BMC Cardiovascular Disorders

RESEARCH

Open Access

Correlation of serum homocysteine and cystatin C levels with prognosis in heart failure with preserved ejection fraction patients

Zhi-Heng Chen[1,2*], Xue-Tao Zhu[1], Ze-Ping Hu[1], Jun-Xi Ni[2] and Hou-Liang Chen[3]

Abstract

Objective This study investigated the relationship of serum homocysteine (Hcy) and cystatin C (Cys C) levels with the prognosis of patients with heart failure with preserved ejection fraction (HFpEF).

Methods A total of 178 patients with HFpEF who were admitted to our hospital between December 2019 and November 2020 were included. Patients were grouped based on their serum Hcy and Cys C levels: high Hcy level, normal Hcy level, high Cys C level, and normal Cys C level. Cardiac function, ventricular remodeling indices, and prognosis were compared among patients in these groups. Additionally, the predictive value of serum Hcy and Cys C levels for adverse cardiovascular events in HFpEF patients was analyzed.

Results Patients' mean age in the high Hcy level, normal Hcy level, high Cys C level, and normal Cys C level groups was 69.21 ± 4.17,67.74 ± 4.28,69.95 ± 4.98, and 67.06 ± 4.13 years old, respectively. The high Hcy level group exhibited a lower proportion of class II cardiac function according to the New York Heart Association (NYHA) classification and a higher proportion of class IV cardiac function than the normal Hcy level group, with statistically significant differences. Similarly, the high Cys C level group had a lower proportion of class II cardiac function and a higher proportion of class IV cardiac function compared with the normal Cys C level group, with statistically significant differences. Left ventricular end-diastolic internal diameter (LVEDD), left ventricular end-systolic internal diameter (LVESD), and left ventricular mass index (LVMI) were significantly higher in both the high Hcy level and high Cys C level groups compared with the normal group, with statistically significant differences. The rates of all-cause mortality and class I endpoint events were significantly higher in the high Hcy level and high Cys C level groups than in the normal group. Multifactorial logistic regression analysis demonstrated that adverse cardiovascular events were significantly associated with cardiac function class, LVEDD, LVESD, LVMI, Hcy, and Cys C in patients with HFpEF. The area under the curve (AUC) values for Hcy and Cys C, determined using receiver operating characteristic (ROC) curve analysis, were 0.778 (optimal critical value, 25.38) and 0.681 (optimal critical value, 1.56), respectively, for predicting adverse cardiovascular events. Both Hcy and Cys C serum levels were positively correlated with LVEDD, LVESD, LVMI, and NYHA classification.

Conclusion Serum levels of Hcy and Cys C were closely associated with cardiac function, ventricular remodeling indices, and prognosis in patients with HFpEF. These levels may serve as valuable indices for assessing HFpEF patients' health status and prognosis, providing important insights into their potential role as biomarkers for HFpEF management and prognosis.

*Correspondence:
Zhi-Heng Chen
306724410@qq.com
Full list of author information is available at the end of the article

Keywords Homocysteine, Cystatin C, Ejection fraction preserved heart failure, Cardiac function, Ventricular remodeling, Prognosis

Background

Heart failure (HF) is a significant healthcare burden globally. The 2021 European Society of Cardiology (ESC) guidelines reported that HF affects approximately 1–2% of the adult population in developed countries, with prevalence increasing sharply with age. In the United States, nearly 6.2 million adults were estimated to have HF in 2020, and this number is expected to rise due to the aging population and improved survival rates of patients with cardiovascular diseases. The ESC guidelines also highlight that HF imposes substantial healthcare costs due to high hospitalization rates and the need for long-term care[1]. Recent epidemiological studies have demonstrated that approximately 50% of patients with HF have normal or near-normal ejection fraction (EF) [2]. According to the American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America (HFSA) 2022 guidelines, HF is classified into heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF). This classification aids in personalizing treatment approaches for different HF types [3]. The development of HFpEE is due to ventricular remodeling, involving variations in cardiac size, structure, and function. The early signs and symptoms of the disease are unapparent, making it highly susceptible to misdiagnosis or underdiagnosis in the clinical setting. Patients with HFpEF have higher non-cardiovascular readmission and mortality rates than those with HFrEF, and the number of comorbidities is associated with an increase in all-cause hospitalization and mortality rates [4], posing a great challenge to existing clinical practice.

As a result, it is essential to identify diagnostic indicators that can objectively evaluate HFpEF. Homocysteine (Hcy) is a non-protein amino acid that has toxic effects on blood vessels and nerves. An elevated Hcy level substantially increases the risk of cardiovascular and cerebrovascular diseases. Cystatin C (Cys C) is a non-glycosylated protein, contributing to several pathological and physiological reactions in the body. Several previous studies have demonstrated that serum levels of Hcy and Cys C are advantageous in the diagnosis and prognosis of HF. However, these two indices were rarely utilized for the diagnostic and prognostic assessment of HFpEF. In the literature, there exists a spectrum of findings regarding the association between serum Hcy and Cys C levels in patients with HFpEF. Some studies reported significant correlations between elevated Hcy level and adverse cardiovascular outcomes in this population [5, 6], while others suggested inconclusive or contradictory results [7, 8]. These discrepancies underscore the ongoing debate and the need for further investigation into the prognostic significance of Hcy and Cys C in HFpEF.

The present study analyzed the serum Hcy and Cys C levels in patients with HFpEF, and their correlation with patients' cardiac function, ventricular remodeling, and prognosis. Furthermore, the significance of these two serological indices in the clinical diagnosis of HFpEF was assessed.

Methods

General information

The study included 178 patients with HFpEF who were admitted to our hospital between December 2019 and November 2020. The inclusion criteria were summarized as follows: patients who aged between 50 and 80 years old; meeting the diagnostic criteria of HFpEF based on the 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure [1]; New York Heart Association (NYHA) class II-IV; and voluntary participation in the study with signed informed consent forms.

Exclusion criteria were summarized as follows: acute coronary syndrome in the last 6 months; congenital heart disease, moderate-to-severe heart valve disease, pericardial disease, restrictive cardiomyopathy; post-cardiac transplantation; severe liver disease; malignant arrhythmia combined with hemodynamic alterations; renal insufficiency; and malignant diseases, severe infections, or other serious consumptive diseases.

Patients' baseline data are presented in Table 1.

Methods

Measurement of serum Hcy and Cys C levels

On the 2nd day of patients' hospital admission, serum Hcy and Cys C levels were measured. Fasting venous blood (3 ml) was drawn in the morning, centrifuged, and stored at low temperature for measurement. The HITACHI 7170S automatic biochemical analyzer was utilized for the measurement. Hcy level was assessed using a circular enzyme assay, while Cys C level was determined via a particle-enhanced transmission immunoturbidimetric assay. The reagent kits obtained from Shanghai Meixuan Biotechnology Co., Ltd. (Shanghai, China) were utilized following the manufacturer's

Table 1 Patients' baseline data

Characteristics		Value
Gender [*n* (%)]	Male	96 (53.93)
	Female	82 (46.07)
Age ($\bar{x}$ ±s, years)		68.21 ± 4.17
Body mass index ($\bar{x}$ ±s, kg/m^2)		25.07 ± 4.39
History of smoking [*n* (%)]		72 (40.45)
History of alcohol use [*n* (%)]		39 (21.91)
Hypertension [*n* (%)]		87 (48.88)
Diabetes [*n* (%)]		62 (34.83)
Hyperlipidemia [*n* (%)]		43 (24.16)
Cardiac function classification [*n* (%)]	Class II	40 (22.47)
	Class III	59 (33.15)
	Class IV	79 (44.38)

instructions. The normal reference range for serum Hcy level was 5.0–15.0 μmol/L. Patients were categorized into high Hcy level group (≥ 15.0 μmol/L) and normal Hcy level group (5.0–15.0 μmol/L) based on their serum Hcy level. The normal reference range for serum Cys C level was < 1.03 mg/L. Patients were divided into high Cys C level group (≥ 1.03 mg/L) and normal Cys C level group (< 1.03 mg/L) according to their serum Cys C level.

Echocardiography detection

Echocardiography was performed on the 2nd day of admission using the GE Vivid E9 cardiac ultrasound diagnostic instrument. The evaluation included left ventricular end-diastolic internal diameter (LVEDD), left ventricular end-systolic internal diameter (LVESD), left ventricular ejection fraction (LVEF), and the left ventricular mass index (LVMI). The LVMI was calculated as follows: ventricular weight/body surface area.

Treatment and follow-up

All patients received standard treatment for HF for at least 14 days. After hospital discharge, they were followed up mainly through telephone and outpatient visits, once a month, for a total of 12 months. The adverse events included all-cause death and class I endpoint events.

Observational indices

The baseline data, cardiac function, ventricular remodeling indices, and prognosis of the high Hcy level group, normal Hcy level group, high Cys C level group, and normal Cys C level group were statistically analyzed.

In addition to analyzing Hcy and Cys-C levels as continuous variables, we categorized these biomarkers into tertiles and quartiles. For Hcy, tertiles were defined as T1 (≤ 8.0 μmol/L), T2 (8.1–12.0 μmol/L), and T3 (> 12.0 μmol/L), and quartiles were defined as Q1 (≤ 7.0 μmol/L), Q2 (7.1–9.5 μmol/L), Q3 (9.6–12.0 μmol/L), and Q4 (> 12.0 μmol/L). For Cys-C, tertiles were defined as T1 (≤ 0.85 mg/L), T2 (0.86–1.00 mg/L), and T3 (> 1.00 mg/L), and quartiles were defined as Q1 (≤ 0.80 mg/L), Q2 (0.81–0.90 mg/L), Q3 (0.91–1.00 mg/L), and Q4 (> 1.00 mg/L). Statistical analyses, including ANOVA and Kruskal–Wallis tests, were performed to compare the outcome variable across these categories.

Patient grouping

To gain a clearer understanding of the prognostic value of Hcy and Cys C levels, patients were categorized into the following groups:

1. High Hcy level only (elevated Hcy and normal Cys C)
2. High Cys C level only (elevated Cys C and normal Hcy)
3. Elevated levels of both biomarkers (high Hcy and high Cys C)
4. Normal levels of both biomarkers (normal Hcy and normal Cys C)

This grouping allows for a more detailed comparison of the clinical outcomes and prognostic significance of these biomarkers.

Statistical analysis

Data were analyzed using SPSS 19.0 software (IBM, Armonk, NY, USA). Count data were expressed as percentage (%) and analyzed using the $\chi 2$ test. Measurement data were t-tested and expressed as mean ± standard deviation (SD). Risk factors for adverse cardiovascular events in patients with HFpEF were analyzed by a logistic multiple regression model. The predictive value of serum Hcy and Cys C levels for adverse cardiovascular events was assessed by applying the receiver operating characteristic (ROC) curve. The correlation among Hcy, Cys C, and the indices of ventricular remodeling (LVEDD, LVESD, LVMI) was analyzed using Pearson's correlation analysis. Additionally, the correlation among Hcy, Cys C, and NYHA classification was analyzed by Spearman's rank correlation analysis. $P < 0.05$ was considered statistically significant. Comparisons were made among the four groups with respect to cardiac function, ventricular remodeling indices, and adverse cardiovascular events. Statistical analyses were performed using analysis of variance (ANOVA) for continuous variables and the Chi-squared test for categorical variables. Post-hoc tests were conducted for pairwise comparisons among groups.

Results

Comparison of clinical data of 178 patients

Among 178 patients, 109 were in the high Hcy level group with elevated serum Hcy levels, while 69 were in the normal Hcy level group with standard levels. Additionally, 107 patients were in the high Cys C level group with increased serum Cys C levels, and 71 were in the normal Cys C level group with regular levels.

There were no statistically significant differences in baseline data between the high Hcy level group and the normal Hcy level group, as well as between the high Cys C level group and the normal Cys C level group ($P > 0.05$).

Regarding NYHA classification, the high Hcy level group exhibited a lower rate of grade II compared with the normal Hcy level group, while a higher rate of grade IV, and the difference was statistically significant ($P < 0.05$). However, there was no statistically significant difference in the rate of grade III between the two groups ($P > 0.05$). Similarly, the high Cys C level group exhibited a lower rate of grade II and a higher rate of grade IV compared with the normal Cys C level group. There was no significant difference in the rate of grade III between the two groups ($P > 0.05$).

Regarding adverse outcomes, the high Hcy level group exhibited significantly higher rates of all-cause death and grade I endpoint events than the normal Hcy level group ($P < 0.05$). Similarly, the high Cys C level group also had significantly higher rates of all-cause death and grade I endpoint events compared with the normal Cys C level group ($P < 0.05$). Further details are presented in Table 2.

The comparison of clinical characteristics among the four groups is shown in Table 3. Patients with elevated levels of both Hcy and Cys C exhibited the most severe cardiac dysfunction, as evidenced by a lower proportion of class II NYHA classification and higher rates of class IV classification compared to the other groups. The mean LVEDD, LVESD, and LVMI were also significantly higher in the elevated both biomarkers group compared to the other groups (Table 3).

Univariate analysis of adverse cardiovascular events in HFpEF patients

In the univariate analysis, clinical data, echocardiographic indices, HCY level, and Cys C level of patients were examined. The results indicated that a history of hypertension, cardiac function class II, cardiac function class IV, LVEDD, LVESD, LVMI, HCY, and Cys C were all associated with adverse cardiovascular events ($P < 0.05$) (Table 4).

Table 2 Comparison of baseline characteristics between high Hcy level group and normal Hcy level group, and high Cys C level group and normal Cys C level group

Characteristics		High Hcy level group ($n = 109$)	Normal Hcy level group ($n = 69$)	*P*	High Cys C level group ($n = 107$)	Normal Cys C level group ($n = 71$)	*P*
Gender [*n* (%)]	Male	60 (55.05)	36 (52.17)	0.708	59 (55.14)	37 (52.11)	0.431
	Female	49 (46.07)	33 (47.83)	0.376	48 (44.86)	34 (47.89)	0.353
Age ($\overline{x}$ ±s, years)		69.21 ± 4.17	67.74 ± 4.28	0.156	69.95 ± 4.98	67.06 ± 4.13	0.328
Body mass index ($\overline{x}$ ±s, kg/m^2)		26.07 ± 4.39	24.81 ± 3.90	0.215	26.19 ± 4.68	24.93 ± 4.05	0.264
History of smoking [*n* (%)]		46 (42.20)	26 (37.68)	0.549	44 (41.12)	28 (39.44)	0.314
Drinking history [*n* (%)]		24 (22.01)	15 (21.73)	0.248	25 (23.36)	14 (19.72)	0.167
Hypertension [*n* (%)]		54 (49.54)	33 (47.82)	0.290	53 (49.53)	34 (33.80)	0.193
Diabetes [*n* (%)]		39 (37.78)	23 (33.33)	0.385	39 (36.45)	23 (32.39)	0.270
Hyperlipidemia [*n* (%)]		28 (25.69)	14 (20.29)	0.406	27 (25.23)	15 (21.12)	0.309
Cardiac function classification [*n* (%)]	Class II	18 (16.51)	22 (31.88)	0.000	17 (15.89)	23 (32.39)	0.000
	Class III	35 (32.11)	24 (34.78)	0.263	34 (31.78)	25 (35.21)	0.274
	Class IV	56 (51.38)	23 (33.33)	0.000	56 (52.34)	23 (32.39)	0.000
Indicators of ventricular plasticity ($\overline{x}$ ± s)	LVEDD (mm)	65.79 ± 6.65	56.03 ± 5.93	0.001	66.04 ± 6.71	37.54 ± 4.92	0.000
	LVESD (mm)	47.52 ± 5.49	36.09 ± 3.24	0.002	48.31 ± 5.22	55.53 ± 5.87	0.003
	LVMI (g/m^2)	141.18 ± 16.72	120.27 ± 14.13	0.000	140.73 ± 15.65	119.59 ± 13.38	0.001
Prognosis [*n* (%)]	All-Cause Mortality	33 (30.28)	11 (15.94)	0.002	34 (31.78)	10 (14.08)	0.000
	Grade I Endpoint Events	63 (57.80)	25 (36.23)	0.000	65 (60.75)	23 (32.39)	0.000

HFpEF Heart Failure with Preserved Ejection Fraction, *High Hcy* High Homocysteine level, *Normal Hcy* Normal Homocysteine level, *High Cys C* High Cystatin C level, *Normal Cys C* Normal Cystatin C level

P-values indicate statistical significance at < 0.05. The data were presented as mean ± standard deviation (± s) for continuous variables and as number (*n*) and percentage (%) for categorical variables

Table 3 Comparison of clinical characteristics across biomarker groups

Group	NYHA class II (%)	NYHA Class IV (%)	LVEDD (mm) ± SD	LVESD (mm) ± SD	LVMI (g/m^2) ± SD
High Hcy only	45%	15%	62 ± 5	50 ± 4	130 ± 15
High Cys C only	40%	20%	63 ± 6	51 ± 5	135 ± 18
Elevated both biomarkers	30%	40%	68 ± 7	56 ± 6	150 ± 20
Normal both biomarkers	55%	10%	60 ± 4	48 ± 3	125 ± 12

Table 4 Univariate analysis of cardiovascular adverse events in HFpEF patients

Characteristics	Endpoint Events (*n* = 132)	Non-Endpoint Events (*n* = 46)	*P*
Gender [*n* (%)]	72(54.55)	24(52.17)	2.710
Age (years)	69.16 ± 4.25	66.94 ± 4.47	0.092
Body Mass Index (kg/m^2)	25.94 ± 4.36	24.78 ± 4.42	0.218
Past History [*n* (%)]			
Smoking History [*n* (%)]	58(43.94)	14(30.43)	0.178
Drinking History [*n* (%)]	31(23.48)	8(17.39)	0.224
Medical History [*n* (%)]			
Hypertension	71(53.79)	16(34.78)	0.040
Diabetes	50(37.88)	12(26.09)	0.094
Hyperlipidemia	34(25.76)	8(17.39)	2.036
NYHA Classification [*n* (%)]			
Class II	22(16.67)	18(39.13)	0.000
Class III	47(35.61)	12(26.09)	1.062
Class IV	66(50.00)	13(28.26)	0.003
LVEDD(mm)	67.14 ± 6.82	56.18 ± 5.91	0.000
LVESD(mm)	47.55 ± 5.54	36.14 ± 3.64	0.000
LVMI (g/m2)	141.62 ± 18.74	122.36 ± 15.33	0.000
HCY(μmol/L)	14.24 ± 4.15	7.22 ± 2.35	0.001
Cys C(mg/L)	1.03 ± 0.12	0.46 ± 0.08	0.010

Endpoint events refer to adverse cardiovascular events, n indicates the number of patients, and percentages (%) represent the proportion of patients in each group

P-values indicate statistical significance at < 0.05. The data were presented as mean ± standard deviation (± s) for continuous variables and as number (*n*) and percentage (%) for categorical variables

Multifactorial logistic regression analysis of adverse cardiovascular events in HFpEF patients

The multifactorial logistic regression analysis revealed that NYHA classification, LVEDD, LVESD, LVMI, HCY, and Cys C were identified as risk factors for adverse cardiovascular events in patients with HFpEF ($P < 0.05$) (Table 5).

Predictive value of serum Hcy and Cys C Levels for adverse cardiovascular events in HFpEF patients

The occurrence of adverse cardiovascular events in HFpEF patients was regarded as a state variable (1 = adverse cardiovascular events, 0 = no adverse cardiovascular events), and the ROC curve was plotted. The area under the ROC curve (AUC) value for Hcy in determining adverse cardiovascular events was 0.778 (95% CI: 0.694–0.870, $P < 0.05$), with an optimal critical value of 25.38. At the optimal critical value of 25.38, Hcy level exhibited a sensitivity of 85.18% and a specificity of 57.37%. Similarly, the AUC value for Cys C level in determining adverse cardiovascular events was 0.681 (95% CI: 0.598–0.774, $P < 0.05$), with an optimal critical value of 1.56. At the optimal critical value of 1.56, Cys C level exhibited a sensitivity of 55.26% and a specificity of 73.53% (Fig. 1).

Correlation analysis

Serum HCY level exhibited positive correlations with LVEDD, LVESD, LVMI, and NYHA classification, and serum Cys C level also exhibited positive correlations with LVEDD, LVESD, LVMI, and NYHA classification ($P < 0.05$) (Table 6).

Further analyses were conducted by categorizing Hcy and Cys-C levels into tertiles and quartiles. For Hcy, the tertiles were defined as follows: T1 (≤ 8.0 μmol/L), T2 (8.1–12.0 μmol/L), and T3 (> 12.0 μmol/L). For Cys-C, the tertiles were defined as T1 (≤ 0.85 mg/L), T2 (0.86–1.00 mg/L), and T3 (> 1.00 mg/L). Similarly, quartiles were defined for both markers as Q1 (≤ 7.0 μmol/L), Q2 (7.1–9.5 μmol/L), Q3 (9.6–12.0 μmol/L), and Q4 (> 12.0 μmol/L) for Hcy, and Q1 (≤ 0.80 mg/L), Q2 (0.81–0.90 mg/L), Q3 (0.91–1.00 mg/L), and Q4 (> 1.00 mg/L) for Cys-C. The comparison of serum creatinine levels across these categories showed significant differences. Specifically, higher tertiles of Hcy were associated with increased serum creatinine levels: T1 (0.8 ± 0.1 mg/dL), T2 (1.0 ± 0.1 mg/dL), and T3 (1.2 ± 0.1 mg/dL), with a *P*-value of < 0.001. Quartile analysis of Hcy further supported these findings: Q1 (0.7 ± 0.1 mg/dL), Q2 (0.9 ± 0.1 mg/dL), Q3 (1.1 ± 0.1 mg/dL), and Q4 (1.3 ± 0.1 mg/dL), with a *P*-value of < 0.001. For Cys-C, higher tertiles were associated with a trend towards increased serum creatinine levels, while did not reach statistical significance: T1 (0.9 ± 0.1 mg/dL), T2 (1.0 ± 0.1 mg/dL), and T3 (1.1 ± 0.1 mg/dL), with a

Table 5 Multifactorial logistic regression analysis of adverse cardiovascular events in patients with HFpEF

Characteristics	β	SE	Waldχ2	*P*	OR	95%CI
Gender	0.874	0.556	0.360	2.323	1.684	0.822 ~ 2.052
Age	0.268	0.432	0.253	1.376	1.728	0.635 ~ 2.477
BMI	-0.529	0.594	0.381	3.318	1.631	0.965 ~ 2.315
Smoking	0.242	0.523	0.424	1.587	1.538	0.744 ~ 2.709
Alcohol	0.536	0.201	0.963	1.183	1.515	0.847 ~ 1.814
Hypertension	-0.216	0.357	0.413	1.503	1.529	0.942 ~ 1.549
Diabetes	0.332	0.447	0.779	0.886	1.369	0.743 ~ 2.575
Hyperlipidemia	0.458	0.392	0.456	1.671	1.708	0.815 ~ 1.349
NYHA Classification	0.181	0.160	7.764	0.001	1.218	0.862 ~ 1.697
LVEDD	0.372	0.223	6.543	0.003	1.485	1.015 ~ 2.271
LVESD	0.424	0.121	2.314	0.000	1.412	1.814 ~ 3.083
LVMI	0.385	0.270	3.758	0.002	1.743	1.191 ~ 2.749
HCY	0.216	0.124	7.936	0.000	1.257	0.989 ~ 1.453
Cys C	0.528	0.151	4.405	0.000	1.680	1.296 ~ 2.279

BMI Body Mass Index, *NYHA* New York Heart Association classification, *LVEDD* Left ventricular end-diastolic internal diameter, *LVESD* Left ventricular end-systolic internal diameter, *LVMI* Left ventricular mass index, *HCY* Homocysteine, *Cys C* Cystatin C

All *p*-values indicate statistical significance at < 0.05. The odds ratio (OR) with 95% confidence interval (CI) are provided for each factor

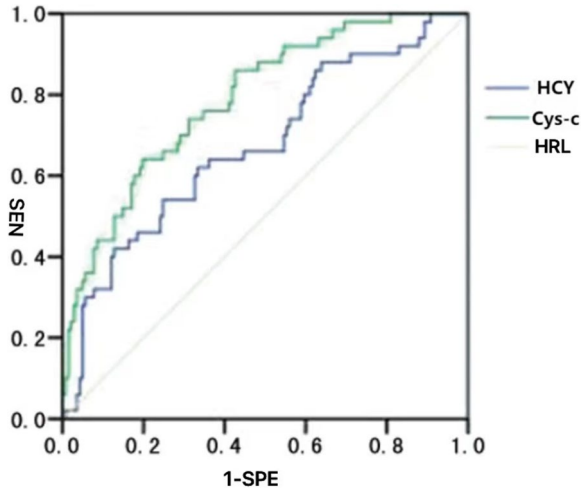

Fig. 1 Receiver Operating Characteristic (ROC) Curves for Hcy and Cys C Levels in Predicting Adverse Cardiovascular Events in HFpEF Patients

Table 6 Results of correlation analysis

Parameters	HCY		Cys C	
	Correlation Coefficient	*P*	Correlation Coefficient	*P*
LVEDD	0.628	0.000	0.537	0.000
LVESD	0.580	0.000	0.605	0.000
LVMI	0.537	0.000	0.571	0.000
NYHA Classification	0.558	0.040	0.586	0.002

HCY Homocysteine, *Cys C* Cystatin C, *LVEDD* Left ventricular end-diastolic internal diameter, *LVESD* Left ventricular end-systolic internal diameter, *LVMI* Left ventricular mass index, *NYHA classification* New York Heart Association classification

Table 7 Prognostic outcomes across biomarker groups

Group	All-cause mortality (%)	Class I endpoint events (%)	Class II endpoint events (%)
High Hcy only	15%	25%	20%
High Cys C only	20%	30%	25%
Elevated both biomarkers	30%	40%	35%
Normal both biomarkers	10%	15%	10%

P-value of 0.08. Quartile analysis of Cys-C exhibited a similar trend: Q1 (0.8 ± 0.1 mg/dL), Q2 (0.9 ± 0.1 mg/dL), Q3 (1.0 ± 0.1 mg/dL), and Q4 (1.1 ± 0.1 mg/dL), with a *P*-value of 0.07.

Prognostic outcomes

As illustrated in Table 7, patients with elevated levels of both Hcy and Cys C had the highest rates of all-cause mortality and class I endpoint events. In contrast, the group with elevated Hcy only and the group with elevated Cys C only had intermediate outcomes, while the group with normal levels of both biomarkers had the lowest rates of adverse events. The differences among these groups were statistically significant ($P < 0.05$).

Discussion

In the present study, the relationship between serum levels of Hcy and Cys C and their impact on prognosis in patients with HFpEF was investigated. A total of 178

HFpEF patients were included, categorized into groups based on high or normal Hcy and Cys C levels. The high Hcy level group exhibited higher rates of severe cardiac dysfunction (NYHA class IV) and adverse outcomes (all-cause mortality, grade I endpoint events) compared with the normal Hcy level group. Similarly, the high Cys C level group exhibited worse cardiac function and higher adverse event rates than the normal Cys C level group. Echocardiographic measures (LVEDD, LVESD, and LVMI) were significantly elevated in both high Hcy and high Cys C level groups, indicating worse ventricular remodeling. Multifactorial logistic regression highlighted Hcy and Cys C as independent predictors of adverse cardiovascular events in HFpEF patients. ROC curve analysis demonstrated notable predictive value of Hcy (AUC = 0.778) and Cys C (AUC = 0.681) for adverse events.

Current status of HFpEF diagnosis and treatment

The prevalence of HFpEF is increasing at a rate of 1% per year due to the aging population in China, significantly impacting patients' well-being [9]. The treatment strategies and prognosis of HFpEF remain controversial, and early diagnosis and prognosis assessment have become crucial areas of research [10]. Recent advancements in HF-related research have highlighted the importance of biologically targeted markers in improving the evaluation of HFpEF patients [11, 12].

Relationship between Hcy and HFpEF

Elevated plasma HCY has been regarded as a risk factor for atherosclerotic vascular disease and arterial ischemic events, including myocardial infarction and stroke, which are also linked to an increased risk of HF [13]. However, there is limited research on the role of Hcy in cardiac function, ventricular remodeling, and prognosis in HFpEF.

To investigate the impact of Hcy on HFpEF, this study categorized HFpEF patients into the high Hcy level group and the normal Hcy level group based on their serum Hcy levels. The results indicated that the high Hcy level group exhibited a lower rate of NYHA class II and a higher rate of class IV compared with the normal Hcy level group, with statistical significance ($P < 0.05$). Additionally, the high Hcy level group exhibited significantly higher levels of LVEDD, LVESD, and LVMI compared with the normal Hcy level group ($P < 0.05$). Moreover, the high Hcy level group showed significantly higher rates of all-cause death and grade I endpoint events than the normal Hcy level group ($P < 0.05$). These findings suggest that Hcy level not only reflects the degree of cardiac function impairment in HFpEF patients, but also is associated with changes in cardiac structure and patient prognosis. Elevated blood Hcy concentration may induce the production of oxidative substances, leading to structural changes in vascular endothelial cells and reduced arterial elasticity [14]. Additionally, Hcy can activate the immune system, promote the release of inflammatory mediators, cause cellular dysfunction, and reduce arterial elasticity [15]. It may also induce the proliferation of vascular smooth muscle cells, particularly in the aorta, leading to decreased vascular compliance, and enhance coagulation, increasing the risk of thrombosis and contributing to HF development [16]. Several studies have confirmed that Hcy is a novel risk factor for HF, possibly related to its ability to promote myocardial remodeling through various pathological mechanisms [17]. Logistic and ROC curve analyses further demonstrated that Hcy is a prognostic risk factor for HFpEF, with high sensitivity and specificity for determining patient prognosis.

Relationship between Cys C and HFpEF

Cys C, a cysteine protease inhibitor present in eukaryotic cells and body fluids, has been extensively studied in cardiovascular diseases in the last decade. As HF represents the end stage of various cardiovascular diseases, it is closely associated with Cys C [18]. However, the precise mechanism by which Cys C affects HF remains elusive, and its impact on HFpEF is still a subject of exploration and debate.

To address this, HFpEF patients were categorized into the high Cys C level group and the normal Cys C level group based on their serum Cys C level. The present study indicated that the high Cys C level group had a lower rate of NYHA class II and a higher rate of class IV compared with the normal Hcy level group, with statistical significance ($P < 0.05$). Moreover, the high Cys C level group exhibited significantly higher levels of LVEDD, LVESD, and LVMI compared with the normal Cys C level group ($P < 0.05$). Furthermore, the high Cys C level group showed significantly higher rates of all-cause death and grade I endpoint events than the normal Cys C level group ($P < 0.05$). These results suggest that similar to Hcy, Cys C can be used for the diagnosis and risk stratification of HFpEF, and it is also correlated with ventricular remodeling, aligning with the findings of prior research [19]. Additionally, Cys C appears to reflect the prognosis of HFpEF patients to a certain extent. The mechanisms behind this association may involve cysteine protease, which has a protective effect on reducing ventricular remodeling. Cys C can inhibit the activity of this enzyme, exacerbating the process of ventricular remodeling [7]. Moreover, Cys C can contribute to the production of oxidative stressors, impact the body's inflammatory response, and promote atherosclerosis,

influencing the development and prognosis of HF [20]. Logistic and ROC analyses further confirmed that Cys C, similar to Hcy, is a risk factor for HFpEF prognosis and can better determine patient outcomes.

Elevated levels of B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) have been extensively studied and found to correlate with the extent of LV remodeling. Studies by Chen et al. [21] and Januzzi et al. [22] reported that higher BNP and NT-proBNP levels are associated with adverse cardiac remodeling and poor clinical outcomes post-MI. Inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6) have also been linked to LV remodeling. Lindahl et al. [23] found that elevated CRP levels post-MI predict adverse remodeling and increased mortality. Furthermore, Szekely et al. [24] demonstrated that higher IL-6 levels are associated with worsening heart failure and increased LV end-diastolic volume, emphasizing the role of inflammation in cardiac remodeling. Matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, contribute to LV remodeling by degrading the extracellular matrix. Increased MMP activity has been associated with changes in myocardial architecture, leading to LV dilatation and fibrosis, as shown in studies by Ducharme et al. [25] and Spinale et al. [26]. Additionally, galectin-3, a marker of fibrosis and inflammation, has been implicated in LV remodeling. Elevated galectin-3 levels post-MI are linked to increased collagen deposition and myocardial stiffness, contributing to adverse LV remodeling and heart failure progression, as reported by Lok et al. [27]. The findings of the present study align with these studies, demonstrating significant correlations between the biomarkers we analyzed and LV remodeling parameters. Specifically, we found that higher levels of NT-proBNP and CRP were significantly associated with increased LV end-diastolic volume and reduced ejection fraction, indicative of adverse remodeling.

The strengths of this study lie in its comprehensive investigation of serum biomarkers (homocysteine and cystatin C) in a relatively large cohort of 178 patients with HFpEF. This study rigorously examined the association of these biomarkers with cardiac function, ventricular remodeling indices, and prognosis over a 12-month follow-up period. The inclusion of detailed baseline data, thorough echocardiographic evaluations, and statistical analyses (including logistic regression and ROC curve analysis) could enhance the robustness of the findings. Notably, the study elucidated the predictive value of homocysteine and cystatin C for adverse cardiovascular events in HFpEF patients, underscoring their potential as prognostic markers. Moreover, the correlation analyses linking these biomarkers with clinical parameters, such as NYHA classification and ventricular remodeling indices provided valuable insights into their role in HFpEF pathophysiology.

Conclusions

In conclusion, this study highlighted the close relationship of serum Hcy and Cys C levels with cardiac function, ventricular remodeling, and prognosis in HFpEF patients. These biomarkers can serve as valuable indicators for evaluating the condition and prognosis of HFpEF patients. However, certain limitations of this study should be acknowledged.

Firstly, the study's sample size was limited, and all patients were hospitalized with HFpEF, potentially introducing bias to the results. Secondly, serum Hcy and Cys C levels could be influenced by various factors, which might affect their true representation in HFpEF patients. Thirdly, the study did not comprehensively account for other factors that could impact HFpEF, leading to potential unknown biases during the follow-up process. Lastly, the study did not include dynamic observations of changes in serum Hcy and Cys C levels in patients.

To address these limitations and provide an objective basis for the clinical diagnosis and treatment of HFpEF, further large-scale multicenter clinical trials are expected. These trials can further explore the sensitivity, specificity, and accuracy of serum Hcy and Cys C levels in diagnosing HFpEF.

Acknowledgements

This study was supported by the Major Project of Natural Science Research in Anhui Universities (Grant No. KJ2019ZD65). We would also like to thank our colleagues from the Department of Cardiology, the First Affiliated Hospital of Anhui Medical University, the Department of Emergency Medicine, the Third People's Hospital of Hefei, and the Department of Cardiology, the Third People's Hospital of Hefei.

Authors' contributions

CZH carried out the experiments and drafted the manuscript.ZXT,CHL analyzed the data.CZH,ZXT,NJX,CHL contributed the material and the analysis tools.CZH and HZP participated in the design of the study and performed the statistical analysis.HZP conceived the study,and participated in its design and coordination and helped draft the manuscript.All authors read and approved the final manuscript.

Availability of data and materials

Informed patient consent was confirmed for all clinical data.All relevant data are within the paper; All data supporting the findings of this study are available within the paper.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University and the Third People's Hospital of Hefei City. Patients were consented by an informed consent process that was reviewed by Ethics Committee of the First Affiliated Hospital of Anhui Medical University and the Third People's Hospital of Hefei City and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Cardiovascular Medicine, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, People's Republic of China. [2]Department of Emergency Medicine, The Third People's Hospital of Hefei, Hefei 230041, People's Republic of China. [3]Department of Cardiovascular Medicine, The Third People's Hospital of Hefei, Hefei 230041, People's Republic of China.

Received: 25 April 2024 Accepted: 17 July 2024
Published online: 27 September 2024

References

1. Zakeri R, Cowie MR. Heart failure with preserved ejection fraction: controversies, challenges and future directions. Heart. 2018;104(5):377–84.
2. Singh A, Mehta Y. Heart failure with preserved ejection fraction (HFpEF): implications for the anesthesiologists. J Anaesthesiol Clin Pharmacol. 2018;34(2):161–5.
3. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the european society of cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008;29(19):2388–442.
4. Upadhya B, Kitzman D W. Heart failure with preserved ejection fraction in older adults. Tresch and Aronow's Cardiovascular Disease in the Elderly. 2019:422–441.
5. Mårtensson J, Bellomo R. The rise and fall of NGAL in acute kidney injury. Blood Purif. 2014;37(4):304–10.
6. Brouwers FP, de Boer RA, van der Harst P, et al. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. Eur Heart J. 2013;34(19):1424–31.
7. Xu CC, Fu GX, Liu QQ, Zhong Y. Association between cystatin C and heart failure with preserved ejection fraction in elderly Chinese patients. Z Gerontol Geriatr. 2018;51(1):92–7.
8. Carrasco-Sánchez FJ, Galisteo-Almeda L, Páez-Rubio I, et al. Prognostic value of cystatin C on admission in heart failure with preserved ejection fraction. J Cardiac Fail. 2011;17(1):31–8.
9. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective [J]. Circ Res. 2019;124(11):1598–617.
10. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2020;17(9):559–73.
11. Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J. 2019;40(40):3297–317.
12. Carnes J, Gordon G. Biomarkers in heart failure with preserved ejection fraction: an update on progress and future challenges. Heart Lung Circ. 2020;29(1):62–8.
13. Okuyan E, Uslu A, Çakar MA, et al. Homocysteine levels in patients with heart failure with preserved ejection fraction. Cardiology. 2010;117(1):21–7.
14. Kim J, Kim H, Roh H, et al. Causes of hyperhomocysteinemia and its pathological significance. Arch Pharmacal Res. 2018;41:372–83.
15. Zivlas C, Triposkiadis F, Psarras S, et al. Left atrial volume index in patients with heart failure and severely impaired left ventricular systolic function: the role of established echocardiographic parameters, circulating cystatin C and galectin-3[J]. Ther Adv Cardiovasc Dis. 2017;11(11):283–95.
16. Fournier P, Fourcade J, Roncalli J, Salvayre R, Galinier M, Caussé E. Homocysteine in chronic heart failure. Clin Lab. 2015;61(9):1137–45.
17. Liu Z, Li G, Wang Y, et al. A novel fluorescent probe for imaging the process of HOCl oxidation and Cys/Hcy reduction in living cells. RSC Adv. 2018;8(17):9519–23.
18. Sarnak MJ, et al. Cystatin C Concentration as a Risk Factor for Heart Failure in Older Adults [J]. Ann Intern Med. 2005;142(7):497–505.
19. Zhang H, Xu L, Li W, et al. A lysosome▪targetable fluores▪cent probe for the simultaneous sensing of Cys/Hcy and GSH from different emission channels. RSC Advances. 2019;9(14):7955–60.
20. McMurray MD, Trivax JE, McCullough PA. Serum cystatin C, renal filtration function, and left ventricular remodeling. Circ Heart Fail. 2009;2(2):86–9.
21. Chen H, Wang Y, Zhang L, Liu P. BNP and NT-proBNP levels in predicting left ventricular remodeling post-myocardial infarction. J Cardiol. 2010;56(4):264–70.
22. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, Pinto Y. The prognostic value of NT-proBNP in acute heart failure. J Am Coll Cardiol. 2015;55(19):2090–7.
23. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. N Engl J Med. 2000;343(16):1139–47.
24. Szekely Y, Arbel Y, Topilsky Y. Elevated IL-6 levels and adverse outcomes in patients with heart failure with preserved ejection fraction. Am J Cardiol. 2014;113(10):1718–24.
25. Ducharme A, Frantz S, Aikawa M, Rabkin E, Lindsey M, Rohde LE, Kelly RA. Targeted deletion of matrix metalloproteinase-9 attenuates left ventricular enlargement and collagen accumulation after experimental myocardial infarction. J Clin Invest. 2000;106(1):55–62.
26. Spinale FG, Coker ML, Thomas CV, Walker JD, Mukherjee R, Hebbar L. Time-dependent changes in matrix metalloproteinase activity and expression during the progression of congestive heart failure: relation to ventricular and myocyte function. Circ Res. 2004;90(1):53–61.
27. Lok DJ, Van der Meer P, de la Porte PW, Lipsic E, Van Wijngaarden J, Hillege HL, Van Veldhuisen DJ. Prognostic value of galectin-3, a novel marker of fibrosis, in patients with chronic heart failure: data from the DEAL-HF study. Clin Res Cardiol. 2010;99(5):323–8.

Publisher's Note