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ORIGINAL RESEARCH

Association of High apoB/apoA1 Ratio with Increased Erythrocytes, Platelet/Lymphocyte Ratio, D-dimer, Uric Acid and Cardiac Remodeling in Elderly Heart Failure Patients: A Retrospective Study

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Background: Previous studies have confirmed that high apolipoprotein B/apolipoprotein A1 (apoB/apoA1) ratio was associated with increased mortality from heart failure (HF). Furthermore, the association of plasma apoB/apoA1 ratio with clinical characteristics and adverse cardiac remodeling is still limited in chronic HF with mildly reduced ejection fraction (HFmrEF) elderly patients. Therefore, this study investigated the association of apoB/apoA1 ratio with clinical characteristics and adverse cardiac remodeling in chronic HFmrEF elderly patients.

Methods: A total of 587 Chinese elderly (≥65 years) with coronary heart disease (CHD), HFmrEF (EF 40–50%) and related blood biochemical data were collected retrospectively. The cross-sectional data of echocardiographic and blood parameters were compared between binary apoB/apoA1 groups.

Results: In the elderly CHD patients with chronic HFmrEF, the univariate correlation analysis showed that apoB/apoA1 was correlated with younger age, increased prevalence of type 2 diabetes, erythrocytes, platelet/lymphocyte ratio (PLR), D-dimer, fibrinogen, high sensitivity C-reactive protein and uric acid, and adverse cardiac remodeling (All $P < 0.05$). However, multivariate logistic binary regression analysis found that high apoB/apoA1 ratio (≥0.62) was independently correlated with younger age, increased erythrocytes, PLR, D-dimer and uric acid, and adverse cardiac remodeling (All $P < 0.05$).

Conclusion: In this retrospective study, the high apoB/apoA1 ratio is found to be associated with younger age, increased erythrocytes, PLR, D-dimer and uric acid, and adverse cardiac remodeling in Chinese CHD elderly with chronic HFmrEF.

Keywords: apolipoprotein B, apolipoprotein A1, platelet/lymphocyte ratio, adverse cardiac remodeling, chronic heart failure, elderly

Introduction

Apolipoprotein (apo) B100 is the main apolipoprotein in all atherogenic lipoprotein, such as very low-density lipoprotein, low-density lipoprotein (LDL) and intermediate-density lipoprotein particles. Each of these atherogenic lipoprotein particles contains only one molecule of the apoB.[1–6] ApoA1 represents the main apolipoprotein in high-density lipoprotein (HDL) particle. It has essential functions as the main cholesterol (C) carrier and acceptor in the cholesterol reverse transport, in which HDL transports cholesterol from the periphery tissues to the liver to be excreted from the body. ApoA1 has anti-atherosclerotic, anti-oxidant and anti-inflammatory effects.[7–10] Therefore, apoB/apoA1 ratio reflects the cholesterol balance between atherogenic and anti-atherogenic lipoprotein particles. Plasma apoB/apoA1

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ratio may be a better marker for the prediction of metabolic syndrome, coronary heart disease (CHD), cardiovascular events and clinical prognosis than LDL-C/HDL-C and non-HDL-C/HDL-C ratios.[6,11,12]

High apoB/apoA1 ratio was confirmed to be associated with metabolic syndrome, CHD and ischemic cardiomyopathy.[11,13,14] Studies have shown that decreased apoA1, increased apoB and apoB/apoA1 ratio are linked to major adverse cardiovascular events, myocardial infarction (MI), CHD and increased all-cause mortality.[6,15–19] Studies have also demonstrated that high apoB/apoA1 ratio was associated with ischemic cardiomyopathy and increased mortality from heart failure (HF).[11,20] However, it is still unclear whether the apoB/apoA1 ratio is associated with the ischemic-related cardiac structural remodeling in HF.

Furthermore, increased apoB/apoA1 ratio and total cholesterol in the erythrocytic membrane were reported to be associated with thrombosis-related acute coronary syndrome.[21] Meanwhile, frequent erythrocyte transfusion, thromboembolism-related high platelet/lymphocyte ratio (PLR) and elevated D-dimer levels may increase cardiovascular mortality in patients with and without HF.[22–27] Moreover, hyperuricemia was confirmed to be related to the higher incidence of CHD and HF, and increased cardiac mortality rate.[28–30] Nevertheless, it has not well documented whether the apoB/apoA1 ratio is associated with blood erythrocyte count, PLR, D-dimer and uric acid levels. Moreover, it is still not fully understood for the pathophysiological mechanism underlying the onset of left ventricular (LV) chronic HF with mildly reduced ejection fraction (HFmrEF, 40% < LVEF < 50%), which is associated with increased incident thromboembolism events.[31] Therefore, this study aims to explore the association of plasma apoB/apoA1 ratio with erythrocyte count, PLR, D-dimer, uric acid and adverse cardiac remodeling in CHD elderly with chronic HFmrEF.

Subjects and Methods

Patients

At the department of cardiology and geriatrics in our hospital, a total of 587 Chinese CHD elderly (aged ≥ 65 years) with chronic HFmrEF were collected retrospectively by review of medical records from 2014 to 2022 in a cross-sectional study. This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the First Affiliated Hospital of Chongqing Medical University (No. 2022-K387). The ethics committee waived the need for patients' written informed consent because of anonymous nature of the clinical data acquired retrospectively.

In the present study, all CHD elderly had HFmrEF confirmed by color Doppler echocardiographic examination and the reported blood biochemical data, which was performed due to clinical reasons.[32] All subjects had diagnosed CHD, which was considered if the patients had at least one main branch of atherosclerotic stenosis (≥50%) in coronary artery confirmed by angiography; or the patient had diagnosed MI; or they had a history of coronary stent placement.

The patients with chronic HFmrEF were divided into low apoB/apoA1 (<0.62, n = 293) and high apoB/apoA1 (≥0.62, n = 294) groups according to the binary of apoB/apoA1 ratio. The plasma apoB and apoA1 were measured by immunoturbidimetric assay, respectively.

We excluded patients with acute stroke or MI, gout attack, hypertrophic, restrictive or dilated cardiomyopathy, valvular or congenital heart diseases, atrial fibrillation or flutter, chronic obstructive pulmonary disease, infection, autoimmune disease, glomerulonephritis and malignant tumor. The patients without echocardiographic examination and the all necessary blood biochemical data have been excluded.

Diagnostic Criteria for Comorbidities

Primary hypertension was defined as followings: after 10 minutes rest and two measurements of blood pressure (BP), the averaged arterial systolic BP ≥140mmHg and/or diastolic BP ≥90mmHg on different days without taking antihypertensive drugs; or the hypertension was diagnosed previously, and the antihypertensive medications has been used regularly, meanwhile secondary hypertension was excluded.[33]

Type 2 diabetes mellitus (DM) was defined as fasting plasma glucose (FPG) ≥7.0 mmol/L and/or the plasma glucose ≥11.1mmol/L at 2 hours after oral 75 g glucose-loaded tolerance test, meanwhile the plasma insulin level was normal or elevated, or previously diagnosed type 2 DM in which the insulin or oral glucose-lowering medication has been used in the patients, meanwhile other types of DM were excluded.[34]

Stroke was defined as positive brain imaging evidences from electronic computed tomography (CT) or magnetic resonance imaging (MRI), or previously confirmed stroke with or without a previous history of hemiparesis.[35]

Measurement of Plasma Lipids, Glucose, Glycated Hemoglobin and High Sensitivity C-Reactive Protein

Fasting plasma TC and TG were assayed enzymatically; while the HDL-C and LDL-C were measured by homogeneous enzyme colorimetry respectively.[36] Plasma glucose was measured by hexose enzyme colorimetry. The HbA1c was detected by high-performance liquid chromatography. High sensitivity C-reactive protein (hsCRP) was determined by immunoturbidimetry.[37] Plasma uric acid was measured by oxidization with the specific enzyme uricase. Fibrinogen was detected by thrombin coagulation method. D-dimer was measured by fluorescent enzyme-linked immunoassay.[38]

Calculation of Glomerular Filtration Rate and Body Mass Index

For men, serum creatinine (Scr) > 80 μmol/L, estimated glomerular filtration rate (eGFR) = 141 × (Scr μmol/L / 88.4/0.9)$^{-1.209}$ × 0.993$^{\text{Age (years)}}$; Scr ≤ 80 μmol/L, eGFR = 141 × (Scr μmol/L / 88.4/0.9)$^{-0.411}$ × 0.993$^{\text{Age (years)}}$. For women, Scr > 62 μmol/L, eGFR = 144 × (Scr μmol/L / 88.4/0.7)$^{-1.209}$ × 0.993$^{\text{Age (years)}}$; Scr ≤ 62 μmol/L, eGFR = 144 × (Scr μmol/L / 88.4/0.7)$^{-0.329}$ × 0.993$^{\text{Age (years)}}$.[39,40] Body mass index (BMI) was calculated as body weight (kg)/[height (m)]^2.[41]

Detection of Cardiac Structure and Function

With the GE Vivid 7 full digital color Doppler ultrasound diagnostic instrument, transthoracic two-dimensional M-mode echocardiography was used to determine:[37] right atrial diameter (RAD), right ventricular diameter (RVD), left atrial diameter (LAD), interventricular septal thickness (IVST), left ventricular (LV) posterior wall thickness (LVPWT), end-systolic diameter (LVESD), end-diastolic diameter (LVEDD) and ejection fraction (LVEF) and early (E)/late (A) diastolic peak mitral inflow velocity.

Statistical Analysis

The statistical package for social science (SPSS) 26.0 software (IBM Company, Chicago, IL, USA) was used for the statistical analysis. The cutoff values of binary apoB/apoA1 ratio were calculated by the SPSS software, according to the apoB/apoA1 values of the elderly HF patients in this study. The continuous data were expressed as mean ± standard deviation. The normally distributed continuous data were analyzed by *t*-test between the two groups. If the continuous data did not follow normal distribution, the Mann Whitney *U*-test was conducted between the two groups. The counting data is expressed as a percentage (%), meanwhile the chi square test was used. The Pearson or Spearman correlation analysis was performed for univariate analysis. Dichotomized logistic regression analysis was performed for multifactorial analysis. Because TC, TG, LDL-C and HDL-C were collinear with apoB/apoA1 ratio, these parameters were not included in the regression analysis. A 2-tailed value of $P < 0.05$ was considered significant statistically.

Results

Clinical Characteristics According to the Binary of apoB/apoA1 Ratio

Compared with the low apoB/apoA1 group, the high apoB/apoA1 group had higher diabetic prevalent ratio, blood erythrocytic count, PLR, D-dimer, fibrinogen, hsCRP, uric acid, TC, LDL-C and TG (All $P < 0.05$), and lower age and HDL-C ($P < 0.05$, Table 1).

The univariate correlation analysis showed that apoB/apoA1 was positively correlated with the prevalent ratio of type 2 DM, erythrocytic count, PLR, D-dimer, fibrinogen, hsCRP, uric acid, TC, LDL-C, and TG ($P < 0.05$), and negatively correlated with age and HDL-C ($P < 0.05$, Table 1).

Table 1 Comparison of Clinical Characteristics Between Binary of apoB/apoA1 Ratio

	Low apoB/apoA1 Ratio (The Ratio < 0.62) n=293	High apoB/apoA1 Ratio (The Ratio ≥ 0.62) n=294	*r*	*P*
ApoB/apoA1 ratio	0.48 ± 0.089	0.85 ± 0.182*	1.000	<0.001
Men, n (%)	172 (58.7)	182 (61.9)	0.033	0.428
Age, years	77.32 ± 7.03	75.33 ± 7.00*	−0.141	0.001
Height, cm	160.29 ± 8.36	160.63 ± 8.65	0.020	0.636
BMI, kg/m^2	23.55 ± 3.51	24.13 ± 3.68	0.081	0.050
Smoke, n (%)	117 (39.9)	135 (45.9)	0.060	0.143
Drink, n (%)	82 (28.0)	95 (32.3)	0.047	0.253
History of CHD, years	3.99 ± 5.71	3.23 ± 5.01	−0.070	0.089
Heart rate, beats/minute	81.40 ± 19.45	84.72 ± 21.67	0.080	0.051
Stroke, n (%)	52 (17.7)	40 (13.6)	−0.057	0.168
Type 2 DM, n (%)	108 (36.9)	137 (46.6)*	0.099	0.017
History of DM, years	3.51 ± 6.56	4.45 ± 7.45	0.067	0.106
Hypertension, n (%)	223 (76.1)	237 (80.9)	0.058	0.159
History of HTN, years	10.61 ± 11.07	10.91 ± 12.00	0.013	0.754
Systolic blood pressure, mmHg	136.12 ± 23.34	136.07 ± 21.95	−0.001	0.975
Diastolic blood pressure, mmHg	76.35 ± 15.57	78.78 ± 16.60	0.075	0.068
Erythrocytes, ×10^9/L	4.09 ± 0.67	4.20 ± 0.71*	0.082	0.046
Platelet/lymphocyte ratio	152.55 ± 77.46	175.37 ± 101.81*	0.125	0.002
D-dimer, mg/L	1.02 ± 0.96	1.40 ± 2.17*	0.111	0.014
Fibrinogen, g/L	3.02 ± 0.88	3.49 ± 1.18*	0.219	<0.001
hsCRP, mg/L	3.51 ± 4.19	4.66 ± 4.09*	0.137	0.002
HbA1c, %	6.44 ± 1.25	6.65 ± 1.34	0.084	0.050
Uric acid, umol/L	381.66 ± 113.15	412.69 ± 126.56*	0.128	0.002
eGFR, mL/min·1.73m^2	60.65 ± 24.44	59.73 ± 26.03	−0.018	0.660
ApoB, g/L	0.63 ± 0.15	0.93 ± 0.23*	0.622	<0.001
ApoA1, g/L	1.31 ± 0.27	1.11 ± 0.23*	−0.381	<0.001
LDL-C, mmol/L	1.77 ± 0.56	2.62 ± 0.83*	0.517	<0.001
HDL-C, mmol/L	1.29 ± 0.36	1.01 ± 0.26*	−0.408	<0.001
TC, mmol/L	3.36 ± 0.78	4.09 ± 0.97*	0.386	<0.001
Triglyceride, mmol/L	1.11 ± 0.66	1.51 ± 1.03*	0.229	<0.001

Notes: Values presented as mean ± SD or n (%). *$p < 0.05$ versus low apoB/apoA1 ratio group.
Abbreviations: BMI, body mass index; CHD, coronary heart disease; DM, diabetes mellitus; HTN, hypertension; hsCRP, high sensitivity C-reactive protein; HbA1C, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Cardiac Remodeling Corresponding to the Binary of apoB/apoA1 Ratio

Compared with the low apoB/apoA1 group, the high apoB/apoA1 group had larger LVPWT, LVESD and LVEDD ($P < 0.05$). Univariate correlation analysis showed that apoB/apoA1 was positively correlated with LVPWT, LVESD and LVEDD ($P < 0.05$, Table 2).

Multivariate Logistic Regression Analysis of apoB/apoA1 with Clinical Characteristics and Echocardiographic Parameters

Multivariate logistic binary regression analysis of high apoB/apoA1 ratio (≥0.62) with clinical characteristics and echocardiographic parameters showed that the high apoB/apoA1 ratio was independently correlated with younger age, increased erythrocytic count, PLR, D-dimer and uric acid, thicker LVPWT and larger LVEDD ($P < 0.05$, Table 3, Figures 1–7).

Table 2 Comparison of Echocardiographic Parameters Between Binary of apoB/apoA1 Ratio

	Low Apob/Apoa1 Ratio (The Ratio < 0.62) n=293	High apoB/apoA1 Ratio (The Ratio ≥ 0.62) n=294	*r*	*P*
RAD, mm	39.65 ± 6.50	39.24 ± 6.14	−0.032	0.440
RVD, mm	20.84 ± 3.52	20.61 ± 2.64	−0.037	0.366
LAD, mm	38.73 ± 6.23	39.04 ± 6.14	0.025	0.539
IVST, mm	10.77 ± 1.64	11.00 ± 1.48	0.074	0.072
LVPWT, mm	10.42 ± 1.46	10.67 ± 1.42*	0.089	0.030
LVESD, mm	42.82 ± 5.12	43.72 ± 5.30*	0.087	0.036
LVEDD, mm	55.43 ± 6.42	56.56 ± 6.63*	0.086	0.037
LVEF, %	45.16 ± 2.37	44.99 ± 2.58	−0.034	0.413
E/A<1, n (%)	134 (77.9)	122 (71.3)	−0.075	0.163

Notes: Values presented as mean ± SD. *p < 0.05 versus low apoB/apoA1 ratio group.
Abbreviations: RAD, right atrial diameter; RVD, right ventricular diameter; LAD, left atrial diameter; IVST, interventricular septal thickness; LVPWT, left ventricular posterior wall thickness; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; E / A, peak early (E) / late (A) filling velocities.

Table 3 Regression Analysis of Parameters Associated with apoB/apoA1 Ratio ≥ 0.602

	β	SE	Wald χ^2	P	OR (95% CI)
Age	−0.017	0.018	16.197	< 0.001	0.932 (0.900–0.964)
Type 2 DM	0.140	0.233	0.362	0.548	1.151 (0.728–1.817)
Erythrocytes	0.671	0.183	13.436	< 0.001	1.957 (1.367–2.802)
Platelet/lymphocyte ratio	0.005	0.001	12.000	0.001	1.005 (1.002–1.008)
D-dimer	0.231	0.090	6.587	0.010	1.260 (1.056–1.502)
Fibrinogen	0.245	0.148	2.742	0.098	1.277 (0.956–1.706)
hsCRP	0.041	0.029	2.024	0.155	1.042 (0.985–1.103)
Uric acid	0.003	0.001	7.586	0.006	1.003 (1.001–1.005)
LVPWT	0.215	0.081	7.079	0.008	1.239 (1.058–1.452)
LVESD	−0.228	0.123	3.426	0.064	0.796 (0.625–1.014)
LVEDD	0.197	0.099	3.983	0.046	1.218 (1.004–1.478)

Abbreviations: β, regression coefficient; SE, standard error; Wald, Chi square value; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; hsCRP, high sensitivity C-reactive protein; LVPWT, left ventricular posterior wall thickness; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter.

Discussion

This study showed that high apoB/apoA1 ratio was independently associated with younger age, increased erythrocytes, PLR, D-dimer and uric acid, and adverse cardiac remodeling in elderly CHD patients with chronic HFmrEF.

Previous investigation found that blood LDL-C and non-HDL-C were negatively associated with age in both sex (≥57 years).[42] It is suggested that LDL-C/HDL-C, non-HDL-C/HDL-C and apoB/apoA1 might be higher in the younger patients. This phenomenon may be explained by the fact that the elderly with relatively younger age could have fewer consumptive diseases and better digestive function. In this study, we found that high apoB/apoA1 was inversely associated with age in the chronic HFmrEF elderly patients.

Recent studies have demonstrated that erythrocyte was able to carry large quantities of apoB- and apoA1-contained lipoproteins in its membrane.[43] Erythrocyte may be involved in the pro-atherosclerotic pathological

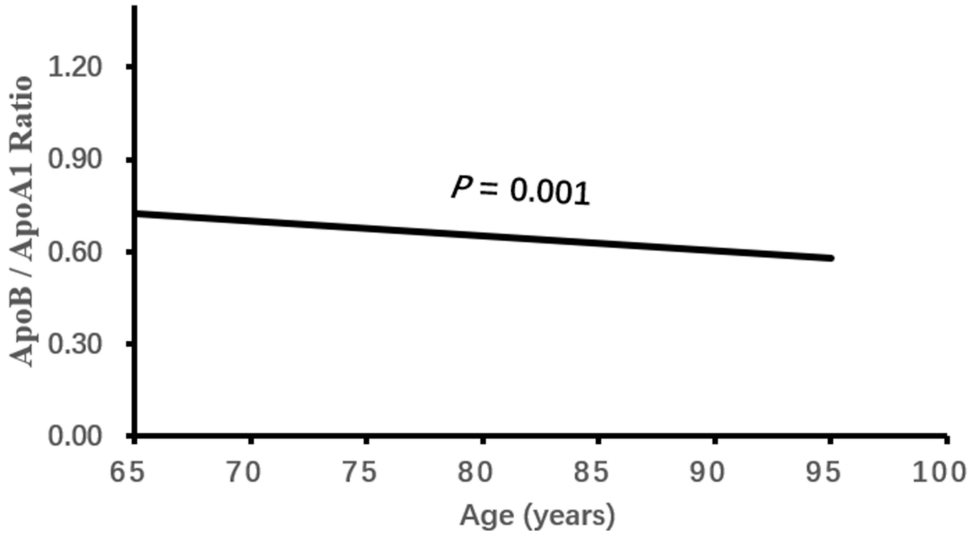

Figure 1 The association of apolipoprotein (apo) B / apoA1 ratio with age.

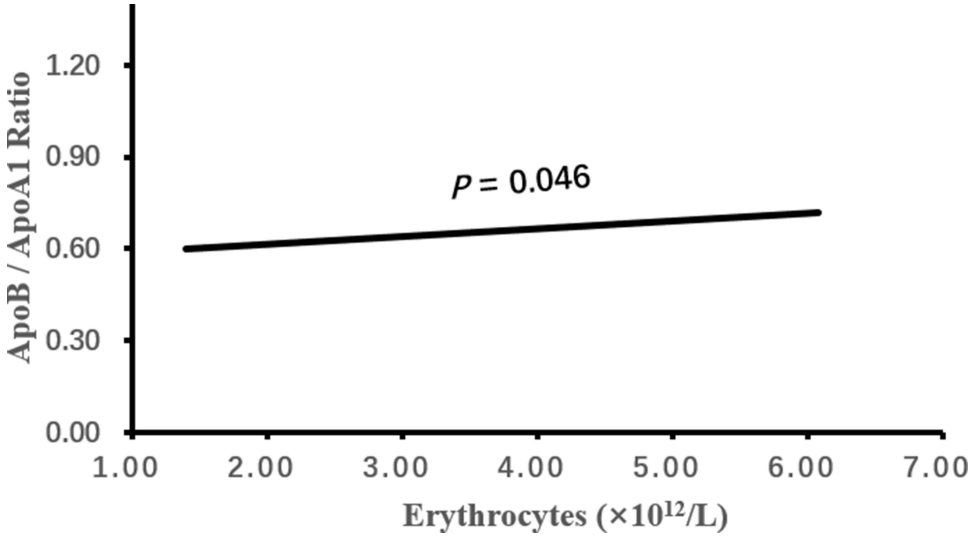

Figure 2 The association of apolipoprotein (apo) B / apoA1 ratio with erythrocytic count.

processes with atherogenic lipid particles.[21] However, there were conflict reports on the role of lipoproteins in the erythrocytic membrane.[44,45] In present study, we discovered the first time that high apoB/apoA1 ratio was associated with increased erythrocytic count in the elderly CHD patients with chronic HFmrEF. However, underlying mechanism is still unclear explaining the association of apoB/apoA1 ratio with the erythrocytic count.

Studies have showed that low HDL-C was associated with increased levels of plasma D-dimer.[46] The apoA1 and HDL owned the effects of anti-platelet and anti-thrombosis,[47,48] while high LDL-C/HDL-C ratio was associated with platelet activation.[49] However, to our knowledge, there are no previous studies showing the relationship between apoB/apoA1 ratio and PLR. In this study, high apoB/apoA1 ratio was firstly confirmed to be associated with elevated PLR and D-dimer in the chronic HFmrEF elderly patients.

High apoB/apoA1 and non-HDL-C/HDL-C ratios have been associated with CHD, MI and ischemic cardiomyopathy.[11,16] Myocardial ischemia can lead to increase of endogenous purines, which may result from the

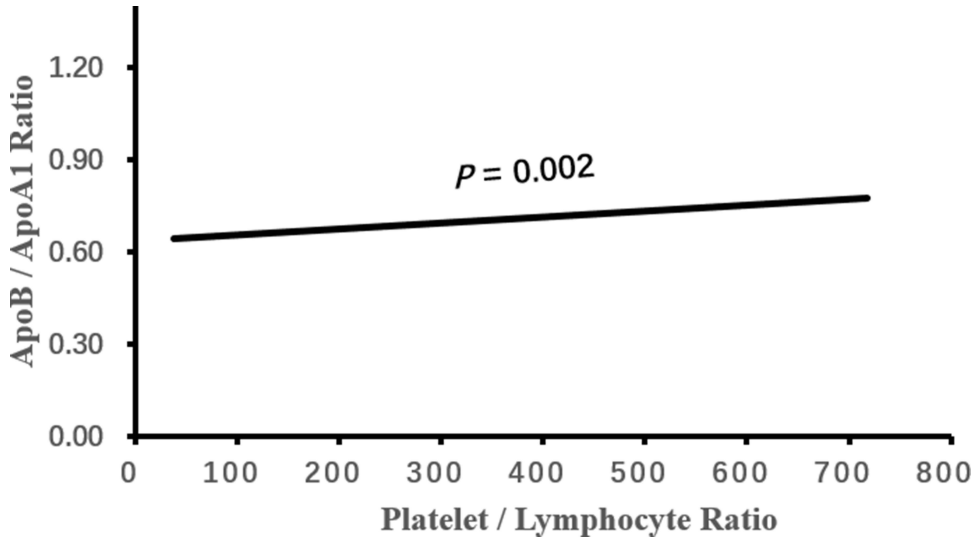

Figure 3 The association of apolipoprotein (apo) B / apoA1 ratio with platelet / lymphocyte ratio.

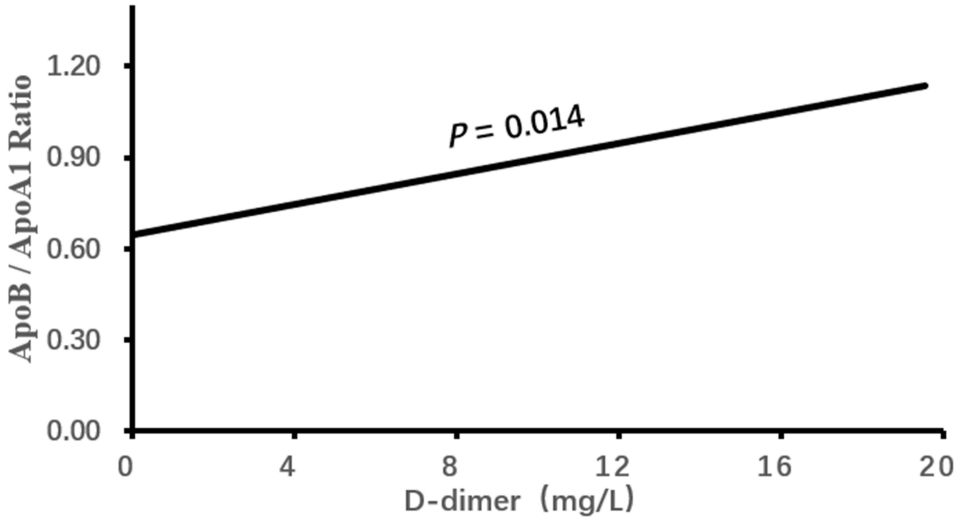

Figure 4 The association of apolipoprotein (apo) B / apoA1 ratio with D-dimer.

ischemic apoptosis and necrosis in the cardiomyocytes. Meanwhile, the ischemia could overly activate xanthine oxidase, which leads to increased production of uric acid.[50] Increased apoB and decrease apoA1 have been associated with atherosclerosis and hyperuricemia.[51] In chronic HFmrEF elderly patients, increased apoB/apoA1 ratio was associated with elevated uric acid. This finding is consistent with the results in the previous study.[51]

Studies have found that increased apoB and apoB/apoA1 ratio could more precisely predict the severity of CHD and adverse cardiovascular events as compared with LDL-C and LDL-C/HDL-C respectively.[3,6,17] Elevated apoB/apoA1 ratio was associated with ischemic cardiomyopathy and increased mortality from HF.[11,20] However, it has not been studied earlier whether the apoB/apoA1 ratio could be related to LV size and other cardiac parameters. In the present study, elevated apoB/apoA1 ratio was found to be associated with LV enlargement accompanied with its thicker wall in chronic HFmrEF elderly patients.

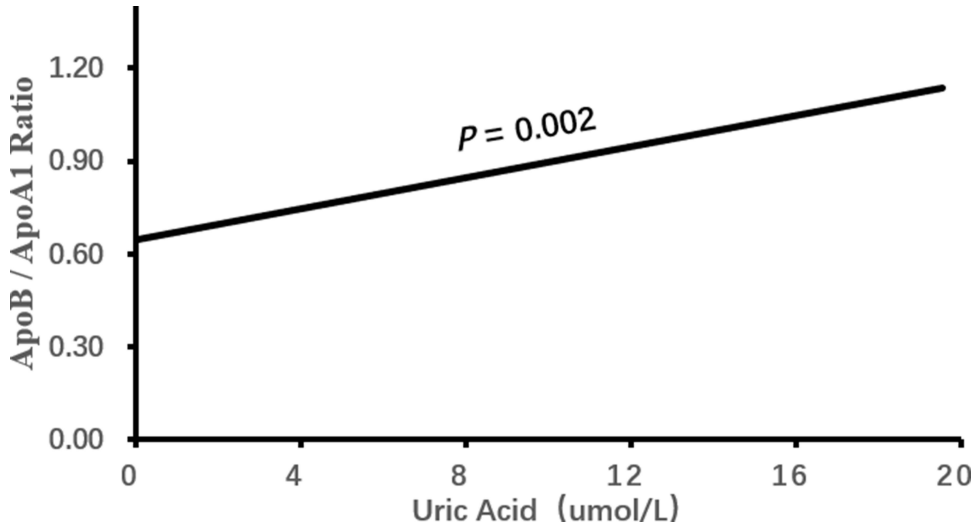

Figure 5 The association of apolipoprotein (apo) B / apoA1 ratio with uric acid.

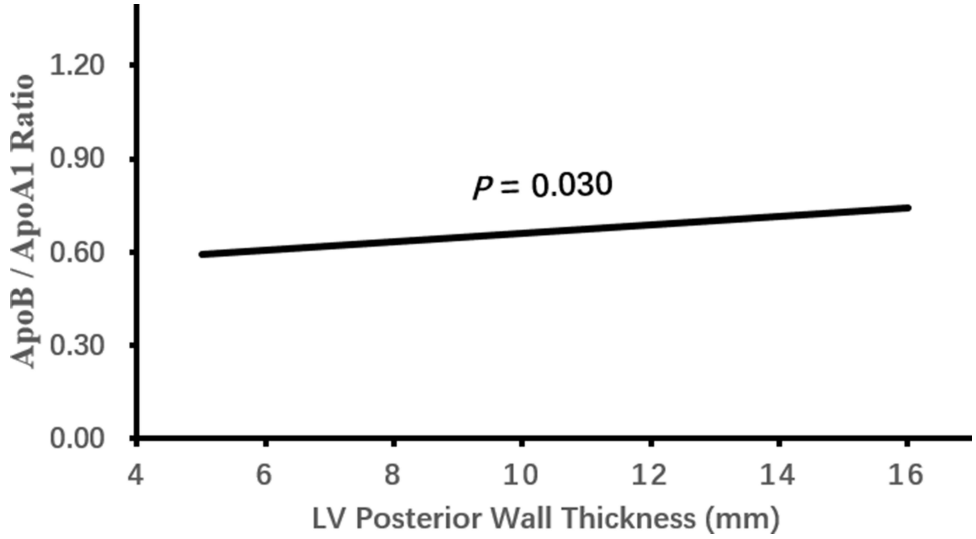

Figure 6 The association of apolipoprotein (apo) B / apoA1 ratio with left ventricular (LV) posterior wall thickness.

This study has some limitations. Firstly, the detailed information on dietary habits, sedentary behavior, sleep disorders and mental stress was not available in our records. Secondly, this is a cross-sectional study using retrospectively collected clinical data, and we cannot accurately determine the causal relationships between cardiovascular risk factors. Thirdly, it is unclear whether the association between apoB/apoA1 and other cardiovascular risk factors would be changed after long-term medical treatment of lipids. In addition, although multivariable regression analyses were performed, there could still be some unmeasured confounding factors that may explain the observed associations. Therefore, the results of this study still need to be explored further in prospective studies and then confirmed in randomized controlled trials.

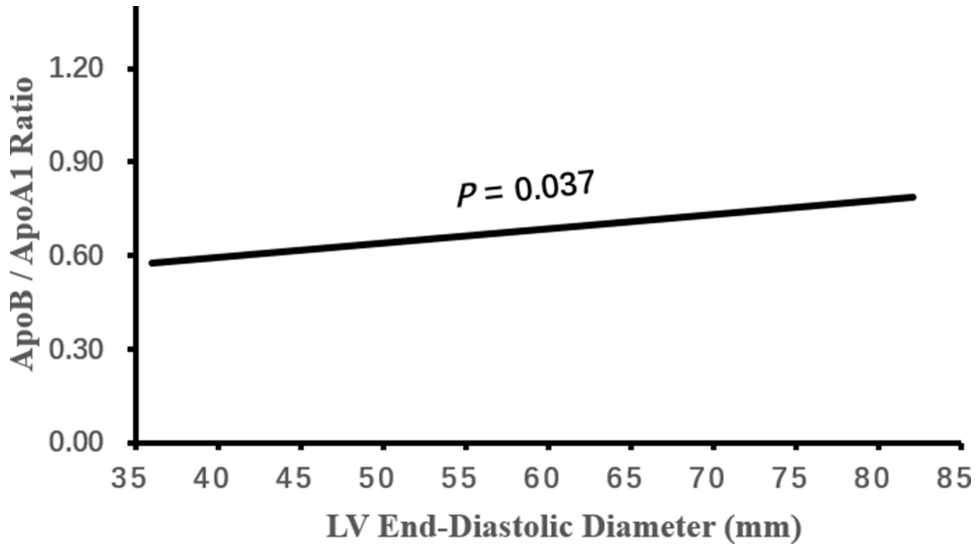

Figure 7 The association of apolipoprotein (apo) B / apoA1 ratio with left ventricular (LV) end-diastolic diameter.

Conclusion

In this retrospective study, the High apoB/apoA1 ratio is discovered to be associated independently with younger age, elevated erythrocytes, PLR, D-dimer and uric acid, and adverse cardiac remodeling in CHD elderly patients with chronic HFmrEF.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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