak. Utilizing the univariate Kaplan-Meier method and applying the Pairwise Log rank test, we delineated survival curves to represent these findings, as illustrated in Figure 3. The data indicate that Group Q1 exhibits the poorest cumulative

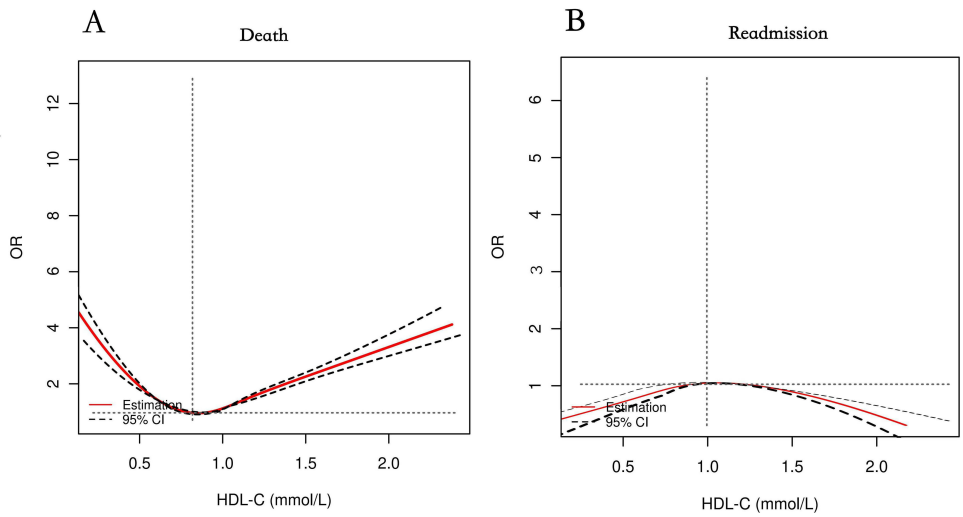

Figure 2 Association Between HDL-C Levels and Clinical Outcomes (**A**) This graph illustrates the U-shaped relationship between all-cause mortality rates and plasma HDL-C levels; (**B**) This graph demonstrates the inverted U-shaped correlation between readmission rates and plasma HDL-C concentration.

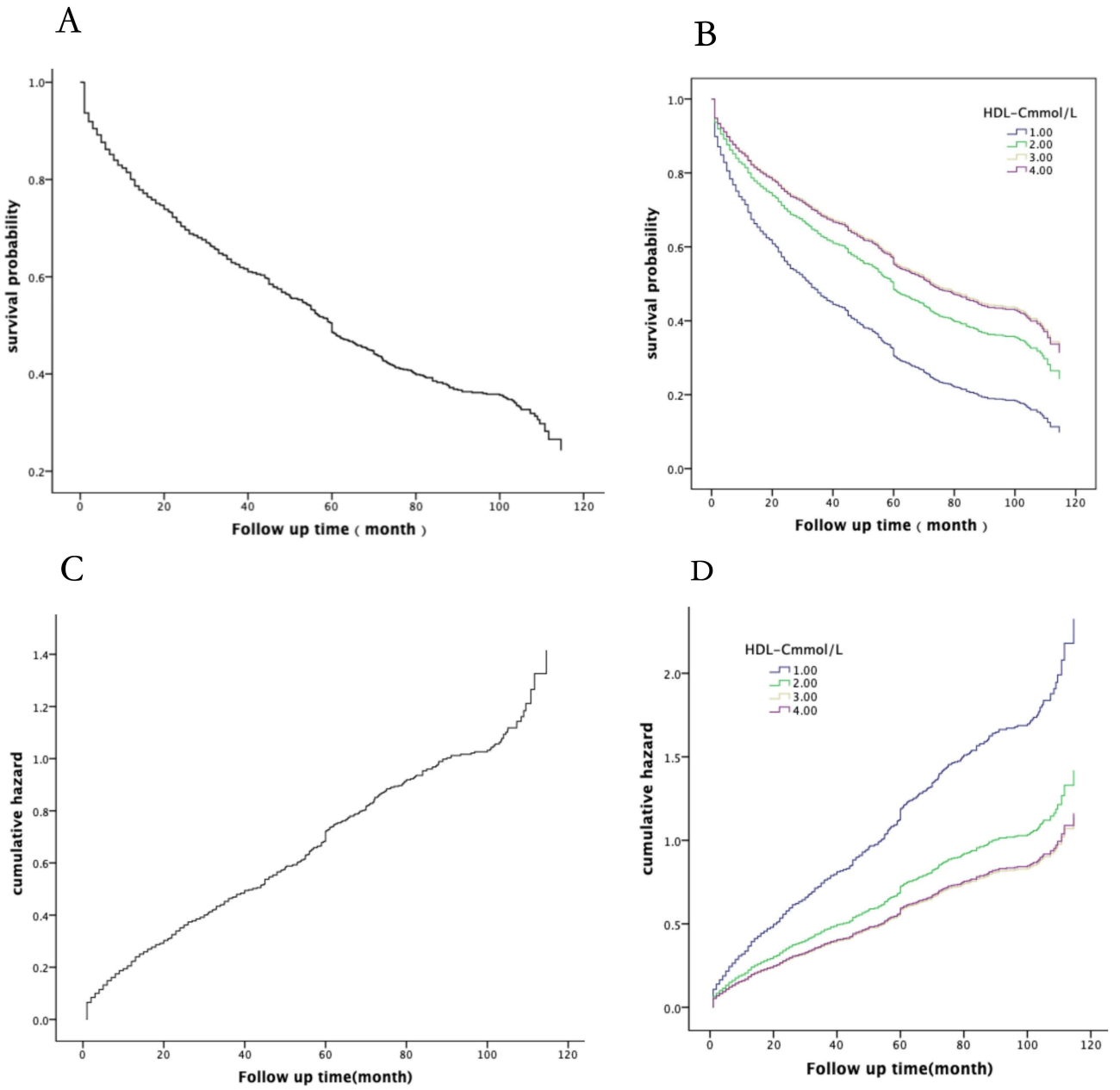

Figure 3 The relationship between HDL-C levels and cardiovascular risk is depicted through Kaplan-Meier survival curves, highlighting the non-linear association with all-cause mortality and readmission rates across different HDL-C quartiles.(**A**). Survival probabilities are assessed using the mean values of covariates. (**B**) Comparative survival analysis among Groups 1 to 4. (**C**) Risk evaluation using the mean values of covariates. (**D**) A specific risk comparison for Groups 1 to 4, emphasizing the U-shaped and inverted U-shaped relationships with HDL-C levels.The Kaplan-Meier method was employed to estimate the survival function, and the Pairwise Log rank test was used to statistically compare the survival curves between groups.The survival curves illustrate the variation in the probability of survival from Group Q1, with the lowest HDL-C levels, to Group Q4, with the highest HDL-C levels.The non-linear relationship between HDL-C levels and the likelihood of mortality is evident across all groups.

survival and the highest risk of death. In contrast, Groups Q3 and Q4 demonstrate the most favorable survival rates and the lowest risk of death, with their survival curves being nearly identical. These observations reinforce the non-linear correlation between HDL-C levels and the risk of mortality.

Analysis Outcomes from the COX Regression

In the univariate Cox regression analysis with HDL-C level as the independent variable and ACM as the endpoint, the reference was set to the HDL-C level group of 0.76–0.93 mmol/L, namely Group Q2. The hazard ratios (HR) for ACM

Table 5 Univariate Cox Regression Analysis of All-Cause Mortality in Heart Failure Patients by HDL-C Level Quartiles

	B	SE	Wald value	P	HR	95.0% CI
HDL-C (Q1)	0.836	0.093	80.838	<0.001	2.303	1.922–2.767
HDL-C (Q2)			100.920	<0.001	1	
HDL-C (Q3)	0.075	0.093	0.656	<0.001	1.078	0.899–1.292
HDL-C (Q4)	0.351	0.092	14.461	<0.001	1.420	1.185–1.702

Notes: "B" represents the regression coefficient."SE" stands for the standard error:"Wald value" is the statistical value from the Wald test. "*P*" denotes the *P*-value, indicating the level of statistical significance. ."HR" is the hazard ratio. ."95% CI" is the 95% confidence interval.The data in the table represent the risk of all-cause mortality in comparison to Quartile Q2 for other HDL-C level quartiles.

Table 6 Multivariate Cox Regression Analysis of All-Cause Mortality in Heart Failure Patients Adjusting for Age and Medication Use, and Other Factors

	B	SE	Wald value	P	HR	95.0% CI
HDL-C (Q1)	0.552	0.096	32.787	<0.001	1.738	1.438–2.099
HDL-C (Q2)			36.86	<0.001	1	
HDL-C (Q3)	0.112	0.098	1.308	<0.001	1.119	0.923–1.355
HDL-C (Q4)	0.238	0.097	6.007	<0.001	1.269	1.049–1.535
V_Age	0.03	0.003	121.836	<0.001	1.03	1.025–1.036
SGLT2 inhibitor	1.836	1.001	3.362	0.067	6.269	0.881–44.592
β-Blockers	4.932	0.708	48.469	<0.001	138.702	34.596–556.074
MAR	2.906	0.709	16.809	<0.001	18.289	4.558–73.378
ACEI	4.181	1.001	17.44	<0.001	65.446	9.197–465.721

Notes: "V_Age" indicates the variable for age as a continuous factor."SGLT2 inhibitor" refers to the use of Sodium-Glucose Transport Protein 2 inhibitors."β-Blockers" indicates the use of beta-blockers. ."MAR" stands for Mineralocorticoid Receptor Antagonists. "ACEI" refers to Angiotensin-Converting Enzyme Inhibitors.

for the remaining groups compared to Q2 were as follows: Group Q1 had an HR of 2.306 with a 95% CI of 1.922–2.767, Group Q3 had an HR of 1.078 with a 95% CI of 0.899–1.292, and Group Q4 had an HR of 1.420 with a 95% CI of 1.185–1.702, all with $P < 0.05$. Furthermore, after adjusting for confounding factors such as age and medication use in the multivariate Cox regression analysis, the results confirmed the persistence of this trend (all $P < 0.05$), as detailed in Tables 5 and 6.

Discussion

HF denotes a clinical condition where the heart's pumping capacity is compromised by diverse causes, leading to insufficient cardiac output to satisfy the body's tissues' metabolic requirements.[17] HF is a burgeoning health risk, marked by a rise in both occurrence and fatality rates. Cardiac decline is linked to processes such as inflammation, cell death, and tissue decay within the heart and blood vessel linings, impairing the heart's ability to contract and relax properly.[18] Stress from oxidative sources, the endoplasmic reticulum, and nitrosative influences triggers an inflammatory response that hastens the decline of heart cells and attracts immune cells, promoting changes in the heart's structure during HF.[19,20] Moreover, the overactivity of certain hormones like angiotensin II and leptin is implicated in the disruption of the heart's

pumping and filling cycles, playing a role in HF's progression.[21–23] Previously, HDL was considered a substitute biomarker for a new inflammatory state. However, the exact role of HDL in HF remains controversial. Population based cohort studies have shown a negative correlation between elevated HDL levels and major adverse cardiovascular events (MACE). Previous epidemiological studies have shown that for every 1 mg/dL increase in HDL levels, the risk of cardiovascular death decreases by approximately 2% to 3%.[5–10] This indicates that HDL has an impact on the structure and function of the heart.[24] In multivariate analysis, HDL is an independent predictor of ACM and MACE. Recent epidemiological and genetic investigations have shown that higher HDL levels may not necessarily be better. Recent studies in populations without cardiovascular disease have shown that very high HDL levels may be associated with an increased risk of death.[25,26] However, the precise interplay between HDL levels and the spectrum of cardiovascular events, particularly in the context of HF, remains an enigma. Evidence suggests that HDL can mitigate oxidative stress, endoplasmic reticulum stress, and nitrosative stress, thereby curbing the secretion and release of inflammatory cytokines such as interleukin-1 β (IL-1 β) and tumor necrosis factor α (TNF- α), which are instrumental in the pathogenesis of HF.[27,28] Conversely, other lines of research indicate that HDL may paradoxically induce oxidative stress and exacerbate pro-inflammatory cytokine secretion, contributing to endothelial and myocardial cell damage, and the progression of HF.[29,30] These contradictory results indicate heterogeneity in the role of high-density lipoprotein in HF regulation, but the exact impact remains to be elucidated.

In our study, we found that HDL levels are a new predictive indicator of poor prognosis in HF patients and exhibit an inverted U-shaped trend. Compared with the patient group with HDL levels between 0.75 and 1.14 mg/dL, the incidence of mortality was significantly higher in both the low concentration and high concentration groups. A study from Japan reported that the risk of atherosclerotic cardiovascular death was significantly higher in individuals with very high HDL levels.[31] In another study targeting the elderly, it was found that the risk ratio of all-cause mortality with HDL-C>90 mg/dL was driven by both cardiovascular and non cardiovascular mortality rates.[32] Liu et al analyzed a group of people with coronary heart disease and found that individuals with low (<30mg/dL) or extremely high (>80mg/dL) HDL-C levels had a higher risk of all-cause and cardiovascular death[33]; Voight et al found that both low and high levels of HDL-C are associated with an increased risk of ischemic and hemorrhagic stroke.[13]

It is worth noting that our study revealed a U-shaped correlation between HDL levels and the prognosis of heart failure, specifically in terms of mortality risk. This finding is consistent with the pattern observed in the risk of readmission. The U-shaped trend suggests that both extremely low and high HDL levels are associated with poorer outcomes for HF patients. However, the underlying mechanisms for this association remain unclear and warrant further exploration.

In this study, we evaluated the relationship between HDL and HF in a population of HF patients caused by various etiologies, including coronary heart disease, hypertension, cardiomyopathy, etc. Therefore, our observation addresses an important knowledge gap in this field.

In fact, in the current algorithms used to calculate cardiovascular risk in the general population, HDL levels are considered a protective factor, and at very high levels, this protective effect does not seem to hold. In fact, it may increase the risk. Before accepting this assumption, there are a few points to consider.

It is worth noting that the exact cutoff values used to define high HDL concentrations may vary in different studies, possibly due to differences in the study population or differences in specific measurements used to measure HDL levels.

During the research process, we recruited 4442 HF patients and conducted long-term follow-up to investigate the correlation between HDL and clinical prognosis. We divided the study population into four subgroups based on HDL levels (Q1: ≤ 0.75; Q2: 0.75–0.93; Q3: 0.93–1.14; Q4:>1.14), and found that the all-cause mortality rates were lower in the Q2 and Q3 HDL groups.

It is worth noting that after adjusting for potential confounding factors, we found significant differences in the incidence of cardiovascular events among the four groups of HF subjects divided by HDL levels. This discovery may suggest the existence of a U-shaped association. However, as previously studied by other investigators, the range of HDL values at the lowest point of the U-shaped curve is quite broad, covering the majority of the population.[25] The change in HDL-C levels at this lowest point does not seem to lead to any related risk changes. Considering the differences in the measurement methods used and the studied population, the high-risk inflection point of HDL-C seems to occur within the range of HDL levels>1.14 mmol/L, indicating that the research results tend to lean towards a U-curve rather than a V-curve.

A previous survey conducted in two groups of people did not draw a conclusion suggesting a U-shaped correlation curve between HDL-C levels and the incidence of ischemic heart disease, myocardial infarction, or ischemic stroke.[25] However, it was observed that lower levels of HDL corresponded to higher incidence of ischemic heart disease, myocardial infarction and ischemic stroke. However, HDL levels in males and females showed a plateau at around 3.22 and 4.23 mmol/L, respectively. When the HDL concentration exceeds these values, the risk will not be further reduced.[25] The differences between these data and our data may be due to differences in global cardiovascular risk among the study population: the general population and HF subjects, or cardiovascular events that also include end-stage HF requiring hospitalization, stable outpatient follow-up patients, coronary artery revascularization at first appearance, angina, hypertension, and atrial fibrillation, which are early evidence of impaired heart function. In either case, a U-shaped correlation was observed between HDL levels and the incidence of cardiovascular events, and the conclusion drawn was that high levels of HDL may lead to an increase in cardiovascular disease-related mortality.

Our observational studies cannot elucidate whether the association between high HDL levels and increased cardiovascular risk is causal, as Mendelian randomization studies do not support the causal role of HDL in cardiovascular events.[13,34] Therefore, we can only speculate on the possible pathogenesis. The observed association may be a phenomenon driven by pathological and physiological abnormalities, as well as immune, genetic, and epigenetic abnormalities, which increase cardiovascular risk in ways that we do not fully understand and confirm the complexity of the pathophysiology of HDL.[35–39] Individuals with extremely high levels of HDL-C may also alter the structure and function of HDL particles.[40,41] It can be assumed that in individuals with extremely high levels of HDL, the function of HDL may be impaired, making it unable to function properly and becoming harmful to the body.

Strengths and Limitations

One limitation of our research is that the number of individuals at the highest end of the HDL concentration spectrum is relatively small. However, the number of HF subjects included in our high HDL group did not prevent the possibility of a significant increase in cardiovascular risk after adjusting for confounding factors. The second limitation is the lack of collection of information on alcohol intake, which is precisely related to higher levels of HDL-C.[42,43] Due to our study conducted at the First Affiliated Hospital of Xinjiang Medical University, where the majority of participants were locals, our results may not be generalizable to other populations. Finally, we did not determine the cholesterol efflux capacity of all patients,[44] nor did we determine HDL apolipoprotein levels, which have recently been associated with mortality in cardiovascular disease patients.[45] We were unable to evaluate whether the use of lipid-lowering drugs affected our research results.

The main advantage of our research is that there is a large population recruited retrospectively, and extremely detailed information about individual clinical conditions is obtained through medical record review, follow-up, and other methods.

Conclusions

The present study has delineated a complex, non-linear relationship between HDL-C levels and clinical outcomes in patients with HF. Our findings indicate that both very low and very high HDL-C levels are associated with increased risks of all-cause mortality, challenging the traditional view of HDL-C as a universally beneficial biomarker.

Over a decade-long follow-up, we observed a U-shaped association between HDL-C levels and mortality, with the lowest risk observed in patients within the intermediate HDL-C range. This suggests that an optimal HDL-C level for HF patients may exist, and that both extreme deficiency and excess may be detrimental. The clinical implications of these findings underscore the need for a reevaluation of HDL-C management strategies in HF, potentially leading to more nuanced treatment approaches.

Moreover, our results highlight the importance of considering HDL-C levels as part of a comprehensive risk assessment in HF patients. The observed associations, while statistically significant, also call for further research to explore the underlying mechanisms linking HDL-C levels to adverse outcomes in HF. Future studies should aim to clarify the role of HDL-C in HF pathophysiology and identify the specific patient populations that may benefit from interventions targeting HDL-C levels.

In conclusion, our study provides valuable insights into the prognostic significance of HDL-C levels in HF and contributes to the growing body of evidence that suggests a reassessment of HDL-C's role in cardiovascular health. These findings may ultimately inform more personalized and effective treatment strategies for patients with HF.

What is Known About This Topic?

• Recently, several cohort studies reported that either extremely low or high HDL-C levels were associated with increased risk of mortality. However, the relation between HDL-C and HF remains unclear.

What Does This Paper Add?

• In the present study, a nonlinear association was identified between HDL-C levels and HF patients, with the lower risk at intermediate levels.

Data Sharing Statement

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Statement

The studies involving human participants were reviewed and approved by Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University. The patients/participants provided their written informed consent to participate in this study.

Acknowledgments

The authors appreciate the participating physicians who contributed patients to the project and helped with the clinical follow-up. All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; 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.All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Funding

This study received financial support from several distinguished sources. Funding was provided by the Natural Science Foundation of Xinjiang Uygur Autonomous Region, which is committed to advancing scientific research in the area. Additionally, we acknowledge the support of the Outstanding Youth Fund, grant number 2022D01E70, which recognizes and nurtures exceptional young scholars. The 2023 Tianchi Talent Science and Technology Innovation Leading Talent Project also contributed to this research, emphasizing the importance of innovation in the field. Lastly, we are grateful for the support from the Key Project of the Natural Science Foundation of Xinjiang Uygur Autonomous Region, with the project number 2021D01D17, which has significantly contributed to the success of our study.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: update From the GBD 2019 Study. *J Am Coll Cardiol*. 76;25:2982–3021.
2. Savarese G, Becher PM, Lund LH, et al. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res*. 2023;118(17):3272–3287. doi:10.1093/cvr/cvac013
3. Wang H, Chai K, Du M, et al. Prevalence and incidence of heart failure among urban patients in China: a national population-based analysis[J]. *Circ Heart Fail*. 2021;14(10):e008406.
4. Zhang Y, Zhang J, Butler J, et al. Contemporary epidemiology, management, and outcomes of patients hospitalized for heart failure in China: results from the China Heart Failure (China-HF) Registry[J]. *J Card Fail*. 2017;23(12):868–875.
5. Wilson PW, Abbott RD. Castelli WP High density lipoprotein cholesterol and mortality. The Framingham Heart Study. *Arteriosclerosis*. 1988;8:737–741. doi:10.1161/01.atv.8.6.737
6. Pekkanen J, Linn S, Heiss G, et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *N Engl J Med*. 1990;322:1700–1707. PubMed: 2342536. doi:10.1056/NEJM199006143222403
7. Sourlas A, Kosmas CE. Inheritance of high and low HDL: mechanisms and management. *Curr Opin Lipidol*. 2019;30:307–313. doi:10.1097/MOL.0000000000000610
8. Casula M, Colpani O, Xie S, Catapano AL, Baragetti A. HDL in atherosclerotic cardiovascular disease: in search of a role. *Cells*. 2021;10:1869. doi:10.3390/cells10081869
9. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. *Four Prospect American Stud Circul*. 1989;79:8–15. PubMed: 2642759. doi:10.1161/01.cir.79.1.8
10. Rader DJ, Hovingh GK. HDL and cardiovascular disease. *Lancet*. 2014;384:618–625. PubMed: 25131981. doi:10.1016/S0140-6736(14)61217-4
11. Silbernagel G, Schöttker B, Appelbaum S, et al. High-density lipoprotein cholesterol, coronary artery disease, and cardiovascular mortality. *Eur Heart J*. 2013;34:3563–3571. PubMed: 24014391. doi:10.1093/eurheartj/eht343
12. Angeloni E, Paneni F, Landmesser U, et al. Lack of protective role of HDL-C in patients with coronary artery disease undergoing elective coronary artery bypass grafting. *Eur Heart J*. 2013;34:3557–3562. PubMed: 23704708. doi:10.1093/eurheartj/eht163
13. Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet*. 2012;380:572–580. PubMed: 22607825. doi:10.1016/S0140-6736(12)60312-2
14. The Heart Failure Group of the Cardiovascular Branch of the Chinese Medical Association. the Heart Failure Professional Committee of the Chinese Medical Association, and the Editorial Committee of the Chinese Journal of Cardiovascular Disease Chinese Guidelines for Diagnosis and Treatment of Heart Failure 2018 [J. *Chin J Cardiovr Dis*. 2018;46(10):760–789. doi:10.3760/cma.j.issn.0253-3758.2018.10.04
15. Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology,American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. *J Am Soc Hypertens*. 2011;5(04):259–352.
16. Olafsdottir E, Andersson DK, Dedorsson I, Stefánsson E. The prevalence of retinopathy in subjects with and without type 2 diabetes mellitus. *Acta Ophthalmol*. 2014;92(02):133–137.
17. Investigators A-H. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365(24):2255–2267.
18. Schmederer Z, Rolim N, Bowen TS, OptimEx study group. Endothelial function is disturbed in a hypertensive diabetic animal model of HFpEF: moderate continuous vs. high intensity interval training. *Int J Cardiol*. 2018;273:147–154.
19. Wu KM. High-density lipoprotein ameliorates palmitic acid-induced lipotoxicity and oxidative dysfunction in H9c2 cardiomyoblast cells via ROS suppression. *Nutr Metab*. 2019;16:36.
20. Schiattarella GG, Altamirano F, Tong D, et al. Nitrosative stress drives heart failure with preserved ejection fraction. *Nature*. 2019;568(7752):351–356.
21. Kristensen SL, Mogensen UM, Jhund PS, et al. N-terminal pro-B-type natriuretic peptide levels for risk prediction in patients with heart failure and preserved ejection fraction according to atrial fibrillation status. *Circ Heart Fail*. 2019;12(3):e005766.
22. Schnorbach J. N-Terminal Pro Brain Natriuretic Peptide Eliminates the Prognostic Effect of Atrial Fibrillation in Patients with Chronic Heart Failure. ESC Heart Fail; 2019.
23. Patel VB, Zhong JC, Grant MB, Oudit GY. Role of the ACE2/angiotensin 1-7 axis of the renin-angiotensin system in heart failure. *Circ Res*. 2016;118(8):1313–1326.
24. Hunter WG, MG RW 3rd, Kelly JP, et al. High-density lipoprotein particle subfractions in heart failure with preserved or reduced ejection fraction. *J Am Coll Cardiol*. 2019;73(2):177–186.
25. Madsen CM, Varbo A, Nordestgaard BG. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. *Eur Heart J*. 2017;38:2478–2486.
26. Ko DT, Alter DA, Guo H, et al. High-density lipoprotein cholesterol and cause-specific mortality in individuals without previous cardiovascular conditions: the CANHEART Study. *J Am Coll Cardiol*. 2016;68:2073–2083.
27. Groenewegen A, Rutten FH, Mosterd A, et al. Epidemiology of heart failure. *Eur J Heart Fail*. 2020;22(8):1342–1356. doi:10.1002/ejhf.1858
28. Hsu JJ, Ziaeian B, Fonarow GC. Heart Failure With Mid-Range (Borderline) Ejection Fraction: clinical Implications and Future Directions. *Jacc-Heart Fail*. 2017;5(11):763–771. doi:10.1016/j.jchf.2017.06.013
29. Rauchhaus M, Clark AL, Doehner W, et al. The relationship between cholesterol and survival in patients with chronic heart failure. *J Am Coll Cardiol*. 2003;42(11):1933–1940. doi:10.1016/j.jacc.2003.07.016
30. Horwich TB, Hamilton MA, Maclellan WR, et al. Low serum total cholesterol is associated with marked increase in mortality in advanced heart failure. *J Card Fail*. 2002;8(4):216–224. doi:10.1054/jcaf.2002.0804216
31. Hirata A, Sugiyama D, Watanabe M, et al. Evidence for Cardiovascular Prevention from Observational Cohorts in Japan Research G. Association of extremely high levels of high-density lipoprotein cholesterol with cardiovascular mortality in a pooled analysis of 9 cohort studies including 43,407 individuals: the EPOCH-JAPAN study. *J Clin Lipidol*. 2018;12:674–684e5.

32. Li ZH, Lv YB, Zhong WF, et al. High-density lipoprotein cholesterol and all-cause and cause-specific mortality among the elderly. *J Clin Endocrinol Metab*. 2019;104:3370–3378.
33. Liu C, Dhindsa D, Almuwaqqat Z, et al. Association between high-density lipoprotein cholesterol levels and adverse cardiovascular outcomes in high-risk populations. *JAMA Cardiol*. 2022;7:672–680.
34. Holmes MV, Asselbergs FW, Palmer TM, et al. UCLEB consortium. Mendelian randomization of blood lipids for coronary heart disease. *Eur Heart J*. 2015;36:539–550.
35. Catapano AL, Pirillo A, Bonacina F, Norata GD. HDL in innate and adaptive immunity. *Cardiovasc Res*. 2014;103:372–383.
36. Lappegård KT, Kjellmo CA, Hovland A. High-density lipoprotein subfractions: much ado about nothing or clinically important? *Biomedicines*. 2021;9:836.
37. Romo EZ, Zivkovic AM. Glycosylation of HDL-associated proteins and its implications in cardiovascular disease diagnosis, metabolism and function. *Front Cardiovasc Med*. 2022;9:928566.
38. Novák J, Olejníčková V, Tkáčová N, Santulli G. Mechanistic role of MicroRNAs in coupling lipid metabolism and atherosclerosis. *Adv Exp Med Biol*. 2015;887:79–100.
39. Clément AA, Desgagné V, Légaré C, et al. HDL-enriched miR-30a-5p is associated with HDL-cholesterol levels and glucose metabolism in healthy men and women. *Epigenomics*. 2021;13:985–994.
40. Theilmeier G, Schmidt C, Herrmann J, et al. High-density lipoproteins and their constituent, sphingosine-1-phosphate, directly protect the heart against ischemia/reperfusion injury in vivo via the S1P3 lysophospholipid receptor. *Circulation*. 2006;114(13):1403–1409. doi:10.1161/CIRCULATIONAHA.105.607135
41. Frias MA, James RW, Gerber-Wicht C, et al. Native and reconstituted HDL activate Stat3 in ventricular cardiomyocytes via ERK1/2: role of sphingosine-1-phosphate. *Cardiovasc Res*. 2009;82(2):313–323. doi:10.1093/cvr/cvp024
42. Taylor AE, Lu F, Carslake D, et al. Exploring causal associations of alcohol with cardiovascular and metabolic risk factors in a Chinese population using Mendelian randomization analysis. *Sci Rep*. 2015;5:14005. doi:10.1038/srep14005
43. Salonen JT. Liver damage and protective effect of high density lipoprotein cholesterol. *BMJ*. 2003;327:1082–1083. PubMed: 14604929. doi:10.1136/bmj.327.7423.1082
44. Rohatgi A, Khera A, Berry JD, et al. HDL cholesterol efflux capacity and incident cardiovascular events. *N Engl J Med*. 2014;371:2383–2393. PubMed: 25404125. doi:10.1056/NEJMoa1409065
45. Natarajan P, Collier TS, Jin Z, et al. Association of an HDL apolipoproteomic score with coronary atherosclerosis and cardiovascular death. *J Am Coll Cardiol*. 2019;73:2135–2145. PubMed: 31047001. doi:10.1016/j.jacc.2019.01.073