International Journal of General Medicine

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

The Clinical Value of Apolipoprotein C3 Combined with FAR and RWT in Heart Failure with Preserved Ejection Fraction

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Objective: Heart failure with preserved ejection fraction (HFpEF) is becoming increasingly prevalent, yet clinical practice lacks specific biomarkers, early diagnostic tools, and reliable risk assessment methods. Given the growing burden of HFpEF, identifying novel diagnostic markers is crucial. This study investigates the diagnostic potential of apolipoprotein C3 (ApoC3) in HFpEF and its correlation with ventricular structure.

Methods: We analyzed data from HFpEF patients admitted to the Kunshan Branch of Gusu College of Nanjing Medical University and the First People's Hospital of Kunshan (March–December 2023). Controls included HFrEF+HFmrEF patients and healthy individuals. Enzyme-linked immunosorbent assay (ELISA) was used to detect the concentration of ApoC3 in all collected cases. The receiver operating characteristic (ROC) curve was plotted to evaluate the diagnostic performance of ApoC3 alone and combined with the fibrinogen-to-albumin ratio (FAR) in plasma, and the relative wall thickness (RWT) in echocardiography for HFpEF.

Results: After exclusions, 80 HFpEF patients (39 male, 41 female), 41 HFrEF+HFmrEF patients (27 male, 14 female), and 79 healthy controls (53 male, 26 female) were included. ApoC3 levels were significantly higher in HFpEF (63136.03±12,113.07 ng/mL) than in HFrEF+HFmrEF (55580.84±13,685.35 ng/mL) and controls (53090.31±5893.25 ng/mL, P<0.001). ROC analysis demonstrated that ApoC3 alone (AUC=0.836) and the combined index (ApoC3+FAR+RWT, AUC=0.891) effectively distinguished HFpEF. Both also aided in differentiating HFpEF from HFrEF+HFmrEF (AUC=0.702 vs 0.823).

Conclusion: ApoC3 is a promising biomarker for HFpEF diagnosis, and the combined index (ApoC3+FAR+RWT) enhances diagnostic accuracy. These findings may improve early detection and clinical management of HFpEF.

Keywords: heart failure with preserved ejection fraction, apolipoprotein C3, fibrinogen-to-albumin ratio, relative wall thickness, diagnosis

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a complex and highly heterogeneous type of heart failure characterized by a normal or near-normal left ventricular ejection fraction (LVEF) (usually ≥ 50%), yet patients still exhibit typical symptoms and signs of heart failure. Epidemiological statistics indicate that in the United States, the HFpEF phenotype accounts for about 50% of heart failure (HF) patients, and the prevalence of HFpEF is increasing at a rate of 1% per year compared to heart failure with reduced ejection fraction (HFrEF). With the aging population and the increase in risk factors such as hypertension, obesity, and diabetes, HFpEF is likely to become the most prevalent HF phenotype.[1] Current research on the diagnosis and treatment of HFrEF has been clearly explained and standardized in HF guidelines.[2] N-terminal pro-B-type natriuretic peptide (NT-proBNP), a common diagnostic indicator for HF, is widely used in clinical practice. However, this indicator is still unsatisfactory in distinguishing between HFpEF and HFrEF, and NT-proBNP testing is affected by various factors such as renal function, gender, and obesity.[3] Moreover, NT-proBNP can also be significantly elevated in other cardiovascular diseases or non-cardiovascular diseases, affecting the specificity of the diagnosis.[4] To date, there is no single feasible indicator for the diagnosis of HFpEF; it is necessary to rely on

Received: 5 April 2025
Accepted: 4 July 2025
Published: 12 July 2025

a comprehensive approach that includes clinical symptoms and signs, laboratory tests, echocardiography, exercise testing, cardiac magnetic resonance imaging, and myocardial biopsy for clarification. Therefore, finding an easily detectable indicator is of significant importance for the early diagnosis of HFpEF.

In recent years, research into the pathological mechanisms of HFpEF development has been intensifying. Although the exact mechanism has not been clearly defined, studies indicate that the pathogenesis involves multiple factors, including myocardial hypertrophy, microvascular dysfunction, inflammatory response, oxidative stress, and metabolic disorders, among others. HFpEF is also associated with a variety of clinical comorbidities. Compared to HFrEF, the 5-year survival rates are similar, but HFpEF carries a higher risk of cardiovascular events and recurrent heart failure hospitalizations.[5] Therefore, exploring new biomarkers and imaging indicators for early assessment and prognosis of HFpEF patients can aid in achieving early intervention in clinical diagnosis and treatment.

The Fibrinogen-to-Albumin Ratio (FAR) is a relatively new biomarker proposed in recent years. It assesses the body's inflammatory state, coagulation function, and nutritional status by calculating the ratio of fibrinogen (Fibrinogen, FIB) levels to albumin (Albumin, ALB) levels. FIB is a glycoprotein synthesized and secreted by the liver, stable and abundant in peripheral blood. Thrombin converts FIB into fibrin, which is crucial for physiological hemostasis. During inflammation within the body, FIB exhibits a ligand-receptor pattern of interaction with various immune cells. It can directly or indirectly interact with vascular endothelial cells, smooth muscle cells, and inflammatory cells, thereby actively participating in the inflammatory response process as a pro-inflammatory factor.[6] ALB is a protein synthesized by hepatocytes, accounting for 40–60% of the total protein in the human body. Both inflammation and malnutrition reduce the synthesis rate of albumin, thus lowering its concentration, making it a negative acute-phase reactant protein. A decrease in its levels typically reflects an enhanced inflammatory state or malnutrition.[7] In recent years, researchers have calculated the ratio of these two to derive the new indicator FAR. An elevated FAR usually indicates an enhanced inflammatory state, hypercoagulability, or malnutrition. Numerous studies have confirmed that a high FAR is associated with an increased risk of recurrent stroke due to large artery atherosclerosis[8] and the occurrence of adverse cardiovascular events.[9] Furthermore, Xu et al analyzed the large database of the Medical Information Mart for Intensive Care (MIMIC-IV v2.0) and its clinical data, concluding that FAR is an independent prognostic factor for 90-day and 1-year all-cause mortality in HF patients.[10] Liu et al further evaluated the prognostic value of FAR in HFpEF and found that FAR has a certain predictive value for adverse outcomes, including heart failure readmission or death within 2 years for HFpEF patients[11.] However, the results of this study lack more clinical data support. Overall, there are fewer clinical correlation studies on FAR and HFpEF, and no studies have explored the diagnostic value of FAR in HFpEF.

Relative Wall Thickness (RWT) is an important indicator for assessing the geometric structure of the left ventricle and is commonly used to distinguish types of left ventricular hypertrophy. A Ganau et al first systematically proposed the cut-off points for RWT in the study of left ventricular hypertrophy and geometric remodeling patterns in patients with essential hypertension, typically 0.42, to differentiate left ventricular geometric morphology. Generally, RWT > 0.42 suggests concentric remodeling or concentric hypertrophy; RWT ≤ 0.42 suggests eccentric hypertrophy or normal geometric morphology.[12] H M Krumholz et al further validated the significance of the RWT cut-off point (0.42) in predicting cardiovascular events based on Framingham Heart Study data, finding that RWT > 0.42 is significantly associated with increased cardiovascular risk.[13] Moreover, studies have found that RWT is an independent predictor of left ventricular systolic and diastolic dysfunction in patients with essential hypertension,[14] with increased RWT being significantly associated with left ventricular diastolic dysfunction. In the guidelines for heart failure,[2] RWT is an important indicator for evaluating the diagnosis of HFpEF, but it is not an independent diagnostic criterion. Currently, we believe that left ventricular diastolic dysfunction is a major mechanism of HFpEF, and Li et al used a nomogram to predict the risk of HFpEF and ultimately concluded that RWT is an independent influencing factor for the risk of HFpEF,[15] associated with adverse outcomes of HFpEF prognosis.

Apolipoprotein C3 (ApoC3) is an apolipoprotein consisting of 79 amino acids, primarily produced by the liver in the body, with a small portion produced by the intestines,[16] mainly involved in the regulation of lipid metabolism. With the deepening of research in recent years, it has been found that elevated levels of ApoC3 are associated with an increased risk of cardiovascular diseases such as atherosclerosis,[17] coronary heart disease,[18] and heart failure.[19] In the development of these diseases, ApoC3 mainly affects the body's metabolism by regulating lipid function[20] participates in systemic

inflammatory responses and oxidative stress, and causes endothelial dysfunction.[21] Through extensive literature review, we found that Gunjan Dixit et al had conducted a plasma proteomic analysis, in which a study analyzed and screened circulating proteins to identify candidate biomarkers for atrial fibrillation (Atrial fibrillation, AF), coronary microvascular disease (Coronary Microvascular Disease, CMD), and HFpEF. The results showed a significant increase in ApoC3 levels in HFpEF.[22] We also found that in a study on the LVDD formation mechanism (the central mechanism of HFpEF), researchers ultimately identified ApoC3 as one of the core proteins involved in the LVDD mechanism induced by ADRB3-KO (β3-adrenergic receptor knockout) through a protein-protein interaction network.[23] In meta-analyses using genome-wide association studies and Mendelian randomization proteomics to identify drug targets for heart failure, seven proteins were identified as potential targets for primary prevention interventions for heart failure. The ApoC3 gene received the highest level of evidence in these analyses (FDR 5% and PP.H4> 0.8),[24] but these results lack more clinical trial evidence, and there are currently few studies on the potential connection between ApoC3 and HFpEF. This study intends to detect the content of ApoC3 in different group samples through clinical data and sample acquisition, further assessing the diagnostic value of ApoC3 in HFpEF. At the same time, considering the potential mechanism of HFpEF onset, according to the literature reviewed, consider selecting clinical indicators FAR and RWT, which have been proven to be of certain significance in the prognosis or diagnosis of HFpEF, and combine them with ApoC3 to form a composite indicator, also conduct its diagnostic value assessment for HFpEF, in the hope of achieving positive results, providing new ideas for the diagnosis, treatment, and prognosis of HFpEF in clinical practice, facilitating standardized diagnosis and treatment throughout the course of HFpEF patients, and improving patient expected survival rates.

Material and Methods

Study Subjects

According to the inclusion, grouping, and exclusion criteria listed below, patient data from March 2023 to December 2023 at the Cardiovascular Department of the Kunshan Branch of the Suzhou College of Nanjing Medical University and the First People's Hospital of Kunshan was selected, including patients with HFpEF. During the same period, data from a subset of patients with HFrEF and heart failure with reduced ejection fraction intermediate (Intermediate heart failure with reduced ejection fraction, HFmrEF) as well as normal control groups were also selected. This study is a prospective study and has been approved by the ethics committee of the Kunshan Branch of the Suzhou College of Nanjing Medical University and the First People's Hospital of Kunshan (Ethics No.202303064).

Inclusion Criteria

(1) Voluntarily participate in this study and obtain informed consent; (2) Meet the HF criteria (cardiac function classification II–IV); (3) Normal control group: healthy physical examination or non-HF hospitalization population.

Grouping Criteria

(1) HFpEF group: Patients clearly diagnosed with HFpEF. According to the guidelines of the American Heart Association/American College of Cardiology and the European Society of Cardiology,[2] diagnosis is made based on the following criteria: 1) Symptoms and/or signs of heart failure (based on the Framingham criteria); 2) LVEF > 50% and no enlargement of the left ventricular cavity (LVMi-AL < 97mL/m^2); 3) Objective indicators of impaired left ventricular diastolic function: ① Concentric left ventricular hypertrophy or remodeling (left ventricular mass index in males > 149g/m^2, females > 122g/m^2, relative wall thickness > 0.42mm); ② NT-ProBNP > 220pg/mL or BNP > 200pg/mL; ③ Other evidence of impaired left ventricular diastolic function (E/E′ within 8–15), including LAVi > 40mL/m2, E/A < 0.5, DT time > 280ms, durArA time > 30ms, atrial fibrillation confirmed by electrocardiogram, etc.

(2) HFrEF+HFmrEF group: 1) Symptoms and/or signs of heart failure (based on the Framingham criteria); 2) LVEF < 50%; 3) Elevated NT-ProBNP or BNP, and meeting at least one of the following: ① Left ventricular hypertrophy and/or left atrial enlargement; ② Abnormal cardiac diastolic function.

(3) Normal control group (healthy physical examination patients): Patients without cardiovascular disease-related risk factors and/or chronic diseases (such as hypertension, diabetes, etc.) but without changes in cardiac structure and function.

Exclusion Criteria

(1) Acute coronary syndrome, bundle branch block, congenital valvular disease, ventricular tachycardia, hyperthyroidism, etc;
(2) Presence of acute or chronic infection-related diseases, such as respiratory, digestive, urinary, skin, etc;
(3) Severe hepatic and renal insufficiency;
(4) Hematological diseases;
(5) Advanced malignant tumors;
(6) Congenital heart disease or severe cardiac structural abnormalities, post-pacemaker implantation.

Research Method

Data Collection

Basic data: All research subjects completed the collection of medical history and inquiry of past history according to the standard hospitalization process, recording the subject's name, gender, age, vital signs (blood pressure, heart rate, respiration, body temperature), height, weight, past medical history (presence or absence of hypertension, diabetes, coronary heart disease, atrial fibrillation, cerebrovascular disease), etc.

Laboratory and instrumental examinations: Including complete blood count, coagulation function, liver and kidney function, complete lipid profile, NT-proBNP, etc. Inpatients received echocardiography, and detailed records of the aortic root diameter (AO), left atrial diameter (LAS), interventricular septum thickness (IVSD), left ventricular end-diastolic diameter (LVD), left ventricular posterior wall thickness (LVPWD), left ventricular end-systolic diameter (LVS), and EF value were made in the heart ultrasound.

Relevant calculation formulas:

Relative wall thickness (RWT) = (interventricular septum thickness + left ventricular posterior wall thickness) / left ventricular end-diastolic diameter;

Fibrinogen to albumin ratio (FAR) = fibrinogen / albumin;

Monocyte to high-density lipoprotein ratio (MHR) = monocyte (M) / high-density lipoprotein (HDL);

Platelet to lymphocyte ratio (PLR) = platelets (PLT) / lymphocytes (L).

Collection and Detection of Serum Biomarkers

Serum Sample Collection

On the day of admission or the next morning, draw 5mL of fasting peripheral blood from the patient. Generally, whole blood samples are stored overnight in a 4°C refrigerator or left at room temperature for 2 hours before being centrifuged at 1000×g for 20 minutes. The supernatant is then transferred to EP test tubes. Each sample should be centrifuged to extract at least 1.5mL of serum, which is then divided into 2–3 tubes (to facilitate alternative experiments or repeat experiments in case of failure in later stages). The samples are stored in a −80°C freezer to ensure stability and to avoid repeated freeze-thaw cycles. Subsequently, all samples are batched together for uniform biomarker detection.

Main Steps of ELISA Detection

(1) Pre-detection preparation: 1) Remove the reagent kit from the refrigerator 20 minutes in advance and allow it to reach room temperature; 2) Take the samples out in advance and allow them to reach room temperature; 3) Dilute the concentrated washing solution with double-distilled water (1:24); 4) Perform serial dilutions of the standards with the standard/sample diluent; 5) 15 minutes before step ② begins, dilute the 100X biotinylated antibody/antigen concentrate with biotinylated antibody/antigen diluent to a working concentration of 1X; 6) 15 minutes before step ④ begins, dilute the 100X HRP enzyme conjugate concentrate with enzyme conjugate diluent to a working concentration of 1X; 7) Turn on the microplate reader to preheat while starting the incubation in step ⑥.

(2) Operational steps: ① Add 100μL of standards or samples to each well, incubate at 37°C for 80 minutes; ② Discard the liquid in the wells, add 100μL of biotinylated antibody/antigen working solution, incubate at 37°C for 60 minutes; ③ Wash 3 times; ④ Add 100μL of enzyme conjugate working solution, incubate at 37°C for 30 minutes; ⑤ Wash 5 times; ⑥ Add 90μL of substrate solution, incubate at 37°C for about 15 minutes; ⑦ Add 50μL of stop solution, immediately measure the OD value at 450nm wavelength, and calculate the results.

Data Statistical Analysis Methods

(1) Baseline data processing: Statistical methods use SPSS 26.0 and Easy to software to conduct statistical analysis on the data of all included subjects. Test to determine whether the relevant indicators meet the normal distribution. Measurement-related indicators use mean ± standard deviation (X±SD) or median (25th, 75th percentile) represented by M (Q1, Q3). When normally distributed and variance is homogeneous, independent sample *t*-test is used for comparison of means between two groups, and Mann–Whitney *U*-test is used for comparison of means between two groups when the indicators are not normally distributed. Count-related indicators are expressed as percentages, and the chi-square test is used for comparison between groups. Factor analysis: Pearson correlation analysis is used for normally distributed index variables, and Spearman correlation analysis is used for non-normally distributed index variables, followed by multiple linear regression and binary Logistic analysis.

(2) Drawing the ROC curve and calculating AUC to assess the diagnostic value of single and combined indicators, with P<0.05 considered statistically significant.

Results

Comparison of General Patient Conditions

This study included a total of 200 patients. Initially, we compared the general conditions based on the patients' basic information and past medical history. It was found that, compared to the HFrEF+HFmrEF group, the HFpEF group had a significantly older average age (P<0.05). However, there were no significant differences between the two groups in terms of body mass index, gender, or the presence of comorbidities such as hypertension, diabetes, and atrial fibrillation. In comparison with the normal group, the HFpEF group showed statistically significant differences in age, gender, diastolic blood pressure, and comorbidities (P<0.05). The HFrEF+HFmrEF group also exhibited differences in age, diastolic blood pressure, and the presence of hypertension and atrial fibrillation, with statistically significant differences (P<0.05). See Table 1.

Analysis of Laboratory Data and Echocardiographic Data

In the analysis of laboratory examination data, it can be observed that compared with the normal group, the HFpEF group showed statistically significant differences (P<0.05) in L, PLT, ALB, triglycerides (Triglycerides, TG), total cholesterol (Total cholesterol, TC), low-density lipoprotein (Low-density lipoprotein, LDL), FIB, and NT-proBNP. Similarly, the HFrEF+HFmrEF group also exhibited statistically significant differences (P<0.05) in L, M, ALB, TC, LDL, FIB, and NT-proBNP. When comparing the HFpEF group with the HFrEF+HFmrEF group, it can be concluded that the PLT, TG, and ALB levels in the HFpEF group are lower than those in the HFrEF+HFmrEF group, which may be related to the inflammatory response and metabolic changes occurring in the body. See Table 2.

In the analysis of echocardiographic data, we can see that the EF value of the normal group is significantly higher than the other two groups (P<0.001), and there is statistical significance in AO, LAS, LVD, LVS, LVPWD, IVSD, RWT compared with the HFpEF group (P<0.001). We also compared the changes in cardiac structure between different

Table 1 Comparison of General Conditions of Patients

Group	HFpEF	HFrEF+HFmrEF	Normal Group	P-Value*
Age, years	75.36 ± 14.94	69.39 ± 12.84[a]	46.78 ± 14.24[bc]	<0.001
BMI, kg/m^2	23.22 ± 4.20	23.91 ± 4.12	23.93 ± 3.39	0.456
SBP, mmHg	137.29 ± 26.12	133.10 ± 20.46	131.86 ± 14.34	0.246
DBP, mmHg	72.78 ± 16.72	77.10 ± 18.85	82.87 ± 10.92[bc]	<0.001
Male, n (%)	39 (48.75%)	27 (65.85%)	53 (67.09%)[b]	0.041
Hypertension, n (%)	50 (62.50%)	29 (70.73%)	22 (27.85%)[bc]	<0.001
Diabetes, n (%)	29 (36.25%)	12 (29.27%)	12 (15.19%)[b]	0.010
AF, n (%)	45 (56.25%)	20 (48.78%)	0 (0.00%)[bc]	<0.001

Notes: * indicates P<0.05 between the HFpEF group, HFrEF+HFmrEF group, and the normal group. a indicates comparison between the HFpEF group and the HFrEF+HFmrEF group, b indicates comparison between the HFpEF group and the normal group, c indicates comparison between the HFrEF+HFmrEF group and the normal group, with P<0.05 between groups.

Table 2 Analysis of Laboratory Indicators and Echocardiography Indicators

Group	HFpEF	HFrEF+HFmrEF	Normal Group	P-Value*
WBC, 10^9/L	6.97 ± 4.39	7.14 ± 2.74	8.09 ± 3.43	0.143
N, 10^9/L	5.15 ± 4.00	4.94 ± 2.42	5.89 ± 3.47	0.271
L, 10^9/L	1.17 ± 0.69	1.33 ± 0.52	1.58 ± 0.64[bc]	<0.001
M, 10^9/L	0.54 ± 0.32	0.63 ± 0.32	0.51 ± 0.24[c]	0.100
PLT, 10^9/L	176.43 ± 82.35	206.80 ± 89.07[a]	206.4± 69.84[b]	0.033
ALB, g/L	34.41 ± 4.82	36.24 ± 4.38[a]	42.92 ± 4.39[bc]	<0.001
TC, mmol/L	3.49 ± 0.86	3.81 ± 1.19	4.21 ± 1.05[bc]	<0.001
TG, mmol/L	1.06 ± 0.55	1.35 ± 0.77[a]	1.39 ± 0.50[b]	0.001
HDL, mmol/L	1.17 ± 0.27	1.14 ± 0.28	1.18 ± 0.29	0.739
LDL, mmol/L	1.98 ± 0.67	2.26 ± 0.95	2.62 ± 0.95[bc]	<0.001
FIB, g/L	3.35 ± 1.32	3.26 ± 0.97	2.57 ± 0.94[bc]	<0.001
NT-proBNP, pg/mL	5827.19 ± 7121.37	6247.29 ± 7792.37	89.96± 97.73[bc]	<0.001
EF, %	59.42 ± 6.24	37.78 ± 6.97[a]	64.80 ± 3.97[bc]	<0.001
AO, mm	30.86 ± 4.53	31.73 ± 6.21	29.48 ± 2.54[bc]	0.017
LAS, mm	45.16 ± 8.49	47.76 ± 7.56[a]	35.42 ± 3.86[bc]	<0.001
LVD, mm	46.98 ± 5.79	58.56 ± 9.16[a]	44.84 ± 3.82[bc]	<0.001
LVS, mm	32.01 ± 4.93	47.66 ± 9.23[a]	29.25 ± 2.22[bc]	<0.001
LVPWD, mm	9.49 ± 1.32	9.12 ± 1.38	8.71 ± 0.99[b]	<0.001
IVSD, mm	10.10 ± 1.98	9.59 ± 1.61	9.06 ± 1.10[b]	<0.001
RWT	0.42 ± 0.09	0.33 ± 0.07[a]	0.40 ± 0.05[bc]	<0.001

Notes: * indicates P<0.05 between the HFpEF group, HFrEF+HFmrEF group, and the normal group. a indicates comparison between the HFpEF group and the HFrEF+HFmrEF group, b indicates comparison between the HFpEF group and the normal group, c indicates comparison between the HFrEF+HFmrEF group and the normal group, with P<0.05 between groups.

subgroups in HF, where LAS, LVD, and LVS in the HFpEF group were lower than those in the HFrEF+HFmrEF group (LAS: 45.16±8.49mm vs 47.76±7.56mm, P<0.05; LVD: 46.98±5.79mm vs 58.56±9.16mm, P<0.001; LVS: 32.01 ±4.93mm vs 47.66±9.23mm, P<0.001), suggesting that the latter may have more pronounced changes in cardiac structure. However, the HFpEF group has a higher RWT level (0.42±0.09 vs 0.33±0.07, P<0.001), suggesting that there may be left ventricular hypertrophy in the HFpEF group. For details, please refer to Table 2.

Analysis of ApoC3, FAR, MHR, PLR Levels Across Different Groups

After calculating the new indicators and detecting the ApoC3 content in the serum of all samples, we conducted a comparison of the indicator levels across different groups. Compared with the other two groups, the HFpEF group had a higher level of ApoC3 content (63136.03±12,113.07ng/mL vs 55580.84±13,685.35ng/mL vs 53090.31 ± 5893.25ng/mL, P<0.001).

In the comparison of new indicators, compared with the normal group, the HFpEF group had higher FAR and PLR levels (FAR: 0.10±0.04 vs 0.06±0.03, P<0.001; PLR: 179.72±99.17 vs 149.00±74.42, P=0.031), suggesting a systemic inflammatory response in the HFpEF group, while there was no statistical significance in MHR (P>0.05); the HFrEF +HFmrEF group had higher FAR and MHR levels (FAR: 0.09±0.03 vs 0.06±0.03, P<0.001; MHR: 0.61±0.41 vs 0.46 ± 0.27, P<0.001). However, compared with the HFrEF+HFmrEF group, there was no significant statistical significance in the three indicators for the HFpEF group (P>0.05). See Table 3.

Multivariate Logistic Regression Analysis of Influencing Factors Between the HFpEF Group and Non-HFpEF Group

To further clarify the role of ApoC3 in HFpEF, we conducted a multivariate logistic regression analysis of influencing factors between the HFpEF group and the non-HFpEF group. The results showed that AF, age, ApoC3, FAR, and RWT could serve as independent risk factors for HFpEF (P < 0.05). See Table 4.

Table 3 Analysis of ApoC3, FAR, MHR, PLR Among Different Groups

Group	HFpEF	HFrEF+HFmrEF	Normal Group	P*
FAR	0.10 ± 0.04	0.09 ± 0.03	0.06 ± 0.03[bc]	<0.001
MHR	0.51 ± 0.40	0.61 ± 0.41	0.46 ± 0.27[c]	0.087
PLR	179.72 ± 99.17	173.61 ± 94.31	149.00 ± 74.42[b]	0.082
APOC3, ng/mL	63136.03±12,113.07	55,580.84±13,685.35[a]	53090.31 ± 5893.25[b]	<0.001

Notes: * indicates P<0.05 between the HFpEF group, HFrEF+HFmrEF group, and the normal group. a indicates comparison between the HFpEF group and the HFrEF+HFmrEF group, b indicates comparison between the HFpEF group and the normal group, c indicates comparison between the HFrEF+HFmrEF group and the normal group, with P<0.05 between groups.

Table 4 Multivariate Logistic Regression Analysis of Influencing Factors Between the HFpEF Group and Non-HFpEF Group

Indicators	B Value	Standard Error	Wald Value	P Value	OR	95% CI
Sex	0.313	0.422	0.549	0.459	1.367	(0.598,3.129)
Age	0.059	0.017	12.624	0.001	1.061	(1.027,1.096)
BMI	0.029	0.059	0.250	0.617	1.030	(0.918,1.156)
Hypertension	−0.099	0.445	0.049	0.825	0.906	(0.738,2.169)
Diabetes	0.618	0.476	1.690	0.194	1.856	(0.731,4.715)
AF	1.111	0.474	5.490	0.019	3.036	(1.199,7.688)
RWT	1.069	0.297	12.943	0.001	2.913	(1.627,5.216)
FAR	0.143	0.060	5.599	0.018	1.154	(1.025–1.299)
ApoC3	0.064	0.024	7.127	0.008	1.066	(1.017,1.117)

Correlation Analysis of ApoC3 with Various Indicators

After the statistics of the above data, we selected several indicators with statistically significant differences, including NT-proBNP, EF, FAR, PLR, and RWT, to further analyze the correlation between ApoC3 and each indicator. The results showed that ApoC3 was positively correlated with NT-proBNP, FAR, and RWT, which was statistically significant (P<0.05), whereas there was no correlation with EF values and PLR (P>0.05). See Table 5.

Diagnostic Value of ApoC3, RWT, FAR, and Their Combined Indicators in HFpEF

Following the correlation analysis, we further established a connection between ApoC3 and RWT, FAR. In the past diagnosis and typing of HF, NT-proBNP and echocardiography data were commonly used, supplemented by clinical symptoms and signs for a comprehensive assessment to clarify the typing diagnosis of HF. However, NT-proBNP has certain limitations in typing HF. Based on our current experimental results, we considered selecting ApoC3, RWT, FAR as diagnostic assessment indicators. The ROC curve was used to evaluate the value of each in the diagnosis of HFpEF,

Table 5 Correlation of ApoC3 with Various Indicators

Variable	Serum ApoC3 Concentration	
	r	P
NT-proBNP, pg/mL	0.1778	0.012
EF, %	0.0257	0.718
FAR	0.2011	0.004
PLR	−0.0111	0.876
RWT	0.3351	<0.001

https://doi.org/10.2147/IJGM.S532542

and the three indicators were combined to construct a composite parameter. The ROC curve was also used to evaluate its diagnostic value. Finally, all ROC curves were merged into one graph for comparison.

Using the HFrEF+HFmrEF Group as the Negative Control, the Diagnostic Value of ApoC3, RWT, FAR, and Their Combined Indicators in HFpEF Was Evaluated

Considering that this operation is for comparing the diagnostic efficacy of different indicators between HF subtype groups, we also set up a comparison group using NT-proBNP, which is commonly used clinically, and finally combined several ROC curves in one graph to compare the diagnostic efficacy.

According to the results of the ROC curve, ApoC3 and the combined indicators (ApoC3+RWT+FAR) have statistical significance in the diagnosis of HFpEF ($P<0.001$), with AUC areas of 0.702 and 0.823, respectively. The sensitivity of ApoC3 is 73.8%, and the specificity is 68.3%; NT-proBNP does not have significant significance in differentiating subtypes (AUC=0.492) with a low specificity; among the indicators with diagnostic efficacy, the combined indicators have a relatively high specificity (90.2%). See Figure 1 and Table 6.

Using the Normal Group as the Negative Control, the Diagnostic Value of ApoC3, RWT, FAR and Their Combined Indicators in HFpEF Was Evaluated

In this operation, we considered that NT-proBNP has a high diagnostic value for HF, so EF was set as a routine indicator for comparison in this data analysis.

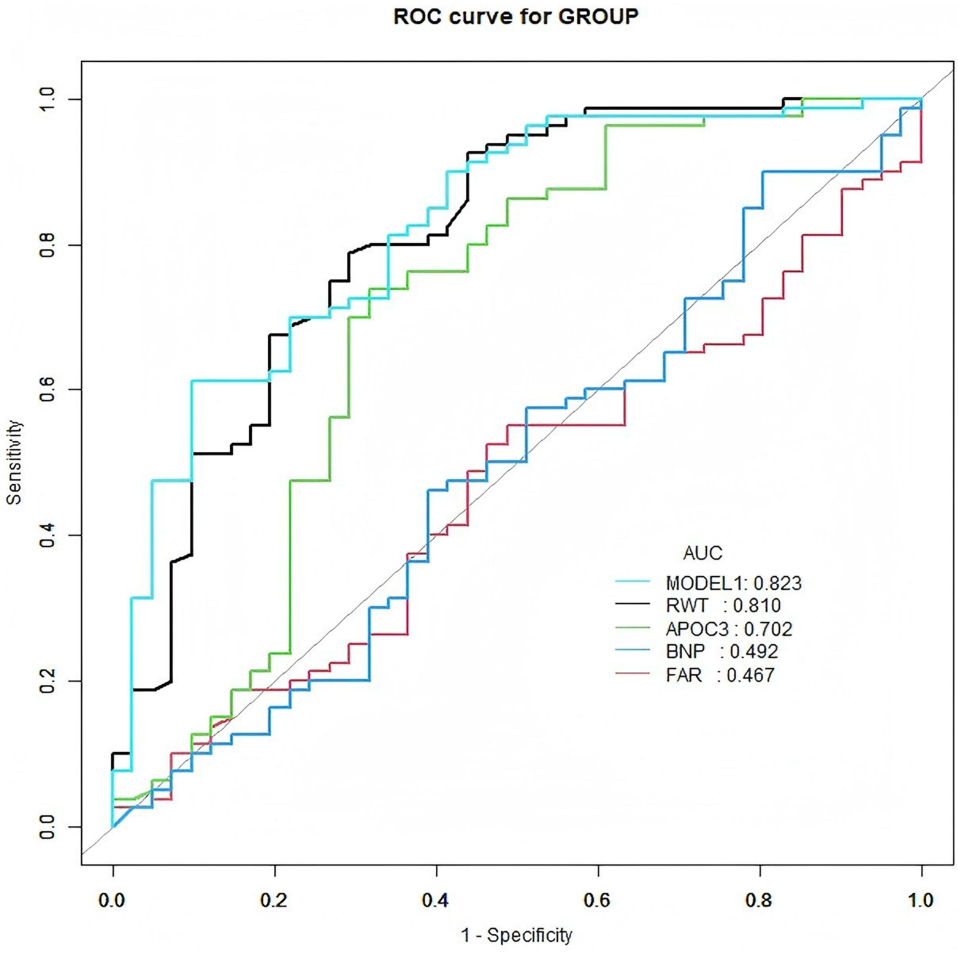

Figure 1 HFrEF+HFmrEF group vs HFpEF group - ROC curves for the diagnosis of HFpEF using ApoC3, RWT, FAR, and their combined indicators.
Notes: MODEL1: ApoC3+RWT+FAR as the dependent variable.

Table 6 Diagnostic Value of ApoC3, RWT, FAR and Their Combined Indicators, Conventional Combined Indicators for HFpEF

Test Variable	AUC	Sensitivity	Specificity	Best Threshold	P	95% CI
RWT	0.810	0.788	0.707	0.356	<0.001	(0.724, 0.896)
FAR	0.467	0.550	0.512	0.090	0.549	(0.359, 0.574)
APOC3	0.702	0.738	0.683	58,107.275	<0.001	(0.591, 0.813)
ApoC3+RWT+FAR	0.823	0.613	0.902	1.300	<0.001	(0.744, 0.902)
NT-proBNP	0.492	0.900	0.195	888.000	0.882	(0.380,0.604)

Note: the best threshold is the boundary value with the maximum sum of sensitivity and specificity.

According to the results of the ROC curve, ApoC3, FAR and the combined indicators (ApoC3+RWT+FAR) have statistical significance (P<0.001) in the diagnosis of HFpEF, with AUC areas of 0.836, 0.816, and 0.891 respectively. The sensitivity of ApoC3 is 70.0%, specificity is 88.6%, and the combined indicators have a sensitivity of 80% and a specificity of 88.6%. Compared with other indicators, the combined sensitivity and specificity evaluation value is high. See Figure 2 and Table 7.

Discussion

The purpose of this study is to explore the value of ApoC3 and its combination with RWT, FAR in the diagnosis evaluation of HFpEF. Through our research, we found that the concentration of ApoC3 in HFpEF patients is higher than

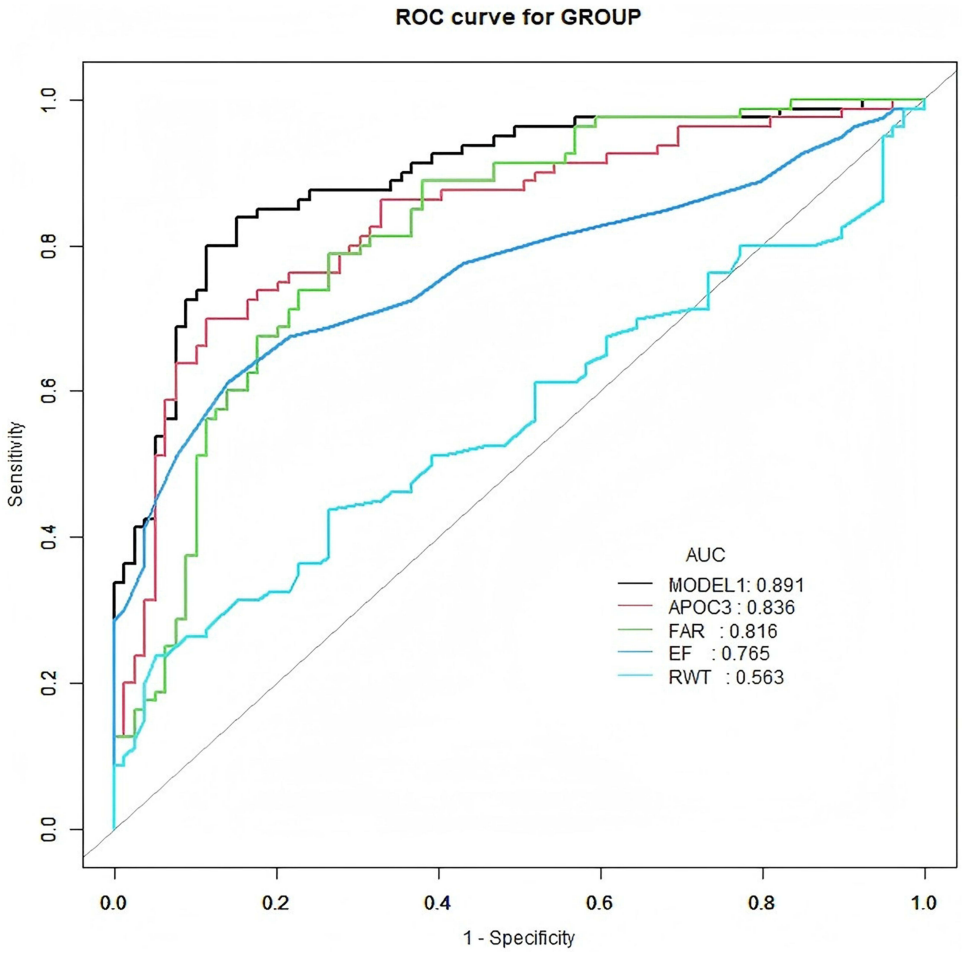

Figure 2 ROC Curve for the Diagnosis of HFpEF in the Normal Group vs HFpEF Group for ApoC3, RWT, FAR, and Their Combined Indicators.
Notes: MODEL1: ApoC3+RWT+FAR as the dependent variable.

https://doi.org/10.2147/IJGM.S532542

Table 7 Diagnostic Value of ApoC3, RWT, FAR, and Their Combined Indicators for HFpEF

Test Variable	AUC	Sensitivity	Specificity	Best Threshold	P	95% CI
FAR	0.816	0.788	0.734	0.067	<0.001	(0.749, 0.882)
RWT	0.563	0.238	0.949	0.476	0.168	(0.473, 0.654)
APOC3	0.836	0.700	0.886	58,945.975	<0.001	(0.772, 0.900)
EF	0.765	0.613	0.861	60.5	<0.001	(0.689,0.841)
ApoC3+RWT+FAR	0.891	0.800	0.886	−0.250	<0.001	(0.840, 0.942)

Note: the best threshold is the boundary value with the maximum sum of sensitivity and specificity.

that in the normal group and the HFrEF+HFmrEF group. ApoC3, FAR, and RWT could serve as independent risk factors for HFpEF. Moreover, ApoC3 has a certain value in distinguishing HFrEF+HFmrEF from HFpEF. At the same time, the combined index we created (ApoC3+RWT+FAR) has higher efficacy in the diagnosis of HFpEF.

HFpEF is a clinical syndrome. According to current epidemiological statistical analysis, the prevalence of HFpEF is increasing year by year and is likely to become the most common phenotype among various HF types.[25] Existing research results indicate that, compared to HFrEF, HFpEF patients are older and predominantly female.[26] This characteristic is similarly reflected in the general situation analysis of this study. At the same time, the ventricular remodeling changes in HFpEF are mainly characterized by concentric hypertrophy, with significant diastolic dysfunction, and a higher incidence of atrial fibrillation.[27] In the comparison between HFpEF and the normal group in this study, similar conclusions were drawn. At present, the exact mechanism of HFpEF onset is not clear and may be related to various factors. The main theoretical mechanisms considered include left ventricular diastolic dysfunction, myocardial fibrosis, systemic inflammatory response, metabolic syndrome, and microvascular dysfunction, etc. Due to the unclear mechanism of HFpEF, compared to HFrEF, there are no clear standards for the standardized diagnosis and treatment of HFpEF in clinical practice. Therefore, finding easily detectable indicators, exploring their correlation with HFpEF, and clarifying their possible mechanisms of action can help provide new directions and paths for the diagnosis and treatment of HFpEF.

ApoC3 is an apolipoprotein secreted by the body, consisting of 79 amino acids, with the primary secretory organ being the liver.[16] Numerous previous studies have thoroughly analyzed the role of ApoC3 in lipid metabolism. As an inhibitor of lipoprotein lipase (LPL), it can inhibit fat breakdown mediated by LPL and the clearance of triglyceride-rich lipoprotein (TRL) remnants in the liver. Overexpression of ApoC3 levels may lead to hypertriglyceridemia.[28] The ectopic fat accumulation in the myocardium of HFpEF patients is much more abundant than in non-HF and HFrEF patients.[29] Lipid accumulation induces myocardial cell hypertrophy and fibrosis, further causing ventricular diastolic dysfunction.[30,31] Moreover, when the uptake of fatty acids (FA) by cardiomyocytes exceeds the FA oxidation capacity, the accumulation of large amounts of TG and its metabolic intermediates, such as diglycerides, ceramides, long-chain fatty acyl-CoA, and acylcarnitines, also exerts lipotoxicity on cardiomyocytes, leading to further deterioration of cardiac function.[32] The pathway of lipids in HFpEF may also be a potential target for ApoC3 action. In addition to its role in lipid metabolism, as research continues to deepen, it has been found that ApoC3 can also act as an inducer of alternative NLRP3 inflammasome activation in human monocytes, by forming a heterotrimer between TLR2, TLR4, and SCIMP, leading to the activation of alternative NLRP3 inflammasomes in human monocytes and the induction of systemic inflammation.[33] In the study of the mechanisms involved in the early development of diabetic nephropathy, it was found that ApoC3 overexpression activates renal Toll-like receptor 2 (TLR2) and nuclear factor-κB (NF-κB) signaling pathways, increasing the renal gene and protein expression levels of downstream inflammatory factors tumor necrosis factor-α (TNF-α), vascular cell adhesion molecule-1 (VCAM-1), and monocyte chemotactic protein-1 (MCP-1),[34] causing renal tissue fibrosis and inhibiting angiogenesis,[35] aggravating the early progression of nephropathy. The inflammatory role of ApoC3 has also been confirmed in certain autoimmune diseases such as systemic lupus erythematosus.[36] Additionally, ApoC3 can affect endothelial function by activating membrane-bound protein kinase C (PKC) β and nuclear factor-kappaB (NF-kappaB), increasing monocyte adhesion, and promoting the formation of atherosclerosis.[37] At the genetic level, researchers have found that loss of ApoC3 function due to gene mutations is associated with a reduced risk of ischemic cardiovascular diseases.[38] Although the functions of ApoC3 in the body are similar to the pathways that may

lead to the development of HFpEF, there is still no clear research exploring whether ApoC3 acts on the development of HFpEF and the main pathways involved. In this study, by measuring the content of ApoC3 in different groups, we found that ApoC3 was significantly elevated in HFpEF patients and positively correlated with RWT, suggesting that ApoC3 may be related to changes in cardiac structure and plays a certain role in promoting left ventricular diastolic dysfunction.

RWT,[15] FAR[11] have both been confirmed in previous studies to have a certain correlation with the diagnosis or prognosis of HFpEF. Considering the limitations of NT-proBNP in distinguishing HF subtypes, which may be influenced by gender, obesity, renal function, etc., but as a common indicator for diagnosing HF, we still constructed a conventional indicator as a control when analyzing the diagnostic effects of ApoC3, RWT, FAR, and combined indicators (ApoC3 +RWT+FAR) in distinguishing HFpEF from HFrEF+HFmrEF. The results showed that ApoC3 has a certain effect in the diagnosis of HFpEF, and the combined indicators improved the diagnostic efficacy in HFpEF (AUC=0.823, P<0.001).

In summary, ApoC3 can currently serve as a potential marker for the diagnosis of HFpEF, and the combined indicators (ApoC3+RWT+FAR) have high value in the diagnosis of HFpEF, providing a new approach for the clinical diagnosis and treatment process of HFpEF.

This study also has several limitations that need attention: 1. This study is a single-center, prospective study with a relatively small sample size, and further validation of the experimental results is needed through a large number of samples and multi-center joint studies. 2. In this study, there may be issues such as memory bias and selection bias affecting the accuracy of data during the collection of materials and follow-up, and this study only initially collected and tested the content of ApoC3 without continuous monitoring. At the same time, other conditions of the subjects (such as medication use, hormones, etc.) were not considered, which may affect the impact of ApoC3. 3. One of the groups in this study statistically analyzed the combination of HFrEF and HFmrEF without further specific subtyping, which may affect the accuracy of the research data analysis.

Conclusion

(1) HFpEF group patients have significantly higher serum ApoC3 levels compared to the HFrEF+HFmrEF group and the normal group;

(2) ApoC3 positively correlates with the novel inflammatory response marker FAR and positively correlates with RWT, but shows no significant correlation with EF values; ApoC3, FAR, and RWT could serve as independent risk factors for HFpEF;

(3) ApoC3 can serve as a potential biomarker for the diagnosis of HFpEF, and the combined indicators (ApoC3+FAR +RWT) have high efficiency in the diagnosis of HFpEF.

Summary and Outlook

Despite the limitations mentioned above, this study provides a new potential biomarker for the clinical evaluation of HFpEF—ApoC3—and has discovered the diagnostic value of ApoC3 and its combined indicators (ApoC3+RWT+FAR) in HFpEF, offering new targets and ideas for the diagnosis and treatment of HFpEF. It is hoped that future studies with larger sample sizes and multicenter randomized controlled trials will validate our preliminary results, and further explore whether ApoC3 is an important pathway in the development and function of HFpEF, with the potential to improve standardized diagnosis and treatment of HFpEF.

Ethical Declaration Statement

This study was approved by the ethics committee of the Kunshan Branch of the Suzhou College of Nanjing Medical University and the First People's Hospital of Kunshan (Ethics No.202303064) and was complies with the Declaration of Helsinki.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used DeepSeek in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Funding

This work was funded by Suzhou Municipal Science and Technology Bureau, China (SKY2023028).

Disclosure

The authors report no conflicts of interest in this work.

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