BMJ Open

Relationship between the HDL-C/CRP ratio and all-cause mortality in patients with chronic heart failure: a retrospective analysis from Yunnan Province, China

Xiongyi Liuzhuang, Sirui Yang, Yunhong Yang, Wenyi Gu, Tao Shi, Chenggong Xu, Lixing Chen

To cite: Liuzhuang X, Yang S, Yang Y, *et al*. Relationship between the HDL-C/CRP ratio and all-cause mortality in patients with chronic heart failure: a retrospective analysis from Yunnan Province, China. *BMJ Open* 2025;**15**:e084099. doi:10.1136/bmjopen-2024-084099

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-084099).

XL and SY are joint first authors.

Received 09 January 2024
Accepted 22 January 2025

Department of Cardiology, Kunming Medical University First Affiliated Hospital, Kunming, Yunnan, China

Correspondence to
Dr Lixing Chen;
ydyyclx@163.com

ABSTRACT

Objective To clarify whether the high-density lipoprotein cholesterol/C reactive protein (HDL-C/CRP) ratio can be used as a new prognosticator of all-cause mortality in patients with chronic heart failure (CHF) (New York Heart Association (NYHA) cardiac class III/IV).

Design Retrospective study.

Background Several papers have revealed that HDL-C and CRP can act as anti-inflammatory and pro-inflammatory factors, respectively, to affect disease progression in patients with heart failure, and the balance of the two has been shown to affect the prognosis of patients with heart failure with preserved ejection fraction (HFpEF), but none of the above studies involved patients with the more severe forms of heart failure with mildly reduced ejection fraction and heart failure with reduced ejection fraction; therefore, the present study is to extend the balance of HDL-C and CRP to the whole range of types of patients CHF to further confirm its importance.

Setting This study is from a single centre in Yunnan Province, China.

Participants After excluding ineligible patients, we finally included 1192 patients with CHF from January 2017 to October 2021.

Primary and secondary measures The primary outcome was all-cause mortality in patients with CHF between January 2017 and October 2021. No secondary outcome measures were performed.

Results All patients were divided into four groups according to the quartiles of the HDL-C/CRP ratio. Using the Kaplan-Meier analysis, the risk of all-cause mortality was always the highest for Q1 (HDL-C/CRP<0.395) and the lowest for group Q4 (HDL-C/CRP≥3.4163). Cox univariate and multivariate regression analyses showed that HDL-C/CRP was consistently an independent risk factor for death from CHF. Based on the receiver operating characteristic curve, the area under the curve for HDL-C/CRP was 0.7254 (p<0.001), with a sensitivity of 65.5% and a specificity of 69.6%.

Conclusions The HDL-C/CRP ratio is an independent prognostic indicator of all-cause mortality in patients with CHF in NYHA cardiac function class III/IV, which has good specificity and sensitivity. Patients with lower levels of the HDL-C/CRP ratio are at a greater risk of death than patients with higher levels of the HDL-C/CRP ratio.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Sufficient sample size.
⇒ Provides a new effective prognostic indicator for patients with chronic heart failure through retrospective analysis.
⇒ This study covered only patients with chronic heart failure who had a New York Heart Association classification of class III or IV.
⇒ The anti-inflammatory marker chosen for this study was high-density lipoprotein cholesterol rather than ApoA-I, which has shown better prognostic performance in epidemiological studies.

INTRODUCTION

Heart failure (HF) is an advanced manifestation of various cardiovascular diseases and portends poor prognosis. With the ageing of the population, the deterioration of the cardiovascular risk and the improvement in the survival rate of patients with acute cardiovascular diseases, the prevalence of HF is increasing.[1] HF was classified into three ejection fraction (EF) categories based on the left ventricular ejection fraction (LVEF), namely, HF with reduced EF (HFrEF), HF with mildly reduced EF (HFmrEF) and HF with preserved EF (HFpEF), according to the EF ranges of ≤40%, 41–49% and ≥50%, respectively.[2] The standardised HF prevalence rate in China was 275 per 100 000 person-years for those ≥25 years of age and 1.38% for those ≥35 years of age.[3] Among patients with chronic heart failure (CHF) in China from 2012 to 2015, 40% had HFrEF, 23% had HFmrEF, and 36% had HFpEF.[3]

Multiple reports have now confirmed that inflammation is a driver of HF, and comorbidity-driven systemic microvascular inflammation is thought to play a key role in the pathogenesis of changes in myocardial structure and function changes.[4–6] The current common pro-inflammatory marker is C reactive protein (CRP), while the anti-inflammatory marker is high-density lipoprotein cholesterol (HDL-C). In patients with coronary artery disease, higher levels of CRP are thought to be associated with poor vascular prognosis, future hospitalisation for hypertension and higher left ventricular filling pressures,[7–9] whereas HDL-C removes deposited cholesterol from macrophages and reduces inflammation.[10] Moreover, Horio *et al* revealed that HDL-C is positively associated with left ventricular diastolic function in patients with essential hypertension on treatment.[11] In further studies, the impact of the HDL-C/CRP ratio (HDL-C mmol/L/CRP mg/dL) has been suggested on the prognosis of HFpEF,[12] but there has not been any relevant research on the HDL-C/CRP ratio in patients with HFmrEF and HFrEF. Therefore, the purpose of our study was to evaluate the clinical prognostic impact of HDL-C/CRP ratio in patients with worsening HF for different EFs.

METHODS

Study population and study design

This study included 1221 patients with a diagnosis of HF admitted to the First Affiliated Hospital of Kunming Medical University from January 2017 to October 2021,which had CHF (New York Heart Association (NYHA) class III or IV) with reduced EF (HFrEF, ie, LVEF≤40%) or preserved EF with mild reduced EF (HFpEF + HFmrEF, ie, left LVEF>40%) and a brain natriuretic peptide (BNP) level of ≥500 pg/mL. The exclusion criteria for the study population were (1) died in the hospital, (2) missing data (blood test results, echocardiographic data), (3) chronic dialysis therapy and (4) no follow-up data. Finally, 1192 patients with CHF were enrolled in the study. Of these patients, 522 had HFrEF (ie, LVEF<40%) and 670 had HFpEF or HFmrEF (HFpEF + HFmrEF; ie, LVEF 40%). After a median follow-up of 750 days, 562 patients (47.1%) died.

The baseline data were retrospectively analysed by clinical follow-up of the above patients with all-cause mortality as the outcome in order to clarify whether HDL-C/CRP ratio is an independent risk factor for all-cause mortality in patients with CHF. Sample size was not estimated for this study, but rather covered baseline data and clinical follow-up outcomes for all 1192 patients with CHF enrolled between January 2017 and October 2021, which has the advantage of minimising selection bias; meanwhile, confounding bias in the study can be controlled for by identifying independent risk factors for patients with CHF by Cox regression analysis while determining that all independent risk factors are not intermediate variables between baseline and study outcome.

Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research.

Statistical analysis

Patients with CHF were divided into group 1 (Q1: HDL-C/CRP<0.3958), group 2 (Q2: HDL-C/CRP≥0.3958 to 1.2321), group 3 (Q3: HDL-C/CRP≥1.2321 to < 3.4163) and group 4 (Q4: HDL-C/CRP≥3.4163) based on the quartiles of HDL-C/CRP. All continuous variables are expressed as mean (SD) or median (25th to 75th percentile), as appropriate. The unpaired t-test was used to analyse comparisons between two groups or the Wilcoxon-Mann-Whitney test for continuous variables. χ^2 test was used for comparison of differences between groups for categorical variables, and Spearman correlation analysis was used to evaluate the correlation between the HDL-C/CRP ratio and all other baseline data. Study endpoints were estimated using Kaplan-Meier curves, and statistical significance was determined using the log-rank test. Univariate analysis was performed using a Cox proportional hazards regression model, and a p value<0.05 was considered to indicate statistical significance. Multivariate analyses using a Cox proportional hazards regression model for all-cause mortality were performed using the factors found to be significant in the univariate analysis. Adjusted HRs and 95% CIs were calculated. A multiple regression model was repeated for relevant parameters and the HDL-C/CRP ratio, with a p value<0.05 considered to indicate statistical significance. To compare the prognostic ability of HDL-C/CRP, time-dependent receiver operating characteristic (ROC) curves and the corresponding area under the curve (AUC) were calculated.

SPSS V.29.0 software and RStudio were used for the statistical analysis. A p value<0.05 was considered to indicate statistical significance. Technical appendix, statistical code and data set are available from the Dryad repository.

RESULTS

Baseline patient characteristics

A total of 1192 patients with HF were included in the study after excluding lost visits and patients with missing data. The median age was 66.84 years, and 62.2% of the patients were male. We divided the patients into four groups according to the quartile of HDL-C/CRP: Q1 (HDL-C/CRP<0.3958), Q2 (HDL-C/CRP≥0.3958 to 1.2321), Q3 (HDL-C/CRP≥1.2321 to <3.4163) and Q4 (HDL-C/CRP≥3.4163). Among the four groups, there were statistically significant differences in NYHA functional class, HR, and laboratory parameters,which include white blood cell (WBC), neutrophil, lymphocyte, red blood cell (RBC), Hb, albumin, Fib, lgBNP, sodium, chlorine, ALT, AST, Cr, UA, GFR, Glu, total cholesterol (TC), HDL-C, LDL-C and CRP (p<0.05) (table 1).

Table 1 Baseline characteristics according to the quartile of the HDL-C/CRP ratio

	Total	HDL-C/CRP				P value
	(n=1192)	Q1 (n=297)	Q2 (n=300)	Q3 (n=296)	Q4 (n=299)	
Clinical demographics						
Age (years)	66.84±12.528	67.74±12.584	67.60±12.414	67.05±13.113	64.84±12.528	0.025
Male, n (%)	741 (62.2)	198 (66.7)	192 (64)	179 (60.5)	172 (57.5)	0.751
BMI (kg/m^2)	23.0157±3.81527	23.1244±3.68657	22.8627±3.73614	23.1497±3.85997	22.9288±3.98259	0.743
SBP (mm Hg)	122.15±22.963	119.19±22.789	123.35±23.395	124.68±24.863	121.37±22.533	0.762
DBP (mm Hg)	76.27±15.034	75.15±15.069	77.12±14.906	76.76±15.278	76.00±14.884	0.404
NYHA functional class IV, n (%)	444 (37.2)	134 (45.1)	116 (38.7)	115 (38.9)	79 (26.4)	<0.01
Medical history						
Smoke status, n (%)	408 (34.2)	121 (40.7)	101 (33.7)	95 (32.1)	94 (31.4)	0.571
Drink status, n (%)	200 (16.8)	58 (19.5)	44 (14.7)	44 (14.9)	55 (18.4)	0.257
DM, n (%)	339 (28.4)	91 (30.6)	97 (32.3)	86 (29.1)	65 (21.7)	0.014
Hypertension, n (%)	659 (55.3)	164 (55.2)	174 (58)	169 (57.1)	155 (51.8)	0.752
CAD, n (%)	618 (51.8)	166 (55.9)	153 (51)	162 (54.7)	140 (46.8)	0.591
AF, n (%)	405 (34)	97 (32.7)	107 (35.7)	108 (36.5)	97 (32.4)	0.388
Laboratory data						
WBC (10^9/L)	6.94 (5.55, 9.07)	8.06 (6.225, 10.87)	7.18 (5.66, 9.03)	6.655 (5.6025, 8.85)	6.2 (5.15, 7.83)	<0.01
Neutrophil (10^9/L)	4.535 (3.49, 6.5)	2.7 (4.075, 8.43)	4,79 (3.66, 6.75)	4.32 (3.47, 5.95)	3.94 (3.08, 5.28)	<0.01
Lymphocyte (10^9/L)	1.4940±0.75961	1.3606±0.70652	1.4646±0.79376	1.5572±0.72289	1.5934±0.74451	0.001
RBC (10^{12}/L)	4.5448±0.76719	4.4305±0.81242	4,5714±0.8103	4.5820±0.72089	4.5947±0.71125	0.03
Hb (g/L)	140 (124,154)	137 (118, 152)	140 (124, 155)	140.5 (125, 154)	142 (128, 154)	0.019
PLT (10^9/L)	191.5 (148, 243)	196 (145.5, 248)	186 (141, 243)	192.5 (150.25, 236.75)	197 (158, 241)	0.46
Albumin (g/dL)	36.678±4.5478	34.968±4.7287	36.127±4.3246	37.364±4.0162	38.251±4.4215	<0.01
Fib (g/L)	3.37 (2.71, 4.15)	3.98 (2.875, 5.075)	3.56 (2.89, 4.23)	3.19 (2.695, 3.8975)	3.03 (2.56, 3.72)	<0.01
lgBNP	3.1672±0.28086	3.23182±0.28967	3.1801±0.28341	3.1501±0.26879	3.1072±0.26754	<0.01
Potassium (mmol/L)	3.895 (3.55, 4.27)	3.86 (3.51,4.285)	3.88 (3.51, 4.3)	3.91 (3.5925, 4.27)	3.9 (3.62, 4.22)	0.768
Sodium (mmol/L)	141.4 (138.4, 143.9)	140.1 (136.7, 142.9)	141.1 (138.28, 143.8)	141.8 (139.1, 144.05)	142 (139.3, 144.6)	<0.01
Chlorine (mmol/L)	103.3 (99.8, 106.2)	101.8 (98.535, 104.8)	103.3 (99.1, 106.1)	103.7 (101.025, 106.3)	104.2 (101, 107.5)	<0.01
ALT (IU/L)	25.2 (16.7, 42.45)	29.9 (17.3, 64.6)	23.6 (16,40)	25.7 (16.9, 41.525)	23.7 (16.1, 35.7)	<0.01
AST (IU/L)	28.65 (20.125, 43.45)	31.5 (21.05, 68.5)	28 (19.8, 46.3)	28.4 (20.65, 41)	26.8 (20, 36.3)	<0.01
Cr (µmol/L)	103.55 (83.2, 134.1)	111.2 (86.4, 147.6)	108.7 (85.6, 138.8)	100.9 (83.25, 123.075)	96.1 (78.9, 124.9)	<0.01
UA (umol/L)	477.4 (372, 588.2)	516.55 (381.25, 623.075)	500.5 (391.4, 611.45)	461.8 (372.85, 49.4)	459,15 (354.925, 559.2)	<0.01
GFR (ml/min)	45.3951±19.51045	43.0840±20.71149	43.4195±19.17942	46.7125±20.17920	48.3599±17.41441	0.001
Glu (mmol/L)	5.03 (4.16, 6.4975)	5.2 (4.33, 7.4)	5.03 (4.16, 6.78)	4.87 (4.13, 6.2)	4.91 (4.13, 5.8)	0.002
TC (mmol/L)	3.6395±1.01525	3.3204±1.02594	3.6734±0.94135	3.6720±0.97587	3.8903±1.03700	<0.01
TG (mmol/L)	1.2721±0.71216	1.2967±0.68583	1.2895±0.89694	1.2742±0.61858	1.2284±0.60906	0.646
HDL-C (mmol/L)	0.9930±0.31990	0.8210±0.30009	0.9754±0.29459	1.0255±0.28714	1.2284±0.60906	<0.01
LDL-C (mmol/L)	2.2944±0.87584	2.1752±0.88416	2.3114±0.87072	2.2829±0.84209	2.4070±0.89406	0.014
CRP (mg/L)	7.5 (3.02, 21.95)	47.90 (28.14, 90.495)	13.15 (10.3425, 18.445)	5.11 (3.5, 6.4725)	1.63 (0.81, 2.5)	<0.01

Continued

Table 1 Continued

	Total		HDL-C/CRP			P value
Echocardiography						
HR (beat/min)	82 (70,97)	87 (74, 104)	83 (72,99)	80 (69.25, 95)	79 (67, 92)	<0.01
LVEF (%)	43 (33, 58)	43 (33, 56.5)	43 (31,57)	45 (34, 59)	44 (31, 60)	0.323
Pharmacotherapy						
Beta blockers, n (%)	832 (69.8)	205 (69)	222 (74)	199 (67.2)	211 (70.6)	0.428
ACEI/ARB/ARNI, n (%)	675 (56.6)	172 (57.9)	177 (59)	167 (56.4)	163 (54.5)	0.429
Diuretics, n (%)	942 (79)	256 (86.2)	242 (80.7)	227 (76.7)	217 (72.6)	0.206
Spironolactone, n (%)	943 (79.1)	256 (86.2)	242 (80.7)	227 (74.7)	236 (78.9)	0.511
Device therapy						
CRT-D, n (%)	116 (9.7)	25 (8.4)	33 (11)	26 (8.8)	32 (10.7)	0.009

The independent-sample t-test was used to compare differences in normally. The Mann-Whitney U rank-sum test was used to compare differences in non-normally. Between-group differences in categorical variables were compared using χ^2 test. p Values were calculated for comparisons of the HDL-C/CRP ratios among quartiles, and a p value<0.05 was considered to indicate statistical significance.
·Q1 (HDL-C/CRP<0.3958), Q2 (HDL-C/CRP≥0.3958 to 1.2321), Q3 (HDL-C/CRP≥1.2321 to <3.4163) and Q4 (HDL-C/CRP≥3.4163).
ACE-I, ACE inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; BNP, brain natriuretic peptide; CRP, C reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RBC, red blood cell; TC, total cholesterol; WBC, white blood cell.

All-cause mortality according to the HDL-C/CRP ratio

The median follow-up was 750 days. 522 patients (46.3%) had died. To test the prognostic value of the HDL-C/CRP ratio in patients with different types of HF, we implemented a Kaplan-Meier analysis. The Kaplan-Meier analysis revealed that the cumulative incidence of all-cause mortality was always highest for Q1 (HDL-C/CRP<0.395) and lowest for Q4 (HDL-C/CRP≥3.4163), regardless of sex (log-rank test, χ^2 2172.5), HFrEF (log-rank test, χ^2 283.83) or HFpEF+HFmrEF (log-rank test, χ^2 287.36) (p<0.0001) (figures 1–3).

Correlation analysis

Among all the patients, according to the Spearman correlation analysis (table 2), the HDL-C/CRP ratio was positively correlated with some laboratory parameters,which include lymphocyte count, RBC, Hb,

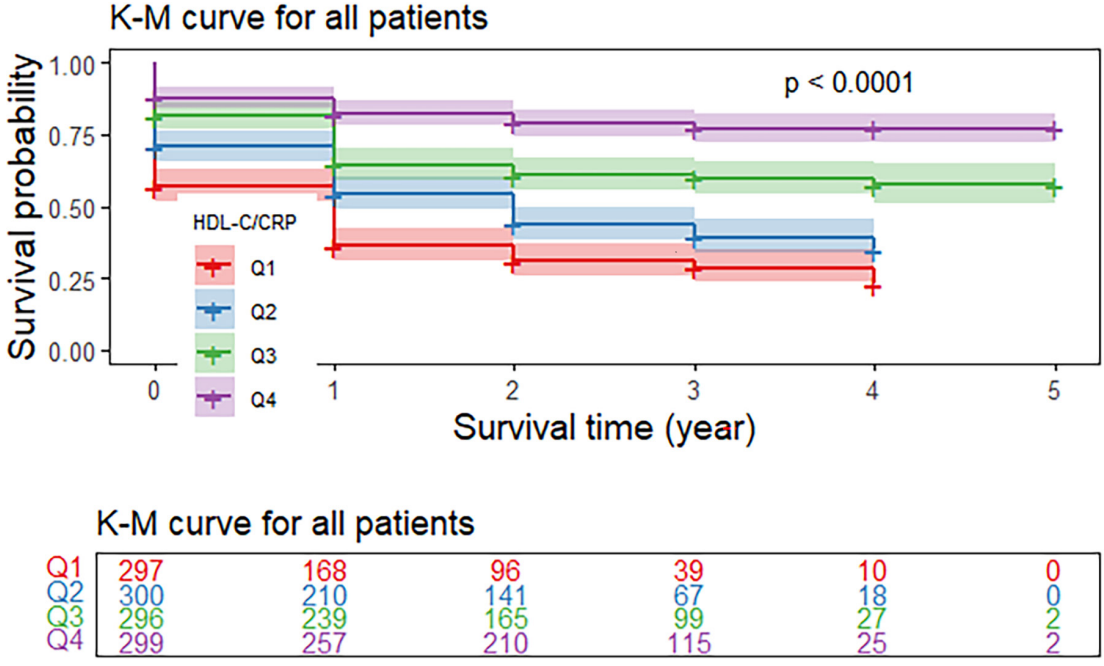

Figure 1 Kaplan-Meier (K-M) analysis of different high-density lipoprotein cholesterol/C reactive protein (HDL-C/CRP) ratios for all patients.

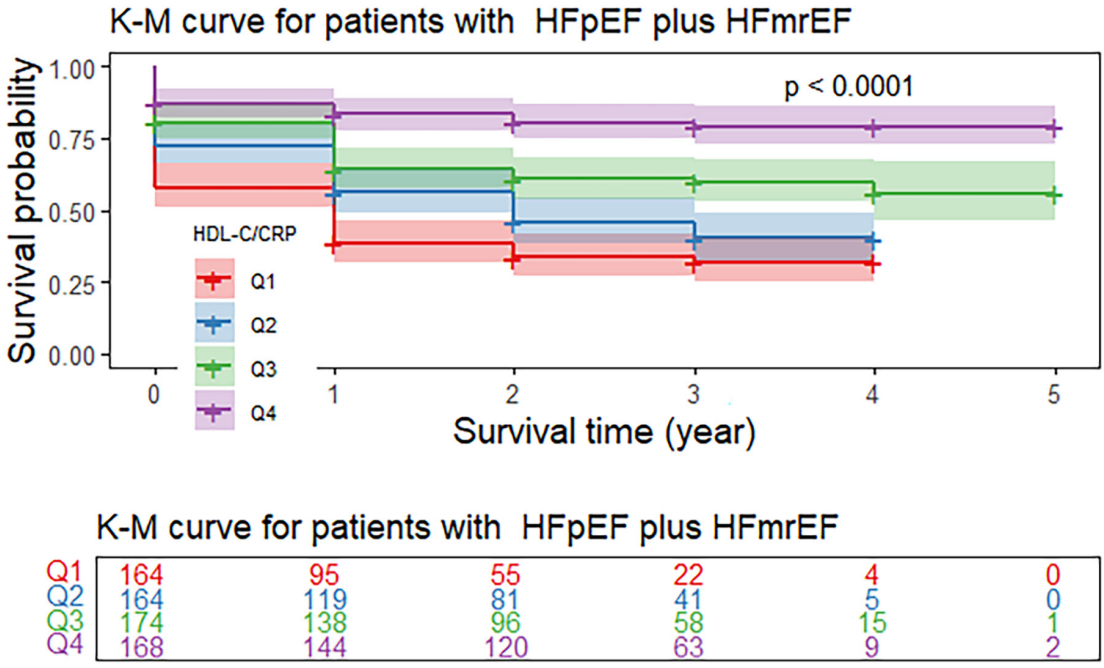

Figure 2 Kaplan-Meier (KM) analysis of different high-density lipoprotein cholesterol/C reactive protein (HDL-C/CRP) ratios for patients with heart failure with preserved ejection fraction (HFpEF) + HF with mildly reduced EF (HFmrEF).

albumin, serum sodium, serum chlorine and total cholesterol (TC) (p<0.01), but negatively correlated with other laboratory parameters,which include WBC, neutrophil, Fib, lgBNP, ALT, AST, Cr, Glu and TG (p<0.01).

HDL-C/CRP ratio is an independent risk factor for all-cause mortality

Univariate Cox regression analysis of baseline data for all patients with all-cause mortality as the endpoint showed that under different subgroups, age, body mass index, SBP, DBP, heart rate, NYHA functional class, and laboratory parameters,which include leukocytes, neutrophils, lymphocytes, erythrocytes, haemoglobin, albumin, lgBNP, sodium, chloride, ALT, AST, Cr, UA, GFR, TC, LDL-C, HDL-C, CRP, HDL-C/CRP were independent risk factors for all-cause mortality (table 3).

Further, age, vital signs and some laboratory parameters were selected among the above independent risk factors,

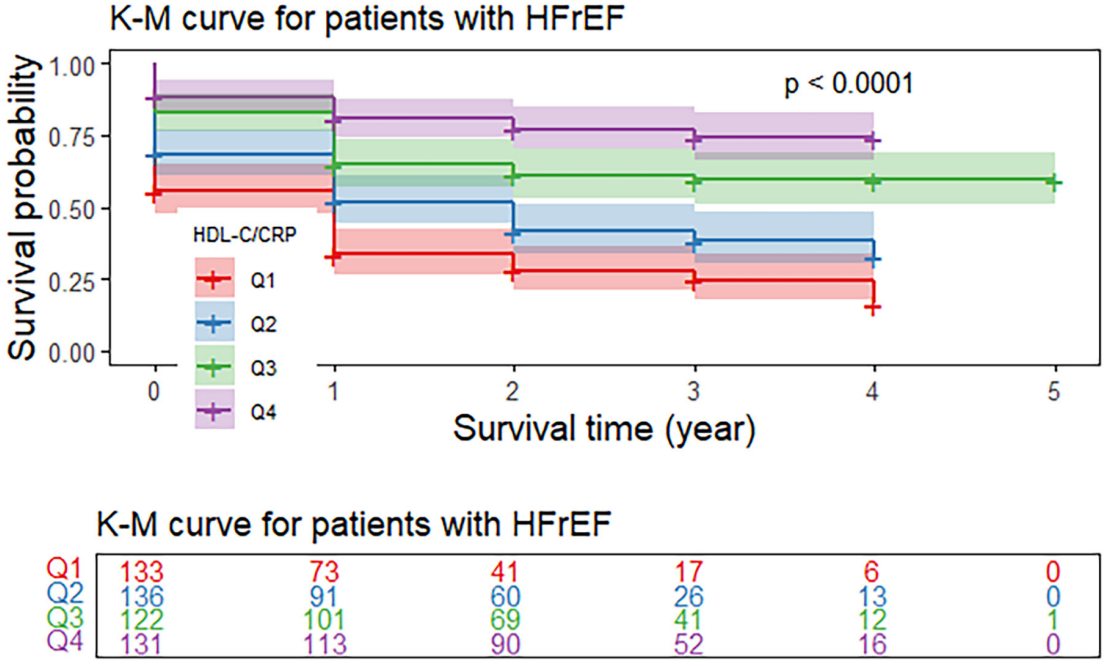

Figure 3 Kaplan-Meier (K-M) analysis of different high-density lipoprotein cholesterol/C reactive protein (HDL-C/CRP) ratios for patients with heart failure with reduced ejection fraction (HFrEF).

Table 2 Spearman correlation analysis of the HDL-C/CRP ratio with laboratory data

Laboratory data	HDL-C/CRP	
	R	P value
WBC (10^9/L)	−0.234	0.000
Neutrophil (10^9/L)	−0.276	0.000
Lymphocyte (10^9/L)	0.153	0.000
RBC (10^{12}/L)	0.081	0.005
Hb (g/L)	0.09	0.002
PLT (10^9/L)	0.014	0.634
Albumin (g/dL)	0.28	0.000
Fib (g/L)	−0.26	0.000
lgBNP	−0.167	0.000
Potassium (mmol/L)	0.012	0.674
Sodium (mmol/L)	0.185	0.000
Chlorine (mmol/L)	0.201	< 0.01
ALT (IU/L)	−0.106	< 0.01
AST (IU/L)	−0.117	0.000
Cr,(μmol/L)	−0.156	0.000
UA (umol/L)	−0.117	0.000
GFR (mL/min)	0.137	0.000
Glu (mmol/L)	−0.117	0.000
TC (mmol/L)	0.205	0.000
TG (mmol/L)	−0.03	0.306
LDL-C (mmol/L)	0.09	0.002

P values can be used to calculate the correlation of HDL-C/CRP ratio with other laboratory indices,and a p value<0.05 was considered to indicate statistical significance.
CRP, C reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RBC, red blood cell; TC, total cholesterol; WBC, white blood cell.

and three new models were suggested for multifactorial Cox regression analysis of HDL-C/CRP, which showed that HDL-C/CRP consistently showed up as an independent risk factor for death from HF across models as well as in different subgroups (table 4).

Ability of the HDL-C/CRP ratio to predict mortality in all patients with CHF

In all patients with chronic HF, ROC curve analysis was performed and it was seen that the ROC curve has an AUC of 0.7254 (p<0.001) for the HDL-C/CRP ratio in all patients, with a sensitivity of 65.5% and a specificity of 69.6% (figure4A), moreover, in patients with HFpEF + HFmrEF, the AUC for the HDL-C/CRP ratio was 0.7168, with a sensitivity of 72.6% and a specificity of 61.9% (p<0.0001) (figure4B); in addition, in patients with HFrEF, the AUC for the HDL-C/CRP ratio was 0.7379, with a sensitivity of 85.5% and a specificity of 69.2% (p<0.0001) (figure4C). In conclusion, prediction using HDL-C/CRP ratio has a good sensitivity and specificity both for all patients with CHF and for categorised patients with CHF. Furthermore, HDL-C/CRP ratio has the highest sensitivity and specificity in the prediction of all-cause mortality in patients with HFrEF.

DISCUSSION

The HDL-C/CRP ratio, an inflammatory marker, was associated with all-cause mortality in patients with HF in this retrospective study, regardless of the type of HF. The Kaplan-Meier analysis revealed that all-cause mortality was always highest in group 1 (HDL-C/CRP<0.395) and lowest in group 4 (HDL-C/CRP≥3.4163), both in patients with HFpEF + HFmrEF and in patients with HFrEF. Using Cox proportional hazards analysis, we identified HDL-C/CRP levels as an independent prognosis of all-cause mortality in all patients with HF and in different HF subgroups (HFpEF + HFmrEF and HFrEF). According to all three Cox proportional hazards models, group 1 always had the highest risk of death when group f4 was used as a reference. According to model 3, among all the patients with HF, the risk of death in group 1 was 3.325 times greater than that in group 4; among the patients with HFpEF + HFmrEF, the risk was 3.466 times greater; and among the patients with HFrEF, the risk was 3.496 times greater. The ROC curves revealed that the AUC for HDL-C/CRP was 0.7254 (p<0.001) in all patients with HF, 0.7168 in patients with HFpEF + HFmrEF and 0.7379 in patients with HFrEF.

In both acute HF and CHF, systemic inflammation is recognised as a common pathobiological feature. In particular, inflammation has been linked to disease initiation, progression and complications, and is predictive of poor outcomes independent of traditional measures such as LVEF or NYHA functional class.[4 12–14] Although inflammation contributes to the development and progression of HF across the spectrum of HFrEF, HFmrEF and HFpEF subtypes, the association of markers of inflammation may be stronger in the context of HFpEF. Differences between patients with HFrEF or HFpEF are not limited to systolic function but also extend to pathophysiology. HFrEF is characterised by eccentric left ventricular remodelling mainly driven by progressive cardiomyocyte loss, but oxidative stress and inflammation appear to be primary triggers of cardiac dysfunction in patients with HFpEF.[5 6]

Among the numerous studies related to inflammation and HF, CRP is the most commonly used inflammatory marker for predicting inflammation and HF.[9 15 16] In patients with acute myocardial infarction, CRP is more elevated in those who go on to develop HF.[17] In addition, large prospective cohort studies have shown that CRP levels can predict HF in elderly patients, regardless of the presence or absence of CAD.[16 18–20] Moreover, another study showed that elevated CRP levels correlate with the NYHA functional class and may also predict the likelihood of rehospitalisation for HF.[21 22] Furthermore, CRP was found to be a

Table 3 Univariate Cox regression analysis

	All		HFrEF		HFpEF + HFmrEF	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Clinical demographics						
Age (years)	1.031 (1.023–1.038)	<0.001	1.024 (1.013–1。035)	<0.001	1.041 (1.030–1.053)	<0.001
Male, n (%)	1.027 (0.865–1.218)	0.764	1.037 (0.795–1.353)	0.786	0.995 (0.792–1.248)	0.962
BMI (kg/m^2)	0.944 (0.923–0.966)	<0.001	0.932 (0.900–0.965)	<0.001	0.954 (0.925–0.984)	0.003
SBP (mm Hg)	0.994 (0.990–0.997)	0.001	0.992 (0.986–0.999)	0.016	0.995 (0.990–1.000)	0.038
DBP (mm Hg)	0.985 (0.980–0.991)	<0.001	0.987 (0.978–0.995)	0.03	0.984 (0.977–0.992)	<0.001
NYHA functional class IV, n (%)	2.2423 (2.0253–2.860)	<0.001	2.264 (1.773–2.891)	<0.001	2.561 (2.044–3.211)	<0.001
Medical history						
Smoke status, n (%)	1.041 (0.876–1.238)	0.648	1.009 (0.787–1.294)	0.944	1.051 (0.824–1.341)	0.688
Drink status, n (%)	0.842 (0.670–1.058)	0.14	0.910 (0.665–1.246)	0.557	0.760 (0.543–1.064)	0.11
DM, n (%)	1.263 (1.058–1.509)	0.091	1.263 (0.96–1.662)	0.095	1.288 (1.019–1.629)	0.034
AF, n (%)	1.088 (0.915–1.294)	0.338	1.461 (1.130–1.889)	0.004	0.892 (0.705–1.128)	0.339
Laboratory data						
WBC (10^9/L)	1.050 (1.030–1.071)	<0.001	1.044 (1.012–1.077)	0.007	1.057 (1.030–1.084)	<0.001
Neutrophil (10^9/L)	1.078 (1.055–1.102)	<0.001	1.086 (1.050–1.124)	<0.001	1.076 (1.047–1.107)	<0.001
Lymphocyte (10^9/L)	0.717 (0.626–0.821)	<0.001	0.669 (0.545–0.821)	<0.001	0.753 (0.628–0.901)	0.002
RBC (10^{12}/L)	0.726 (0.648–0.813)	<0.001	0.684 (0.576–0.812)	<0.001	0.742 (0.637–0.846)	<0.001
Hb (g/L)	0.990 (0.987–0.994)	<0.001	0.99 (0.987–0.994)	<0.01	0.990 (0.986–0.995)	<0.001
PLT (10^9/L)	0.998 (0.996–0.999)	<0.001	0.999 (0.997–1.000)	0.096	0.997 (0.995–0.999)	<0.001
Albumin (g/dL)	0.930 (0.913–0.948)	<0.001	0.926 (0.898–0.955)	<0.001	0.930 (0.907–0.954)	<0.001
Fib (g/L)	1.042 (0.978–1.112)	0.204	1.056 (0.950–1.173)	0.314	1.047 (0.964–1.137)	0.272
lgBNP	5.241 (3.849–7.136)	<0.001	7.811 (4.686–13.018)	<0.001	4.982 (3.273–7.583)	<0.001
Potassium (mmol/L)	1.164 (1.013–1.337)	0.033	1.116 (0.895–1.390)	0.329	1.199 (1.001–1.435)	0.048
Sodium (mmol/L)	0.938 (0.920–0.956)	<0.001	0.944 (0.918–0.972)	<0.001	0.934 (0.910–0.958)	<0.001
Chlorine (mmol/L)	0.931 (0.914–0.947)	<0.001	0.94 (0.915–0.965)	<0.001	0.925 (0.903–0.947)	<0.001
ALT (IU/L)	1.003 (1.002–1.004)	<0.001	1.003 (1.002–1.005)	<0.001	1.003 (1.002–1.004)	<0.001
AST (IU/L)	1.004 (1.003–1.005)	<0.001	1.004 (1.002–1.005)	<0.001	1.004 (1.003–1.005)	<0.001
Cr (μmol/L)	1.003 (1.002–1.003)	<0.001	1.004 (1.002–1.005)	<0.001	1.002 (1.001–1.003)	<0.001
UA (umol/L)	1.001 (1.001–1.002)	<0.001	1.002 (1.001–1.003)	<0.001	1.001 (1.000–1.002)	0.016
GFR (mL/min)	0.976 (0.971–0.981)	<0.001	0.971 (0.963–0.979)	<0.001	0.977 (0.970–0.984)	<0.001
Glu (mmol/L)	1.054 (1.032–1.077)	<0.001	1.033 (0.997–1.070)	0.075	1.069 (1.041–1.098)	<0.001
TC (mmol/L)	0.820 (0.751–0.895)	<0.001	0.800 (0.701–0.911)	<0.001	0.837 (0.744–0.942)	0.003
TG (mmol/L)	0.892 (0.777–1.024)	0.105	0.765 (0.603–0.971)	0.028	0.969 (0.825–1.139)	0.705
LDL-C (mmol/L)	0.838 (0.757–0.928)	<0.001	0.804 (0.691–0.935)	0.005	0.866 (0.754–0.994)	0.041
HDL-C (mmol/L)	0.632 (0.477–0.837)	0.001	0.590 (0.384–0.904)	0.015	0.680 (0.468–0.989)	0.044
CRP (mmol/L)	1.011 (0.1009–1.012)	<0.001	1.011 (1.008–1.014)	<0.001	1.010 (1.008–1.012)	<0.001
HDL-C/CRP	0.889 (0.860–0.918)	<0.001	0.862 (0.817–0.909)	<0.001	0.908 (0.873–0.945)	<0.001
Echocardiography						
HR (beat/min)	1.007 (1.003–1.011)	<0.001	1.008 (1.002–1.014)	0.011	1.006 (1.001–1.011)	0.014
LVEF (%)	0.995 (0.990–1.000)	0.041	0.981 (0.964–0.998)	0.028	0.994 (0.984–1.005)	0.283
Pharmacotherapy						
Dapagliflozin, n (%)	1.212 (1.000–1.469)	0.051	0.095(0.701–0.287)	0.074	1.447 (1.126–1.860)	0.004
Beta blockers, n (%)	0.911 (0.762–1.089)	0.306	0.963 (0.735–1.263)	0.786	0.868 (0.684–1.101)	0.243
ACEI/ARB/ARNI, n (%)	1.091 (0.923–1.290)	0.309	1.085 (0.850–1.395)	0.514	1.114 (0.884–1.404)	0.359
Diuretics, n (%)	1.140 (0.925–1.406)	0.219	1.055 (0.786–1.416)	0.721	1.235 (0.916–1.664)	0.167

Continued

Table 3 Continued

	All		HFrEF		HFpEF + HFmrEF	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Spironolactone, n (%)	0.936 (0.766–1.143)	0.516	0.960 (0.724–1.274)	0.778	0.928 (0.697–1.236)	0.609

P values were used to calculate whether the different variables could be used as independent risk factors for all-cause mortality in patients with chronic heart failure, and a p value < 0.05 was considered to indicate statistical significance.

ACE-I, ACE inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CRP, C reactive protein; HDL-C, high-density lipoprotein cholesterol; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RBC, red blooc cell; TC, total cholesterol; WBC, white blood cell.

strong and independent prognostic indicator of all-cause mortality, particularly cardiovascular mortality, in patients with HFpEF, whereas this association was less pronounced in patients with HFrEF. With regard to comorbidities, the level of CRP was a significantly stronger predictor in patients with HFpEF without CAD than in those with CAD. Finally, CRP levels provided additional prognostic information beyond that of NT-proBNP, the current laboratory gold standard for diagnosis and risk prediction in patients with HF.[23]

In addition to CRP, HDL-C is also commonly used for studying the prognosis of HF. From the perspective of pathophysiological mechanisms, HDL has a proven protective and anti-inflammatory role in autoimmune and inflammatory conditions. Their

Table 4 Cox regression of the HDL-C/CRP ratio according to the different models

	All		HFrEF		HFpEF + HFmrEF	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Unadjusted						
Q4	Ref		Ref		Ref	
Q3	2.014 (1.485–2.732)	<0.001	1.805 (1.149–2.835)	0.01	2.205 (1.456–3.339)	<0.001
Q2	3.425 (2.571–4.564)	<0.001	3.35 (2.214–5.071)	<0.001	3.497 (2.348–5.206)	<0.001
Q1	5.029 (3.798–6.661)	<0.001	5.027 (3.354–7.534)	<0.001	5.055 (3.421–7.470)	<0.001
Adjusted model 1						
Q4	Ref		Ref		Ref	
Q3	1.879 (1384–2.55)	<0.001	1.694 (1.077–2.667)	0.023	2.056 (1.357–3.114)	<0.001
Q2	3.219 (2.415–4.292)	<0.001	3.284 (2.169–4.973)	<0.001	3.135 (2.104–4.672)	<0.001
Q1	4.772 (3.601–6.322)	<0.001	4.818 (3.211–7.229)	<0.001	4.747 (3.211–7.016)	<0.001
Adjusted model 2						
Q4	Ref		Ref		Ref	
Q3	1.969 (1.350–2.674)	<0.001	1.789 (1.134–2.823)	<0.001	2.153 (1.421–3.263)	<0.001
Q2	3.294 (2.468–4.396)	<0.001	3.318 (2.183–5.042)	<0.001	3.254 (2.182–4.852)	<0.001
Q1	4.634 (3.490–6.154)	<0.001	4.812 (3.190–7.258)	<0.001	4.543 (3.067–6.730)	<0.001
Adjusted model 3						
Q4	Ref		Ref		Ref	
Q3	1.017 (1.008–2.460)	<0.001	1.627 (1.028–2.576)	0.038	2.148 (1.410–3.273)	<0.001
Q2	2.748 (2.052–3.680)	<0.001	2.942 (1.929–4.487)	<0.001	2.823 (1.880–4.239)	<0.001
Q1	3.325 (2.476–4.466)	<0.001	3.496 (2.266–5.391)	<0.001	3.466 (2.313–5.193)	<0.001

Q1 (HDL-C/CRP < 0.3958), Q2 (HDL-C/CRP ≥ 0.3958 to 1.2321), Q3 (HDL-C/CRP ≥ 1.2321 to < 3.4163) and Q4 (HDL-C/CRP ≥ 3.4163). Model 1 (includes age); model 2 (includes model 1 + SBP, DBP, HR, BMI); model 3 (includes model 2 + WBC, RBC, Hb, lgBNP, sodium, chlorine, ALT, AST, GFR, LDL-C).

P values were used to calculate whether HDL-C/CRP ratio could be used as an independent risk factor for all-cause mortality in patients with chronic heart failure under different classifications, and a p value < 0.05 was considered to indicate statistical significance.
BMI, body mass index; CRP, C reactive protein; HDL-C, high-density lipoprotein cholesterol; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL-C, low-density lipoprotein cholesterol; RBC, red blood cell; WBC, white blood cell.

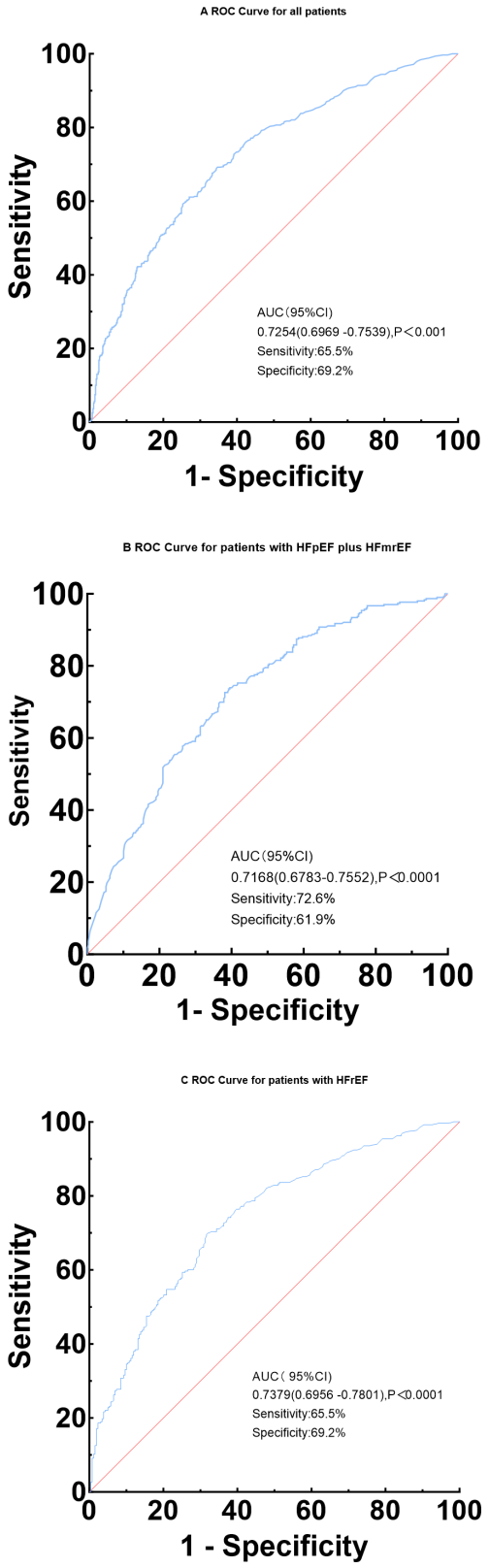

Figure 4 (A) Receiver operating characteristic (ROC) curve of the high-density lipoprotein cholesterol/C reactive protein (HDL-C/CRP) ratio for patients. (B) ROC curve of the HDL-C/CRP ratio for patients with heart failure with preserved ejection fraction (HFpEF) + HF with mildly reduced EF (HFmrEF). (C) ROC curve of the HDL-C/CRP ratio for patients with HF with reduced EF (HFrEF). AUC, area under the curve.

pathophysiological relevance directly implies the regulation of both immune and vascular cell functions that influence the common inflammatory processes underlying disease progression and associated CV risk.[10 24 25] According to clinical research, low HDL-C levels correlate with adverse outcomes independent of aetiology and predict clinical worsening or death in patients with advanced HF.[26 27]

The above studies were univariate studies of HF prognosis based on CRP and HDL-C levels, and in our study, when a new univariate Cox regression analysis was performed, the HR values of CRP were >1 in different subgroups, whereas the mean value of HDL-C was <1 for different scores, which confirms the conclusion that CRP is a worsening factor and HDL-C is a protective factor.

On this basis, considering that the combination of HDL-C and CRP can more effectively reflect the balance between anti-inflammatory and pro-inflammatory, and then further evaluate the impact of the patient's internal environment on the prognosis, people have combined the two as HDL-C/CRP and used this index to further predict the prognosis of patients with HF.[12] The prediction results also exhibited high sensitivity and specificity; however, the limitation is that this study is only a review of patients with HFpEF, and the findings of this study may be based on the strong correlation between the pathogenesis of HFpEF and inflammation. In our study, we extended the sample size from patients with HFpEF to patients with all types of HF. Regardless of the type of HF, the HDL-C/CRP ratio had high specificity and sensitivity, and the lower the HDL-C/CRP ratio was, the greater the mortality rate. These findings could lead to the identification of new targets for future treatment, achieving better therapeutic effects through anti-inflammatory effects and elevated HDL-C levels in patients with CHF. At present, studies have confirmed that statins are the main drugs for increasing HDL-C levels,[28] but most treatments related to CRP are still based on controlling the underlying disease without specific anti-inflammatory treatment.[29] Thus, inflammatory management of CHF will remain as a promising area waiting to be explored in the future.

Strengths and limitations of this study

The strengths of this study are the adequate sample size and the fact that the retrospective analysis provides a new validated prognostic indicator for patients with CHF. Also, this study has its limitations. First, this study covered only patients with CHF in NYHA class III or IV and did not examine the prognostic value of the HDL-CRP ratio for all-cause mortality in patients in NYHA class I or II. Second, large-scale epidemiological studies have shown a 'U'-shaped relationship between HDL-C concentrations and all-cause mortality, with both very high and very low concentrations associated with a high risk of all-cause mortality. Approximately 90–95% of plasma ApoA-I is

located on HDL, and ApoA-I tends to outperform HDL-C in predicting endpoint events in patients with ischaemic and non-ischaemic hypertension. However, because this is a retrospective study, ApoA-I was not carried out as a routine laboratory test in our patients from 2017 to 2021, so there would be a lot of missing data if only ApoA-I was used in the data collection process, which would make it impossible to carry out the study, thus HDL-C was chosen in the study as the main influencing factor for prognostic studies.

CONCLUSIONS

As a new prognostic indicator, the HDL-C/CRP ratio is associated with all-cause mortality in patients with CHF (NYHA class III or IV), independently of high or low EF values, the lower the HDL-C/CRP ratio was, the greater the risk of death. Moreover, prediction using HDL-C/CRP ratio has good sensitivity and specificity both for all patients with CHF (NYHA class III or IV) and categorised patients with CHF, and the HDL-C/CRP ratio has the highest sensitivity and specificity in the prediction of all-cause mortality in patients with HFrEF.

Contributors XL and SY researched literature and conceived the study. YY, WG, TS, CX and LC were involved in protocol development, gaining ethical approval, patient recruitment and data analysis. XL wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript. LC is the guarantor.

Funding The study was funded by the Applied Basic Research Program of the Yunnan Province Science and Technology Department and Kunming Medical University (Project No. 202301AY070001-130).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was carried out in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of the First Affiliated Hospital of Kunming Medical University. The ethics approval of the study was (2022) ethics LNo. 173. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iD

Lixing Chen http://orcid.org/0000-0002-0746-6706

REFERENCES

1 Dunlay SM, Roger VL. Understanding the epidemic of heart failure: past, present, and future. *Curr Heart Fail Rep* 2014;11:404–15.
2 McDonagh TA, Metra M, Adamo M, *et al*. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2023;44:3627–39.
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. *Circ Heart Fail* 2021;14:e008406.
4 Murphy SP, Kakkar R, McCarthy CP, *et al*. Inflammation in Heart Failure. *J Am Coll Cardiol* 2020;75:1324–40.
5 Aimo A, Castiglione V, Borrelli C, *et al*. Oxidative stress and inflammation in the evolution of heart failure: From pathophysiology to therapeutic strategies. *Eur J Prev Cardiol* 2020;27:494–510.
6 Paulus WJ, Tschöpe C. A Novel Paradigm for Heart Failure With Preserved Ejection Fraction. *J Am Coll Cardiol* 2013;62:263–71.
7 Strandberg TE, Tilvis RS. C-reactive protein, cardiovascular risk factors, and mortality in a prospective study in the elderly. *Arterioscler Thromb Vasc Biol* 2000;20:1057–60.
8 Chew DP, Bhatt DL, Robbins MA, *et al*. Incremental prognostic value of elevated baseline C-reactive protein among established markers of risk in percutaneous coronary intervention. *Circulation* 2001;104:992–7.
9 Benz AP, Aeschbacher S, Krisai P, *et al*. Biomarkers of Inflammation and Risk of Hospitalization for Heart Failure in Patients With Atrial Fibrillation. *J Am Heart Assoc* 2021;10:e019168.
10 Kontush A. HDL-mediated mechanisms of protection in cardiovascular disease. *Cardiovasc Res* 2014;103:341–9.
11 Horio T, Miyazato J, Kamide K, *et al*. Influence of low high-density lipoprotein cholesterol on left ventricular hypertrophy and diastolic function in essential hypertension. *Am J Hypertens* 2003;16:938–44.
12 Yano M, Nishino M, Ukita K, *et al*. High density lipoprotein cholesterol / C reactive protein ratio in heart failure with preserved ejection fraction. *ESC Heart Fail* 2021;8:2791–801.
13 Libby P, Hansson GK. Inflammation and Immunity in Diseases of the Arterial Tree. *Circ Res* 2015;116:307–11.
14 Van Linthout S, Tschöpe C. Inflammation - Cause or Consequence of Heart Failure or Both? *Curr Heart Fail Rep* 2017;14:251–65.
15 Li X, Peng S, Guan B, *et al*. Genetically Determined Inflammatory Biomarkers and the Risk of Heart Failure: A Mendelian Randomization Study. *Front Cardiovasc Med* 2021;8:734400.
16 Kalogeropoulos A, Georgiopoulou V, Psaty BM, *et al*. Inflammatory markers and incident heart failure risk in older adults: the Health ABC (Health, Aging, and Body Composition) study. *J Am Coll Cardiol* 2010;55:2129–37.
17 Berton G, Cordiano R, Palmieri R, *et al*. C-reactive protein in acute myocardial infarction: association with heart failure. *Am Heart J* 2003;145:1094–101.
18 Vasan RS, Sullivan LM, Roubenoff R, *et al*. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation* 2003;107:1486–91.
19 Gottdiener JS, Arnold AM, Aurigemma GP, *et al*. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol* 2000;35:1628–37.
20 Cesari M, Penninx BWJH, Newman AB, *et al*. Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. *Circulation* 2003;108:2317–22.
21 Alonso-Martínez JL, Llorente-Diez B, Echegaray-Agara M, *et al*. C-reactive protein as a predictor of improvement and readmission in heart failure. *Eur J Heart Fail* 2002;4:331–6.
22 Yin W-H, Chen J-W, Jen H-L, *et al*. Independent prognostic value of elevated high-sensitivity C-reactive protein in chronic heart failure. *Am Heart J* 2004;147:931–8.
23 Koller L, Kleber M, Goliasch G, *et al*. C-reactive protein predicts mortality in patients referred for coronary angiography and symptoms of heart failure with preserved ejection fraction. *Eur J Heart Fail* 2014;16:758–66.
24 Tall AR, Yvan-Charvet L. Cholesterol, inflammation and innate immunity. *Nat Rev Immunol* 2015;15:104–16.
25 Von Eckardstein A, Kardassis D, eds. *High Density Lipoproteins: From Biological Understanding to Clinical Exploitation*. Cham: Springer International Publishing, 2015. Available: http://link.springer.com/10.1007/978-3-319-09665-0
26 Aronow WS, Ahn C. Frequency of congestive heart failure in older persons with prior myocardial infarction and serum low-density lipoprotein cholesterol > or = 125 mg/dl treated with statins versus no lipid-lowering drug. *Am J Cardiol* 2002;90:147–9.
27 Mehra MR, Uber PA, Lavie CJ, *et al*. High-density lipoprotein cholesterol levels and prognosis in advanced heart failure. *J Heart Lung Transplant* 2009;28:876–80.
28 Yamashita S, Tsubakio-Yamamoto K, Ohama T, *et al*. Molecular Mechanisms of HDL-Cholesterol Elevation by Statins and Its Effects on HDL Functions. *JAT* 2010;17:436–51.
29 Mann DL. Inflammatory mediators and the failing heart: past, present, and the foreseeable future. *Circ Res* 2002;91:988–98.