


High density lipoprotein cholesterol / C reactive protein ratio in heart failure with preserved ejection fraction

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Abstract

Aims The impacts of high density lipoprotein cholesterol (HDL-C) as an anti-inflammatory and C reactive protein (CRP) as inflammatory properties on the pathogenesis of heart failure were reported. At present, the clinical significance of the HDL-C/CRP ratio in heart failure with preserved ejection fraction (HFpEF) patients remains unknown.

Methods and results We examined the data on 796 consecutive HFpEF (left ventricular ejection fraction $\geq 50\%$) patients hospitalized due to acute decompensated heart failure from the PURSUIT-HFpEF registry, a prospective, multicentre observational study. We calculated the HDL/CRP ratios and evaluated the relationship between the values and clinical outcomes, including degree of cardiac function. The mean follow-up duration was 420 ± 346 days. All-cause death occurred in 118 patients, of which 51 were cardiac deaths. HDL/CRP ≤ 4.05 was independently and significantly associated with all-cause death (odds ratio = 1.84, 95% CI: 1.06–3.20, $P = 0.023$), and HDL/CRP ≤ 3.14 was associated with cardiac death by multivariate Cox proportional hazard analysis (odds ratio = 2.86, 95% CI: 1.36–6.01, $P = 0.003$). HDL-C/CRP ratio significantly correlated with the product of the left atrial volume and left ventricular mass index as well as the tricuspid annular plane systolic excursion by multiple regression analysis (standardized beta-coefficient = -0.085 , $P = 0.034$ and standardized beta-coefficient = 0.081 , $P = 0.044$, respectively).

Conclusions HDL-C/CRP ratio was a useful marker for predicting all-cause death and cardiac death and correlated with left ventricular diastolic function and right ventricular systolic function in HFpEF patients.

Keywords Heart failure with preserved ejection fraction; Inflammation; High density lipoprotein cholesterol/C reactive protein ratio; Left ventricular diastolic function; Right ventricular systolic function

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Introduction

Heart failure (HF) is a major public health burden in the world and its prevalence is correlated with age. HF with preserved ejection fraction (HFpEF) accounts for >50% of chronic HF cases.^{1,2} The number of patients with HFpEF is markedly increasing as the world population ages. The proportion of HFpEF patients hospitalized with acute decompensated heart failure (ADHF) is increasing.³ Along with the high prevalence of HFpEF, patients with HFpEF remain at high risk for adverse events, with few evidence-based disease-modifying therapies. The reasons for these disappointing results may be due to non-cardiac co-morbidities.⁴

Several reports have demonstrated the role of inflammation in the pathogenesis of HF.⁵ In HFpEF patients, comorbidity-driven systemic microvascular inflammation is postulated to play a key role in the pathogenesis of myocardial structural and functional changes.⁴ Higher C-reactive protein (CRP) levels are associated with adverse vascular outcomes but also future HF hospitalizations and higher left ventricular filling pressures in patients with coronary artery disease.^{6,7} In HFpEF, CRP was predictive of mortality, and another study demonstrated increased exercise tolerance with anti-inflammatory therapy in patients with elevated CRP.⁸ High density lipoprotein cholesterol (HDL-C) plays a scavenger role removing deposited cholesterol from macrophages and relieves inflammation.⁹ Moreover, in treated essential hypertension patients, HDL-C is favourably associated with left ventricular diastolic function.¹⁰

The combination of CRP and HDL-C as an inflammatory status marker in HFpEF patients has not been well studied. We aimed to reveal the relationship between the combination of CRP and HDL-C and clinical outcomes in HFpEF patients.

Methods

PURSUIT-HFpEF registry

We enrolled patient data from the PURSUIT HFpEF (Prospective, mUlticenteR, obServational stUdy of patlenTs with Heart Failure with Preserved Ejection Fraction) registry. The PURSUIT-HFpEF is a prospective, multicentre (32 hospitals) observational study in which collaborating hospitals in the Osaka region of Japan (UMIN-CTR ID: UMIN000021831).^{11,12} The comprehensive diagnostic algorithm for HFpEF was recently introduced by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC).^{13,14} This algorithm consists of four steps: Step 1, pre-test assessment; Step 2, echocardiographic and natriuretic peptide heart failure with preserved ejection fraction diagnostic score; Step 3, functional testing; and Step 4, final aetiology. The HFA-PEFF

score is a scoring system in the Step 2 evaluating echocardiographic parameters and laboratory tests (natriuretic peptide), and the clinical utility of Step 2 was recently showed by Aizpurua *et al.*¹⁵ Based on the algorithm, we defined HFpEF from the echocardiographic parameter and the laboratory test as follows. The enrolled patients were hospitalized with ADHF based on the Framingham criteria and had left ventricular ejection fraction (LVEF) \geq 50% using transthoracic echocardiography. Brain natriuretic peptide was \geq 100 ng/L or N-terminal pro brain natriuretic peptide (NT-pro BNP) \geq 400 ng/L on admission. The exclusion criteria were (i) severe aortic stenosis, aortic regurgitation, mitral stenosis, or mitral regurgitation due to structural changes of the valve detected by transthoracic echocardiography; (ii) age <20 years; (iii) acute coronary syndrome on admission; (iv) poor 6 month prognosis due to non-cardiac diseases; (v) no measurements of HDL-C or CRP levels on admission; (vi) status post heart transplantation. Non-cardiac co-morbidities, such as infectious diseases and pulmonary disease, were not included in the exclusion criteria.

We followed each patient and collected outcome data of all-cause death and cardiac death. All patients had given informed consent for their participation in this study, which was approved by the ethics committee in all participating facilities. This study was conducted according to the Declaration of Helsinki. The present study protocol has been approved by the Institutional Review Board of all participating facilities.

Study population

Our study cases were enrolled from the PURSUIT-HFpEF registry between June 2016 and February 2020.

Data collection

Investigative cardiologists and trained research nurses recorded the patient data such as medical history, comorbidities, exacerbation factors of heart failure, therapeutic procedures, and clinical events from the medical records and by direct interview of the patients and family members during their hospital stay. They also obtained vital signs, body mass indices, echocardiographic data, admission laboratory data, and medications at discharge.

Clinical outcomes

After discharge, all patients were followed up by their treating hospital. Coordinators and investigators obtained clinical data by direct contact in an outpatient setting, telephone interview with patient families, or by mail.

Laboratory measurement

Blood samples were collected on emergency admission. Laboratory measurements were performed by standard methods in the clinical laboratory of each participating hospital. The HDL-C/CRP ratio was calculated as follows: HDL-C/CRP ratio = HDL-C (mmol/L)/CRP (mg/dL) as previously described.¹⁶

Echocardiography

Echocardiography was performed on admission and at discharge. Left ventricular diastolic diameter (LVDD), left ventricular systolic diameter (LVSD), interventricular septum thickness diameter (IVSTd), left ventricular posterior wall thickness diameter (LVPWTd), left atrial diameter (LAD), and left atrial volume (LAV) were measured by the modified Simpson method. Tricuspid annular plane excursion (TAPSE) and inferior vena cava diameter (IVCD) were measured as previously described.^{17,18} LVEF was measured by the modified Simpson method.¹⁷ Left ventricular mass was calculated by linear methods as follows:

$$\text{Leftventricularmass} = 0.8 \times [1.04 ((\text{interventricularseptumthicknessdiameter}) + (\text{LVDD}) + (\text{leftventricularposteriorwallthicknessdiameter}))^3 - (\text{LVDD})^3] + 0.6.$$

Left ventricular mass index was indexed to body height (LVMI = g/m^{2.7}). The product of LAV and LVMI, which more strongly correlated with diastolic dysfunction in HFpEF patients than E/e', LAV, and LVMI, was calculated as previously reported.¹⁹ Tricuspid regurgitation pressure gradient (TRPG) was measured by a simplified Bernoulli equation.²⁰

Statistical analysis

JMP 15 statistical software (SAS Institute Inc., Cary, North Carolina, USA) was used for the statistical analysis. Continuous variables are expressed as median [interquartile range]. Two-group comparisons were analysed by the unpaired *t*-test or the Wilcoxon–Mann–Whitney test for continuous variables. Categorical data were expressed as a number (percentage) and were compared using Fisher's exact test for categorical variables. Study endpoints were estimated using Kaplan–Meier curves, and statistical significance was determined using the log-rank test. Univariate analysis with Cox proportional hazards regression model was performed, and a *P* value <0.05 was considered significant. Multivariate analyses with Cox proportional hazards regression model for all-cause death and cardiac death were performed using the factors found significant in the univariate analysis. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated. A multiple

regression model for relevant parameters and HDL-C/CRP ratio was generated again with a *P* value <0.05 considered significant.

Results

Clinical characteristics

A total of 871 cases were enrolled from the PURSUIT-HFpEF registry between June 2016 and February 2020. Seventy-five cases were excluded because they had no measurement of HDL-C or CRP on admission. A total of 796 cases were enrolled in this study. The median age was 82 years [76, 87], and 44.8% of the population was male. Baseline characteristics and the Framingham diagnostic criteria for heart failure in the HFpEF patients with ADHF are shown in *Table 1* and Supporting Information, *Table S1*, respectively.

Clinical outcomes

Average follow-up duration was 420 ± 346 days. All-cause death occurred in 118 patients and included 51 cardiac deaths. A receiver operating characteristics (ROC) analysis revealed good accuracy of predicting all-cause death by HDL-C/CRP ratio (AUC-ROC: 0.61). With a cutoff of 4.05 for the HDL-C/CRP ratio, sensitivity of 79.7% and specificity of 38.2% were achieved (*Figure 1*). ROC analysis revealed good accuracy of predicting cardiac death by HDL-C/CRP ratio (AUC-ROC: 0.61). With a cutoff of 3.14 for the HDL-C/CRP ratio, sensitivity of 78.4% and specificity of 44.6% were achieved (*Figure 1*). Kaplan–Meier analysis demonstrated that patients with HDL-C/CRP ratios ≤4.05 had a significantly greater risk of all-cause death than patients with HDL-C/CRP ratios >4.05 (*Figure 2*) and that patients with HDL-C/CRP ratio ≤3.14 had a significantly greater risk of cardiac death than patients with HDL-C/CRP ratio >3.14 (*Figure 2*).

Univariate Cox proportional hazards analysis showed that HDL-C/CRP ≤ 4.05, body mass index (BMI), albumin, log NT-pro BNP, LVDD, and E/e' were significantly associated with all-cause death (*Table 2*). Multivariate Cox proportional hazards analysis showed that HDL-C/CRP ≤ 4.05 (HR 1.84, 95% CI: 1.06–3.20, *P* = 0.023), age (HR 1.07, 95% CI: 1.04–1.10, *P* < 0.001), albumin (HR 0.56, 95% CI: 0.34–0.90, *P* = 0.016), log NT-pro BNP (HR 1.83, 95% CI: 1.05–3.22, *P* = 0.034), and LVDD (HR 0.95, 95% CI: 0.92–0.99, *P* = 0.007) were independently and significantly associated with all-cause death (*Table 2*). Univariate Cox proportional hazards analysis showed that HDL-C/CRP ≤ 3.14, age, BMI, albumin, log NT-proBNP, and LVDD were significantly associated with cardiac death (*Table 3*). Multivariate Cox proportional hazards analysis showed that HDL-C/CRP ≤ 3.14 (HR 2.86, 95% CI: 1.36–6.01, *P* = 0.003), age (HR

Table 1 Baseline patient characteristics

On admission	
Age, years	82 [76, 87]
Male, <i>n</i> (%)	357 (44.8)
Body mass index, kg/m ²	24 [21, 27]
Previous heart failure hospitalization, <i>n</i> (%)	188 (23.6)
Hypertension, <i>n</i> (%)	676 (84.9)
Diabetes mellitus, <i>n</i> (%)	267 (33.5)
Dyslipidaemia, <i>n</i> (%)	329 (41.3)
Stroke, <i>n</i> (%)	111 (13.9)
Atrial fibrillation, <i>n</i> (%)	387 (48.6)
NYHA classification	
1, 2	75 (9.4)
3	287 (36.1)
4	434 (54.5)
Echocardiographic parameters	
LVDD, mm	46 [42, 51]
LVDs, mm	30 [26, 34]
IVSTd, mm	10 [9, 11]
LVPWTd, mm	10 [9, 11]
LADs, mm	44 [39, 50]
LVEF, %	60 [55, 65]
E/e' (septal)	16 [12, 21]
Inferior vena cava diameter, mm	18 [15, 22]
TRPG, mmHg	36 [28, 44]
Laboratory data	
White blood cells, 10 ⁹ /L	6.6 [5.3, 8.9]
Haemoglobin, g/L	110 [100, 130]
Creatinine, µmol/L	97 [71, 133]
Albumin, g/L	35 [32, 38]
CRP, nmol/L	57 [19, 200]
NT-pro BNP, ng/L	3,257 [1710, 6,650]
HDL-C, mmol/L	1.3 [1.0, 1.5]
LDL-C, mmol/L	2.1 [1.7, 2.7]
T-Chol, mmol/L	4.0 [3.5, 4.6]
TG, mmol/L	0.8 [0.6, 1.2]
At Discharge	
NYHA classification	
1, 2	726 (91.2)
3	57 (7.2)
4	13 (1.6)
Echocardiographic parameters	
LVDD, mm	45 [41, 50]
LVDs, mm	29 [26, 33]
IVSTd, mm	10 [9, 11]
LVPWTd, mm	10 [9, 11]
LADs, mm	44 [39, 49]
LAV, mL	74 [54, 98]
LVEF, %	61 [55, 66]
E/e' (septal)	15 [12, 20]
TAPSE, cm	17 [15, 20]
Inferior vena cava diameter, mm	13 [11, 17]
TRPG, mmHg	27 [22, 32]
Medication	
ACEI or ARB, <i>n</i> (%)	366 (46.0)
Beta-blocker, <i>n</i> (%)	358 (45.0)
Diuretics (loop), <i>n</i> (%)	437 (54.9)
Aldosterone antagonist, <i>n</i> (%)	171 (21.5)
Statin, <i>n</i> (%)	239 (30.0)

AAD, anti-arrhythmic drug; ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CRP, C reactive protein; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; LAAD, left atrial appendage flow; LAD, left atrial diameter; LVDD, left ventricular end-diastolic diameter left ventricular diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction.

Continuous data are presented as the median (interquartile range). Categorical variables are presented as numbers (percentage).

1.06, 95% CI: 1.02–1.11, *P* = 0.001), BMI (HR 0.84, 95% CI: 0.85–0.99, *P* = 0.035), log NT-pro BNP (HR 3.27, 95% CI: 1.51–7.17, *P* = 0.003), and LVDD (HR 0.94, 95% CI: 0.89–0.99, *P* = 0.016) were independently and significantly associated with cardiac death (Table 3). We analysed the association HDL-C/CRP values and clinical outcomes (all-cause death and cardiac-death) in male and female separately and could obtain the same results as the overall population (Supporting Information, Figures S1 and S2).

Univariate Cox proportional hazards analysis showed that HDL-C was not significantly associated with all-cause death, but HDL-C was independently and significantly associated with cardiac death (HR 0.35, 95% CI: 0.13–0.86, *P* = 0.021) in multivariate Cox proportional hazards analysis (Supporting Information, Table S2). CRP was significantly associated with all-cause death in univariate Cox proportional hazards analysis, but multivariate analyses with Cox proportional hazards regression model, performed using the factors found significant in the univariate analysis showed no significant association with all-cause death (Supporting Information, Table S3).

Relationship between HDL-C/CRP ratio and cardiac function

We investigated the relationship between HDL-C/CRP ratio and relevant echocardiographic parameters at discharge, whose values reflected cardiac function under the condition of optimal heart failure treatment, using multiple regression analysis. LVEF was used as an index of left ventricular systolic function; the product of LAV and LVMI was used as an index of left ventricular diastolic function, and TAPSE was used as an index of right ventricular systolic function. The product of LAV and LVMI, and TAPSE were independently and significantly determinant of HDL-C/CRP ratio (Table 4). In connection with the correlation of HDL-C/CRP ratio with TAPSE, we evaluated the association between liver function and HDL-C/CRP ratio. The comparison of aspartate transaminase (AST), alanine transaminase (ALT), γ -glutamyltransferase (γ -GTP), and FIB-4 score was calculated as follows: $[(\text{Age} \times \text{AST (IU/L)}) / ((\text{platelet})(10^9/\text{L}) \times \text{ALT}^{1/2}(\text{IU/L}))]$, between the patients with low and high value of HDL-C/CRP ratio (Supporting Information, Table S4). No significant differences of liver function values was found between the patients with low and high value of HDL-C/CRP ratio.

Discussion

Main findings

The main findings of the present study are that (i) low HDL-C/CRP ratio had a higher risk of all-cause death and cardiac

Figure 1 ROC analysis of HDL-C/CRP ratio in predicting (A) all-cause death and (B) cardiac death. AUC, area under the curve; CRP, C reactive protein; HDL-C, high density lipoprotein cholesterol; ROC, receiver operating characteristics.

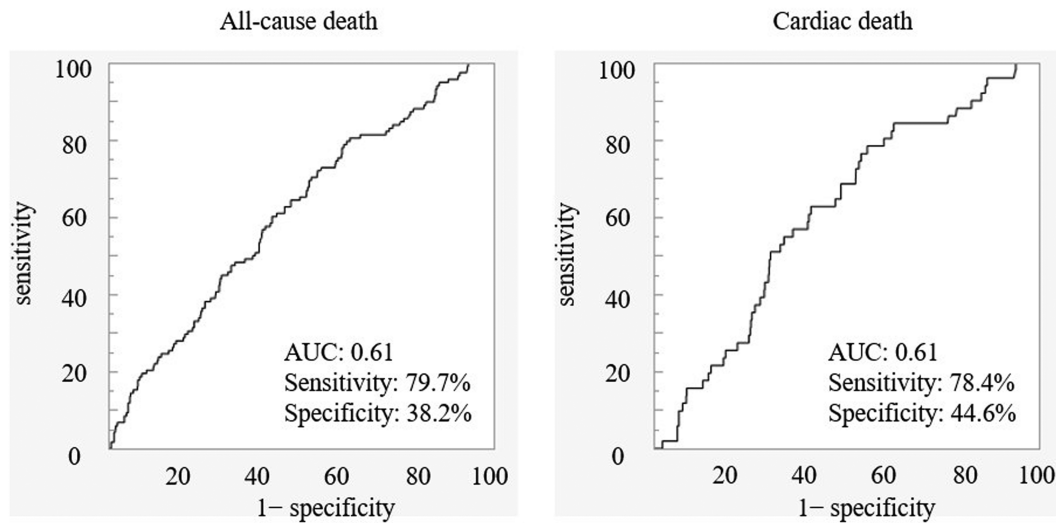
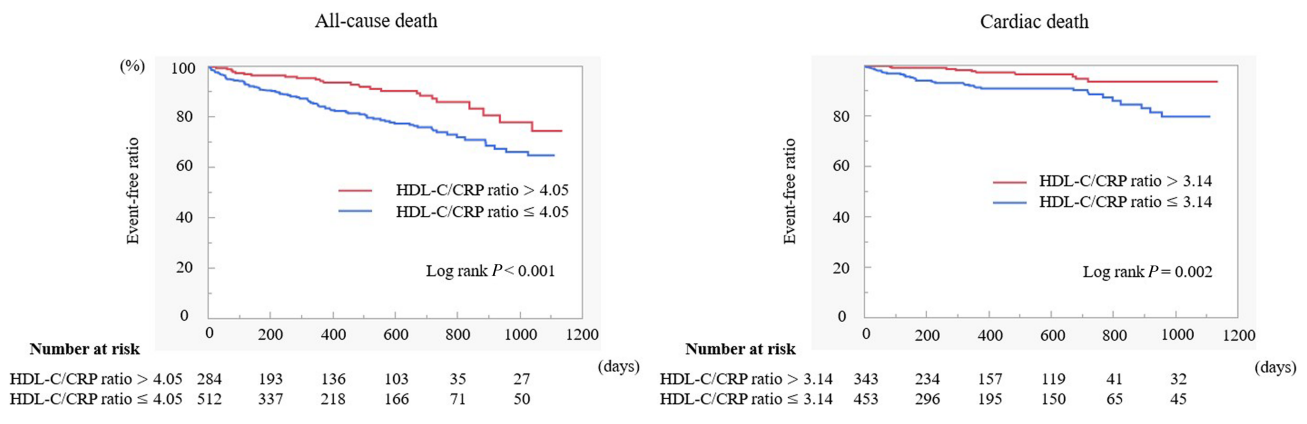


Figure 2 (A) Kaplan–Meier analysis of all-cause death between the patients with HDL-C/CRP ratio ≤ 4.05 and HDL-C/CRP ratio > 4.05 . (B) Kaplan–Meier analysis of cardiac death between the patients with HDL-C/CRP ratio ≤ 3.14 and HDL-C/CRP ratio > 3.14 . CRP, C reactive protein; HDL-C, high density lipoprotein cholesterol.



death in HFpEF patients. (ii) HDL-C/CRP ratio was an independent predictor for all-cause death and cardiac death in HFpEF patients. (iii) HDL-C/CRP ratio on admission was significantly associated with left ventricular diastolic function and right ventricular systolic function. These findings suggest HDL-C/CRP ratio was a simple and useful marker for predicting clinical outcome.

CRP and HDL-C as inflammatory and anti-inflammatory factors in HFpEF patients

Several studies have identified the importance of inflammation in the development and progression of HF.⁵

Inflammation and HF are strongly interconnected and mutually reinforce each other.²⁰ The inflammation associated with abnormal substrates underlying heart disease and co-morbidities impacts on the pathogenesis of HF.^{21–24} In HFpEF patients, co-morbidity-driven systemic microvascular inflammation is postulated to play a key role in the pathogenesis of myocardial structural and functional changes.⁴ Several studies have shown the relationship between CRP and clinical outcome in HFpEF patients. CRP was associated with several pro-inflammatory co-morbidities and markers of HF severity (brain natriuretic peptide and NYHA classification) and was predictive of all-cause and cardiovascular mortality.⁸ In the present study, average CRP level was 96.2 nmol/L, which was lower compared with other studies, and CRP was not

Table 2 Cox proportional hazard analysis for all-cause death

	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
HDL-C/CRP \leq 4.05	2.10	1.35–3.27	<0.001	1.84	1.06–3.20	0.023
Age	1.08	1.06–1.11	<0.001	1.07	1.04–1.10	<0.001
Female	1.00	0.70–1.44	0.993			
BMI	0.91	0.87–0.95	<0.001	0.96	0.91–1.02	0.166
Hypertension	0.67	0.42–1.05	0.093			
Diabetes mellitus	0.78	0.53–1.17	0.221			
Haemoglobin	0.94	0.86–1.03	0.184			
Creatinine	1.09	0.96–1.21	0.155			
Albumin	0.33	0.23–0.48	<0.001	0.56	0.34–0.90	0.016
Log NT-pro BNP	2.32	1.52–3.51	<0.001	1.83	1.05–3.22	0.034
LVDd	0.94	0.91–0.96	<0.001	0.95	0.92–0.99	0.007
E/e'	1.02	1.00–1.04	0.033	1.02	1.00–1.04	0.091
TRPG	1.01	0.99–1.02	0.285			
IVCD	0.99	0.95–1.02	0.418			

BMI, body mass index; CRP, C-reactive protein; HDL-C, high density lipoprotein cholesterol; IVCD, inferior vena cava diameter; LVDd, left ventricular diastolic diameter; NT-pro BNP, N-terminal pro-brain natriuretic peptide; TRPG, tricuspid pressure gradient.

Table 3 Cox proportional hazard analysis for cardiac death

	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
HDL-C/CRP \leq 3.14	2.74	1.41–5.35	0.003	2.86	1.36–6.01	0.003
Age	1.08	1.04–1.12	<0.001	1.06	1.02–1.11	0.001
Female	1.12	0.69–2.10	0.524			
BMI	0.88	0.82–0.94	<0.001	0.84	0.85–0.99	0.035
Hypertension	0.77	0.38–1.58	0.491			
Diabetes mellitus	1.04	0.58–1.87	0.886			
Haemoglobin	0.94	0.82–1.07	0.350			
Creatinine	1.14	0.95–1.30	0.139			
Albumin	0.36	0.21–0.63	<0.001	0.85	0.45–1.64	0.634
Log NT-pro BNP	3.32	1.81–5.96	<0.001	3.27	1.51–7.17	0.003
LVDd	0.92	0.88–0.96	<0.001	0.94	0.89–0.99	0.016
E/e'	1.02	0.99–1.05	0.222			
TRPG	1.02	1.00–1.04	0.076			
IVCD	1.00	0.95–1.05	0.961			

BMI, body mass index; CRP, C-reactive protein; HDL-C, high density lipoprotein cholesterol; IVCD, inferior vena cava diameter; LVDd, left ventricular diastolic diameter; NT-pro BNP, N-terminal pro-brain natriuretic peptide; TRPG, tricuspid pressure gradient.

Table 4 Multiple regression analysis for relevant parameters and HDL-C/CRP ratio

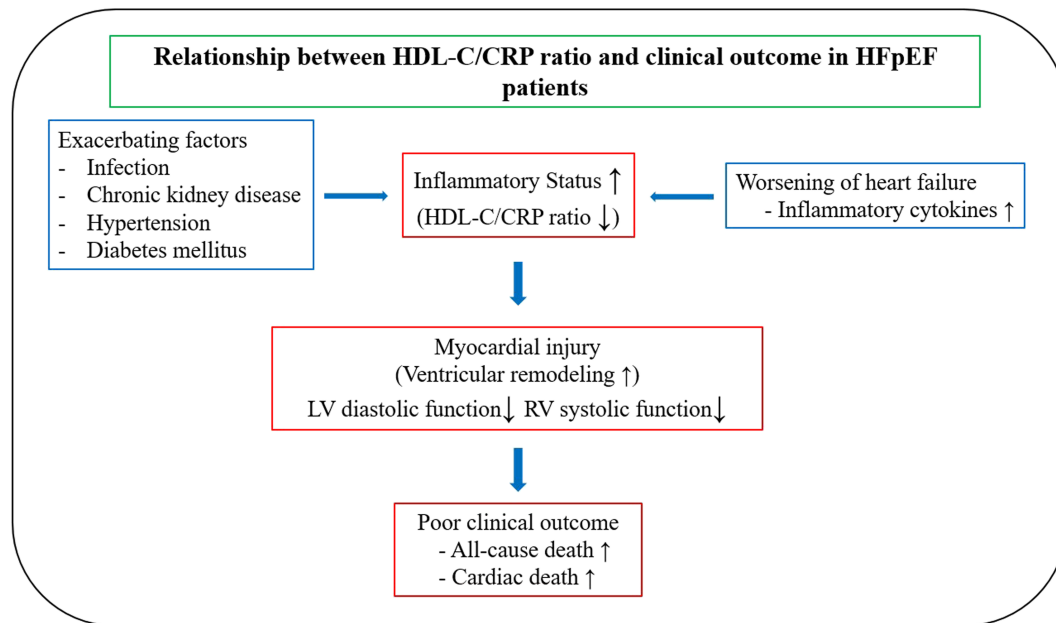
	Standard β coefficient	P value
LVEF	–0.009	0.823
Product of LAV and LVM index	–0.085	0.034
TAPSE	0.081	0.044

CRP, C reactive protein; HDL-C, high density lipoprotein cholesterol; LAV, left atrial volume; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion.

associated with all-cause death and cardiac-death. The possible reason for this result is that the median age was >80 years in our registry. A previous study demonstrated that CRP was inversely associated with age.²⁵ They showed that other inflammatory markers, IL-6 and TNF- α , were strongly associated

with incident HF risk, whereas CRP was not associated with incident heart failure in competing risks models. In our study, we evaluated the correlation of CRP and HDL-C as anti-inflammatory markers and showed their effect on clinical outcome. HDL-C plays a scavenger role, removing deposited cholesterol from macrophages and relieves inflammation.^{9,26} HDL-C neutralizes the proinflammatory and pro-oxidant effects of monocytes via inhibiting the migration of macrophages.²⁷ HDL-C levels are associated with congestive HF in patients with ischaemia and also predict HF exacerbations and adverse cardiovascular events in patients without ischaemia.^{28–31} We demonstrated that the combination of inflammatory and anti-inflammatory markers was a strong predictive factor for all-cause death and cardiac death in HFpEF patients. This index may be useful as a unique predictor of clinical outcome in elderly HFpEF patients because the

Figure 3 Relationship between HDL/CRP ratio and clinical outcome in HFpEF patients. Exacerbation factors and deterioration of heart failure promote inflammatory status and give myocardial injury. The damage induces left ventricular diastolic dysfunction and right ventricular systolic dysfunction and lead to poor clinical outcomes. CRP, C reactive protein; HDL-C, high density lipoprotein cholesterol; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle, RV, right ventricle.



association between inflammatory markers, associated comorbidities, and heart failure risk was strong in HFpEF compared with heart failure with reduced ejection fraction as previously reported.²⁵

HDL-C/CRP ratio and left ventricular diastolic function

Diastolic function was evaluated by left ventricular (LV) hypertrophy, LV mass, peak early/late mitral flow velocity (E/A), deceleration time, isovolumic relaxation time, and peak early mitral flow velocity/early transmitral annular velocity (E/e').^{17,19,32} Melenovsky *et al.* showed that LV hypertrophy, LVMI, and LAV were only weakly correlated with diastolic function and that the product of LVMI and LAV best identified HFpEF patients (84% sensitivity and 82% specificity).¹⁹ In the present study, the product of LVMI and LAV was significantly correlated with HDL-C/CRP ratio (Table 4). A previous study showed that in HFpEF patients, the high prevalence of co-morbidities induce a systemic proinflammatory state and causes coronary microvascular endothelial inflammation and reduction in protein kinase G activity in adjacent cardiomyocytes. These changes ameliorate cardiomyocyte stiffness and interstitial fibrosis and contribute to high diastolic LV stiffness and HF development.⁴ Our results showed HDL-C/CRP ratio, as an inflammatory status marker, is associated with LV diastolic function in HFpEF patients.

HDL-C/CRP ratio and right ventricular systolic function

Interestingly, there is a significant relationship between HDL-C/CRP ratio and TAPSE (Table 4). TAPSE is easily obtainable, reproducible, and highly predictive of poor outcome in a wide spectrum of HF cohorts for right ventricular (RV) systolic function assessment.^{33,34} In the cohort of patients with relatively advanced HFpEF, RV dysfunction was common.³⁵ RV pressure overload and inflammation were associated with RV dysfunction.³⁶ High CRP levels was associated with RV dysfunction in HFpEF patients, and reduced RV function was related to lower HDL-C in individuals free from hypertension, diabetes, and cardiovascular disease.^{37,38} RV dysfunction is an important factor in HFpEF patients and HDL-C/CRP ratio may be a useful marker of right ventricular function. The relationship between HDL-C/CRP ratio and TAPSE is not associated with decreased liver function accompanied with congestive liver because liver function and HDL-C/CRP ratio did not correlate in the present study.

Clinical implication

The measurement of HDL-C and CRP was performed at the usual clinical setting of patients with HFpEF. Our study showed that HDL-C/CRP ratio is an important predictor for all-cause death and cardiac death in HFpEF patients because

the exacerbation of HF is associated with inflammatory status. Possible mechanisms of the relationship between HDL/CRP ratio and clinical outcome in HFpEF patients are shown in *Figure 3*. Various non-cardiac co-morbidities in HFpEF patients such as infection and exacerbation of HF increase inflammatory cytokines and the inflammatory response induce myocardial injury, including LV diastolic dysfunction and RV systolic dysfunction. Recently, statin use has been shown to exert a beneficial effect on mortality in HFpEF even in the absence of coronary artery disease.³⁹ Statins have not only low density lipoprotein cholesterol-lowering effects but also HDL-C-elevating effects.⁴⁰ Management of non-cardiac co-morbidities such as infection and nutrition status, and controlling HDL-C levels by using statins, may be the therapeutic goals in HFpEF patients.

Study limitations

This study has several limitations. First, we evaluated only CRP as an inflammatory marker. Other inflammatory markers, white blood cell (WBC), and the complete blood count parameters, such as neutrophil-lymphocyte ratio (NLR), were measured in the present study. These markers may be partially associated with the clinical outcome in HFpEF patients, but they cannot be established as stronger predictive markers for both all-cause death and cardiac death than the combination of HDL-C and CRP. Whether or not other inflammatory markers may be more useful for predicting the prognosis of HFpEF patients is unknown. Second, HDL-C was independently and significantly associated with cardiac death in the present results (Supporting Information, *Table S2*). HDL-C has various cardioprotective actions such as anti-inflammation, anti-oxidation, anti-apoptosis, and anti-thrombus effects. Future research would reveal the mechanism of HDL-C various actions on HFpEF. Third, in this study, the median age of the enrolled patients was 82 years [76, 87], and they have various non-cardiac co-morbidities. The risk of death in patients with HFpEF increases with co-morbidity burden, especially in the elderly.^{4,41,42} Analysis of our cohort including such populations was thought to be important and give a novel findings to the next studies. The ratio of the patients treated with ACE/ARBs, beta-blockers, and aldosterone antagonists was relatively low in our cohort. The reasons for low rates of the above mentioned medications are due to high age (the median age was 82 years old) and impaired renal function (the median eGFR was 44 mL/min/1.73 m²) in our cohort. The 249 patients with heart rate (HR) of <60 b.p.m., 70 patients with chronic obstructive pulmonary disease/asthma, and 350 patients with atrial fibrillation which had the risk of the bradycardia-tachycardia syndrome in this study. Fifth, in the present cohort, 119 patients (14.9%) died during a follow-up period of 420 days. The value was relatively high, but several studies showed that

1 year mortality in HFpEF varies from 20% to 29%.^{1,2,43} We believe that the value was not high compared with the previous reports.

Conclusions

In this prospective, multicentre, and observational study, HDL-C/CRP ratio, as an inflammation marker, was associated with all-cause death and cardiac death in HFpEF patients, and left ventricular diastolic function and right ventricular systolic function significantly correlated to HDL-C/CRP ratio.

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Conflict of interest

Daisaku Nakatani has received honoraria from Roche Diagnostics. Shungo Hikoso has received personal fees from Daiichi Sankyo Company, Bayer, Astellas Pharma, Pfizer Pharmaceuticals, and Boehringer Ingelheim Japan and received grants from Roche Diagnostics, FUJIFILM Toyama Chemical, and Actelion Pharmaceuticals. Yasushi Sakata received personal fees from Otsuka Pharmaceutical, Ono Pharmaceutical, Daiichi Sankyo Company, Mitsubishi Tanabe Pharma Corporation, and Actelion Pharmaceuticals and received grants from Roche Diagnostic, FUJIFILM Toyama Chemical, Abbott Medical Japan, Otsuka Pharmaceutical, Daiichi Sankyo Company, Mitsubishi Tanabe Pharma Corporation, and Biotronik. Other authors have no conflicts of interest to disclose.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. (A) ROC analysis of HDL-C/CRP ratio in predicting all-cause death in male. (B) ROC analysis of HDL-C/CRP ratio in predicting all-cause death in female. (C) ROC analysis of HDL-C/CRP ratio in predicting cardiac death in male. (D) ROC analysis of HDL-C/CRP ratio in predicting cardiac death in female.

AUC, area under the curve; CRP, C reactive protein; HDL-C, high density lipoprotein cholesterol; ROC, receiver operating characteristics.

Figure S2. (A) Kaplan–Meier analysis of all-cause death between the males with HDL-C/CRP ratio ≤ 1.73 and HDL-C/

CRP ratio > 1.73 . (B) Kaplan–Meier analysis of all-cause death between the males with HDL-C/CRP ratio ≤ 2.86 and HDL-C/CRP ratio > 2.86 . (C) Kaplan–Meier analysis of cardiac death between the males with HDL-C/CRP ratio ≤ 4.17 and HDL-C/CRP ratio > 4.17 . (D) Kaplan–Meier analysis of cardiac death between the males with HDL-C/CRP ratio ≤ 3.97 and HDL-C/CRP ratio > 3.97 .

CRP, C reactive protein; HDL-C, high density lipoprotein cholesterol.

Table S1 Framingham criteria.

Table S2 Cox proportional hazard analysis for cardiac death.

Table S3 Cox proportional hazard analysis for all-cause death.

Table S4. Supporting Information.

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