RESEARCH ARTICLE

# Apolipoprotein A1 is associated with pulmonary vascular resistance and adverse clinical outcomes in patients with pulmonary hypertension secondary to heart failure

Wande Yu[1] ⓘ | Xie Dujiang[1] | Wang Yi[2] | Ding Guanwen[3] |
Zhang Mengyu[2] | Pan Chang[1] | Zhang Aikai[2] | Zhang Juan[1] | Zhu Linlin[1] |
Zhang Hang[1]

[1]Division of Cardiology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China

[2]Division of Cardiology, Nanjing Medical University, Nanjing, China

[3]Department of Biology, Nanjing Foreign Language School, Nanjing, China

**Correspondence**
Zhang Hang, Division of Cardiology, Nanjing First Hospital, Nanjing Medical University, 68 Changle Road, Nanjing 210006, China.
Email: dxh_nari@sina.com

## Abstract

Pulmonary hypertension secondary to heart failure (HF-PH) combined with pulmonary vascular remodeling has a high mortality rate. Apolipoprotein A1 (ApoA1) has been shown to adversely affect outcomes in patients with HF. A prospective follow-up study was performed on 239 consecutive patients with HF-PH who underwent right heart catheterization. Proteomics technology was used to analyze different proteins in plasma between post- and precapillary pulmonary hypertension (CpcPH) and isolated postcapillary pulmonary hypertension (IpcPH) filtered by propensity score matching. Ultimately, 175 patients were enrolled and followed for an average of 4.4 years. Lipoprotein components in plasma were measured, and the following clinical events were tracked. Proteomics data showed that lipid metabolism and inflammation were different between CpcPH and IpcPH. ApoA1 levels in HF-PH patients with CpcPH were lower than those in HF-PH patients with IpcPH. The patients with lower ApoA1 levels (≤1.025 g/L) were in a higher New York Heart Association class and had high levels of NT-proBNP, mean pulmonary artery pressure, PVR, and diastolic pressure gradient. Besides, HF-PH patients with lower ApoA1 levels had a 2.836-fold higher relative risk of comorbid CpcPH compared with patients with higher ApoA1 levels. Moreover, patients with lower ApoA1 levels had a lower survival rate after adjusting for CpcPH. In conclusion, ApoA1 levels were negatively correlated with PVR levels. Lower ApoA1 levels were an independent risk factor for pulmonary vascular remodeling in HF-PH patients. The survival of HF-PH patients with lower ApoA1 levels was reduced.

**KEYWORDS**
ApoA1, pulmonary hypertension, pulmonary hypertension secondary to heart failure, pulmonary vascular remodeling

---

Wande Yu and Xie dujiang contributed equally to the manuscript.

-------------------------------------------------------------------------------

# INTRODUCTION

Heart failure (HF) is a complex clinical syndrome resulting from abnormal changes in the structure and/or function of the heart for a variety of reasons.[1] As the symptoms of HF worsen, pulmonary venous return is blocked, pulmonary venous pressure rises, and secondary pulmonary hypertension (PH) occurs.[2,3] HF-PH combined with pulmonary vascular resistance (PVR) ≥3 wood units (WU) is defined as combined post- and precapillary pulmonary hypertension (CpcPH), and the opposite is defined as isolated postcapillary pulmonary hypertension (IpcPH).[4] CpcPH manifests as pulmonary vascular remodeling in patients with HF-PH.[5] Recent advances have clarified that CpcPH indicates poor clinical prognosis in HF-PH patients.[2,4,6] However, monitoring PVR and diastolic pressure gradient (DPG) is difficult in routine clinical practice. Therefore, hematological indicators are very meaningful for evaluating CpcPH in patients with HF-PH to identify pulmonary vascular remodeling.

Apolipoprotein A1 (ApoA1) is a major constituent of high-density lipoprotein (HDL) and plays a prognostic role in chronic HF.[7,8] ApoA1 gene transfer was able to reverse heart abnormalities, reduce diastolic resistance and improve cardiac metabolism.[9] Several reports have shown that ApoA1 adversely affects outcomes in patients with HF,[10,11] even those with nonischemic HF.[12] Low levels of ApoA1 might reflect high inflammation and oxidation states, which are associated with the deterioration of heart function.[13] High levels of ApoA1 have protective effects in pulmonary arterial hypertension and acute lung injury, a cause of aggravating HF.[14,15]

Based on the above evidence and considerations, we hypothesized that an interaction exists between pulmonary hemodynamics and ApoA1 in HF-PH patients. By analyzing the relationship between ApoA1 and CpcPH, we further clarified the predictive value of ApoA1 in pulmonary vascular remodeling in patients with HF-PH.

# METHOD

## Study patients

The study included 239 consecutive patients with HF (2016 ESC HF Guideline[16]) whose pulmonary artery systolic pressure ≥50 mmHg by echocardiographic and followed by right heart catheterization (RHC) confirmed mean pulmonary artery pressure (mPAP) ≥25 mmHg at Nanjing First Hospital from November 2014 to December 2019. Subjects with acute myocardial infarction, neoplasm, or PH (Groups I, III, IV, and V) were excluded. All

hematology indicators, including HDL, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), ApoA1 and lipoprotein a (Lp(a)), were measured using PUZS-300 Automatic Biochemical Analyzer on blood collected between 6 and 8 a.m. on the second day of admission after 8 h of fasting. Fasting blood samples were collected in tubes coated with ethylenediaminetetraacetic acid and then centrifuged at 1500g for 15 min. The plasma was separated from the blood cells and stored frozen at −80°C until the analysis was carried out. On the day of admission, echocardiography was performed with GE Vivi7. At the time of the patient's first admission, clinical characteristics were collected. For all subjects, the composite clinical event of death and rehospitalization were followed up at 1 year by telephone and verified through the Electronic Information Platform of Heart Failure Special Disease at our hospital. Continued follow-up was performed after 1 year until March 31, 2021, and the average follow-up time was 4.4 years. Fifty-eight subjects were excluded due to any one of the following treatments during hospitalization: 19 patients with cardiac resynchronization therapy defibrillator (CTR-D), 14 patients with implantable cardioverter defibrillator, 22 patients with valve replacement and 3 patients with heart transplant. Six subjects were lost to follow-up, of whom 1 had an incorrect phone registration. All patients provided written informed consent, and institutional review board.

## Hemodynamic protocol

A 7.5-Fr Swan-Ganz thermodilution catheter (model 774F75; Edwards Lifesciences) was advanced via the right jugular vein into the pulmonary artery wedge position. Cardiac output was measured using the thermodilution method (Vigilance II; Edwards Lifesciences). In patients with atrial fibrillation, at least five cardiac cycles were used to assess mPAP and mPAWP. Derived hemodynamic variables were calculated by standard formulas.

## Proteomic analysis

We assembled 1:1 propensity score-matched pairs of patients between the CpcPH group and IpcPH group to balance the differences in baseline variables among the 239 patients with HF-PH. Age, Sex, body mass index, hypertension, diabetes, atrial fibrillation, cause of disease, New York Heart Association (NYHA) as baseline characteristics were used for propensity matched analysis. The match tolerance was 0.02. Fuzzy matching

obtained 23 pairs of cases, a total of 46 patients. We selected blood samples from the first 30 patients for omics analysis. According to the matching method, 30 blood samples from patients with HF-PH with reduced ejection fraction were selected from each of the two groups, and then 5 samples of equal volume were mixed. To reduce intergroup differences, we also matched baseline variables in each group. Finally, 3 mixed blood samples were obtained for each of the two groups.

Proteins were labeled with isobaric tags for relative and absolute quantitation (iTRAQ) reagent after extraction from mixed blood samples. TripleTOF 5600 + LC-MS/MS was used to collect and analyze peptide signals. Protein identification was performed by using ProteinPilot TM V4.5. Blast2GO software was used to obtain the protein Gene Ontology (GO) annotation. An expected value <0.001 was used as the cut-off value for BLAST results. The Student $t$ test and $p < 0.05$ were used to identify differential proteins.

## Statistical analysis

Data are expressed as the mean ± standard deviation and as frequency (%). The cutoff values of ApoA1 for the prediction of HF-PH patients with CpcPH were analyzed by receiver operating characteristic (ROC) analysis. The mean value and frequency between the two groups were compared using the Student unpaired $t$ test and Chi-square analysis, respectively. For skewed variables, the

Kolmogorov–Smirnov test was used. The association of various factors with CpcPH in HF-PH patients was assessed by univariate and multivariate logistic regression. We incorporated variables with $p < 0.2$ in the univariate logistic regression analysis into the multivariate logistic regression analysis. Chi-square analysis was used to analyze clinical events between the two groups. Log-rank test was performed to compare the survival curves between lower and higher ApoA1 levels after adjustment for CpcPH. SPSS version 24.0 (IBM) was used for statistical analyses. Statistical significance was defined as a $p$ value <0.05.

## RESULT

### Proteomic analysis in PH secondary to HF

The demographics of the patients whose blood was included in each of the six mixed samples are summarized in Table S1. The clinical variables were not significantly different among the groups except for the left ventricular ejection fractions and 6MWD (6 min walk distance), which were lower in the IpcPH group than in the CpcPH group.

Mass spectrometry identified 544 proteins, of which 83 were found to be significantly different between the IpcPH group and the CpcPH group, screened according to up_regulate ≥1.5 or down_regulate ≤0.67, $p$_value ≤0.05. The top 20 molecular functions and biological processes are shown in Figure 1A,B by comparing
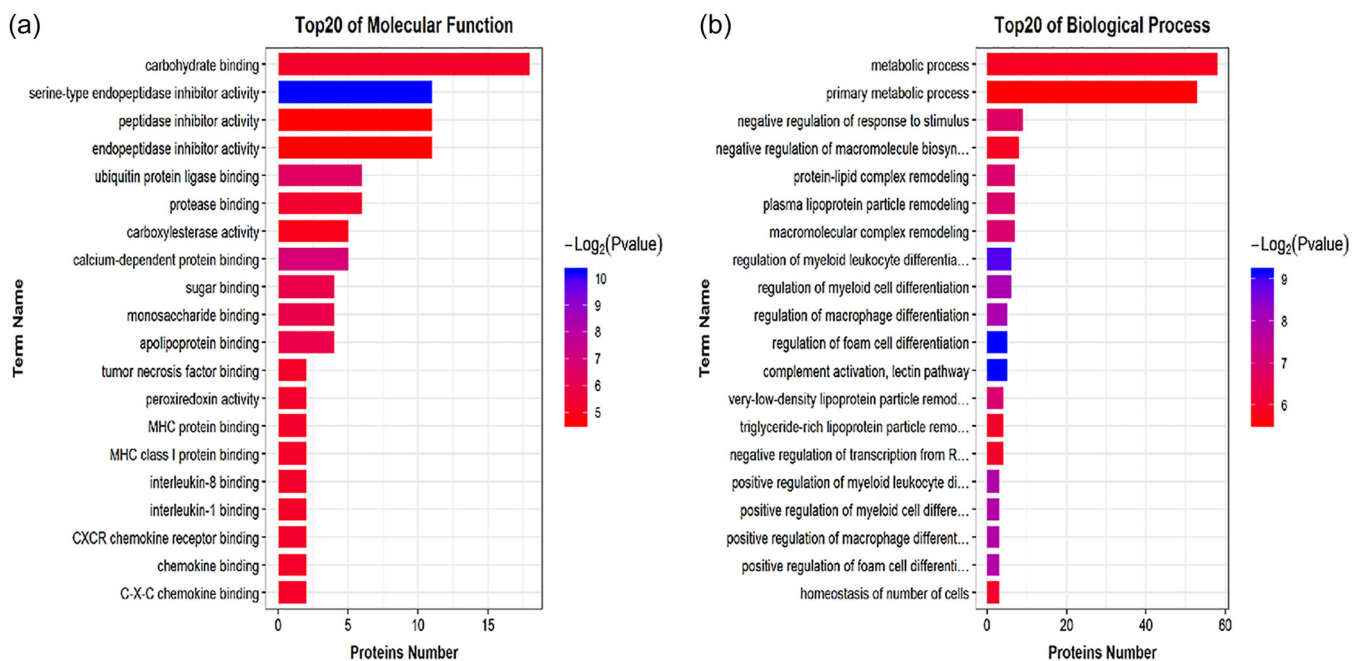


**FIGURE 1** Top 20 classification of identified proteins based on their functional annotations using gene ontology

**Pulmonary Circulation**

differential protein GO functional enrichment results. Lipid transport, metabolic processes, and inflammation involved in lipoproteins play an important role in the biological processes and molecular functions of differential proteins.

Next, we examined all lipoproteins among the 544 identified proteins and listed them in Table S2. The levels of 12 plasma lipoproteins, including ApoA1, in the CpcPH group were lower than those in the IpcPH group, and the levels of three plasma lipoproteins in the CpcPH group were higher than those in the IpcPH group. We further verified the levels of lipoprotein components by biochemical testing of the serum of all HF-PH patients. Only ApoA1 levels in HF-PH patients with CpcPH were lower than those in HF-PH patients with IpcPH (1.11 ± 0.26 g/L vs. 1.23 ± 0.25 g/L, $p < 0.01$), and 59.4% of HF-PH patients had ApoA1 levels below the normal range (1.2–1.76 g/L). There were no differences in the levels of other lipoprotein components between the two groups (Table 1).

**TABLE 1** Lipoprotein components of biochemical testing and baseline characteristics of Cpc-PH and Ipc-PH

| | Ipc-PH (n = 80) | Cpc-PH (n = 95) | p value |
|---|---|---|---|
| Age (years) | 61 ± 13 | 62 ± 15 | 0.648 |
| Male (%) | 53 (66.3%) | 54 (56.8%) | 0.203 |
| BMI (kg/m²) | 24.8 ± 3.9 | 25.2 ± 5.3 | 0.602 |
| Hypertension (%) | 37 (46.3%) | 48 (50.5%) | 0.573 |
| Diabetes (%) | 18 (22.5%) | 17 (17.9%) | 0.448 |
| MI (%) | 4 (5.0%) | 9 (9.5%) | 0.261 |
| PCI (%) | 8 (10.0%) | 19 (20.0%) | 0.068 |
| Atrial fibrillation (%) | 32 (40.0%) | 39 (41.1%) | 0.888 |
| Uric acid (μmol/L) | 414.1 ± 165.3 | 455.7 ± 160.0 | 0.093 |
| SCr (μmol/L) | 86.8 ± 33.4 | 91.6 ± 44.9 | 0.426 |
| eGFR ml/(min. 1.73 m²) | 79.5 ± 30.2 | 76.5 ± 33.5 | 0.546 |
| NT-proBNP (pg/ml) | 1245.0 (1535.6) | 1939.0 (2708.6) | 0.01 |
| EF (%) | 49.2 ± 15.1 | 47.8 ± 15.8 | 0.553 |
| mPAP (mmHg) | 27.9 ± 9.5 | 40.1 ± 12.2 | 0.000 |
| PCWP (mmHg) | 19.7 ± 9.0 | 19.7 ± 8.8 | 0.969 |
| CO (L/min) | 4.8 ± 1.4 | 3.7 ± 1.4 | 0.000 |
| PVR (Wood units) | 1.8 ± 0.8 | 6.3 ± 4.3 | 0.000 |

**TABLE 1** (Continued)

| | Ipc-PH (n = 80) | Cpc-PH (n = 95) | p value |
|---|---|---|---|
| DPG (mmHg) | 1.0 (6.8) | 7.1 (11.2) | 0.000 |
| NYHA | | | |
| I, II (%) | 31 (38.8%) | 21 (22.1%) | 0.025 |
| III, IV (%) | 49 (61.3%) | 74 (77.9%) | 0.025 |
| Cause of heart failure | | | |
| ICM (%) | 8 (10.0%) | 13 (13.7%) | 0.445 |
| DCM (%) | 28 (35.0%) | 22 (26.9%) | 0.084 |
| Valvular disease (%) | 9 (11.3%) | 15 (23.2%) | 0.384 |
| HCM (%) | 6 (7.5%) | 9 (9.5%) | 0.642 |
| HHD (%) | 3 (3.8%) | 3 (3.2%) | 0.830 |
| ApoA1 (g/L) | 1.23 ± 0.25 | 1.11 ± 0.26 | 0.002 |
| ApoB (g/L) | 0.78 ± 0.24 | 0.74 ± 0.25 | 0.380 |
| Lp(a) (mg/L) | 120.0 (168.8) | 138.6 (173.3) | 0.354 |
| HDL (mmol/L) | 1.1 ± 0.4 | 1.0 ± 0.3 | 0.183 |
| LDL-C (mmol/L) | 2.4 ± 0.9 | 2.2 ± 0.8 | 0.205 |
| TC (mmol/L) | 4.0 ± 1.1 | 3.7 ± 1.0 | 0.110 |
| TG (mmol/L) | 1.5 ± 1.3 | 1.3 ± 0.7 | 0.264 |

Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CO, cardiac output; Cpc-PH, combined post- and precapillary pulmonary hypertension; DPG, diastolic pressure gradient; EF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; Ipc-PH, isolated postcapillary pulmonary hypertension; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; MI, myocardial infarction; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal-pro B-type natriuretic peptide; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention; PCWP, pulmonary capillaries wedge pressure; RVR, pulmonary vascular resistance; SCr, serum creatinine; TC, total cholesterol; TG, total triglycerides.

## Comparisons of basic clinical characteristics in patients with HF-PH according to ApoA1 levels

The cutoff value of ApoA1 levels (1.025 g/L, AUC = 0.783) determined by ROC analysis had a sensitivity of 63.2% and specificity of 81.3% for the prediction of PVR ≥3 WU. The patients with lower ApoA1 levels (≤1.025 g/L) were in a higher NYHA class and had high levels of NT-proBNP, mPAP, PVR, and DPG ($p < 0.05$) (Table 2). Consistent with the "cholesterol paradox" reported in previous studies, patients with high ApoA1 levels also had better heart function and higher levels of total cholesterol and HDL.

**TABLE 2** Characteristics of the subgroups patients with lower or higher ApoAI level than optimal ROC

| | All patients (n = 175) | ApoA1 ≤1.025 g/L (n = 56) | ApoA1 >1.025 g/L (n = 119) | p value |
|---|---|---|---|---|
| Age (years) | 61 ± 14 | 58 ± 16 | 63 ± 13 | 0.051 |
| Male (%) | 107 (61.1%) | 39 (69.6%) | 68 (57.1%) | 0.114 |
| BMI (kg/m$^2$) | 25.0 ± 4.7 | 25.5 ± 5.7 | 24.8 ± 4.2 | 0.447 |
| Hypertension (%) | 85 (48.6%) | 30 (53.6%) | 55 (46.2%) | 0.364 |
| Diabetes (%) | 35 (20.0%) | 12 (21.4%) | 23 (19.3%) | 0.746 |
| MI (%) | 13 (7.4%) | 5 (8.9%) | 8 (6.7%) | 0.604 |
| PCI (%) | 27 (15.4%) | 8 (14.3%) | 19 (16.0%) | 0.774 |
| Atrial fibrillation (%) | 71 (40.6%) | 23 (41.1%) | 48 (40.3%) | 0.926 |
| Uric acid (μmol/L) | 436.6 ± 163.3 | 473.9 ± 173.7 | 419.1 ± 155.8 | 0.038 |
| SCr (μmol/L) | 89.4 ± 40.0 | 97.9 ± 40.6 | 85.4 ± 39.2 | 0.054 |
| eGFR ml/(min. 1.73 m$^2$) | 77.9 ± 32.0 | 78.3 ± 33.3 | 77.6 ± 31.5 | 0.911 |
| NT-proBNP (pg/ml) | 1600.9 (1933.0) | 2103.2 (2955.0) | 1334.5 (1756.8) | 0.005 |
| EF (%) | 48.4 ± 15.5 | 45.7 ± 16.6 | 49.7 ± 14.8 | 0.121 |
| mPAP (mmHg) | 34.5 ± 12.6 | 40.5 ± 12.0 | 32.3 ± 7.8 | 0.000 |
| PCWP (mmHg) | 19.7 ± 8.9 | 21.9 ± 8.3 | 22.9 ± 8.4 | 0.211 |
| CO (L/min) | 4.2 ± 1.5 | 4.2 ± 1.6 | 4.2 ± 1.4 | 0.527 |
| PVR (Wood units) | 4.2 ± 3.9 | 4.8 ± 4.6 | 3.5 ± 2.7 | 0.002 |
| DPG (mmHg) | 4.0 (9.0) | 7.0 (12.0) | 7.8 (3.0) | 0.000 |
| NYHA | | | | |
| I, II (%) | 52 (29.7%) | 10 (17.7%) | 42 (35.3%) | 0.025 |
| III, IV (%) | 123 (70.3%) | 45 (80.3%) | 77 (64.7%) | 0.025 |
| TC (mmol/L) | 3.9 ± 1.1 | 3.4 ± 1.0 | 4.1 ± 1.0 | <0.001 |
| TG (mmol/L) | 1.4 ± 1.0 | 1.4 ± 0.8 | 1.4 ± 1.1 | 0.970 |
| HDL (mmol/L) | 1.0 ± 0.4 | 0.9 ± 0.4 | 1.2 ± 0.3 | <0.001 |
| LDL-C (mmol/L) | 2.3 ± 0.9 | 2.2 ± 0.8 | 2.4 ± 0.9 | 0.178 |
| Lp(a) (mg/L) | 126.0 (169.5) | 105.0 (135.4) | 138.0 (186.8) | 0.965 |
| ApoB (g/L) | 0.76 ± 0.25 | 0.75 ± 0.25 | 0.76 ± 0.25 | 0.699 |
| Cause of heart failure | | | | |
| ICM (%) | 21 (12.0%) | 7 (12.5%) | 14 (11.8%) | 0.889 |
| DCM (%) | 50 (28.6%) | 18 (32.1%) | 32 (26.9%) | 0.473 |
| Valvular disease (%) | 24 (13.7%) | 7 (12.5%) | 17 (14.3%) | 0.794 |
| HCM (%) | 15 (8.6%) | 8 (14.3%) | 7 (5.9%) | 0.064 |
| HHD (%) | 6 (3.4%) | 0 | 6 (5.0%) | 0.087 |
| RHD (%) | 7 (4.0%) | 1 (1.8%) | 6 (5.0%) | 0.305 |
| Other (%) | 52 (29.7%) | 15 (26.8%) | 37 (31.1%) | 0.561 |
| Medication | | | | |
| AECI/ARB/ARNI (%) | 87 (49.7%) | 26 (46.4%) | 61 (51.2%) | 0.551 |
| β-block (%) | 110 (62.9%) | 37 (66.1%) | 73 (61.3%) | 0.546 |

(Continues)

**TABLE 2** (Continued)

| | All patients (*n* = 175) | ApoA1 ≤1.025 g/L (*n* = 56) | ApoA1 >1.025 g/L (*n* = 119) | *p* value |
|---|---|---|---|---|
| Digoxin (%) | 58 (33.1%) | 34 (35.8%) | 24 (30.0%) | 0.418 |
| Ivabradine (%) | 16 (9.1%) | 6 (10.7%) | 10 (8.4%) | 0.621 |
| Diuetic (%) | 140 (80%) | 74 (77.9%) | 64 (80.0%) | 0.556 |
| statins (%) | 57 (32.6) | 19 (33.9%) | 38 (31.9%) | 0.793 |

Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BMI, body mass index; CO, cardiac output; DCM, dilated cardiomyopathy; DPG, diastolic pressure gradient; EF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HDL, high-density lipoprotein; HHD, hypertensive heart disease; ICM, ischemic cardiomyopathy; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; MI, myocardial infarction; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal-pro B-type natriuretic peptide; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention; PCWP, pulmonary capillaries wedge pressure; RHD, rheumatic heart disease; ROC, receiver operating characteristic; RVR, pulmonary vascular resistance; SCr, serum creatinine; TC, total cholesterol; TG, total triglycerides.

**TABLE 3** Multiple linear regression model for evaluating PVR level in patients with heart failure

| | *B* | 95% CI for B | *t* | *p* value |
|---|---|---|---|---|
| Constant | −2.27 | −4.876 to 4.422 | −0.097 | 0.923 |
| logNT-proBNP (pg/ml) | 2.306 | 1.123 to 3.489 | 3.850 | 0.000 |
| ApoA1 (g/L) | −2.590 | −4.540 to −0.639 | −2.630 | 0.010 |

*Note*: Model: logNT-proBNP, ApoA1, SCr, Uric acid, sex, age, BMI, EF ApoB, Lp(a).

Abbreviations: BMI, body mass index; CI, confidence interval; PVR, pulmonary vascular resistance.

## Association between ApoA1 and PVR in patients with HF-PH

Multiple linear regression analysis revealed that ApoA1 was significantly associated with PVR after adjustment for potential confounding variables. Then, a model including logNT-proBNP, ApoA1 was constructed to predict PVR levels of patients with HF-PH (Table 3). Univariate logistic regression analysis showed that lower ApoA1 levels and NT-proBNP were significantly associated with CpcPH in HF-PH patients. Multivariate logistic regression analysis showed that HF-PH patients with lower ApoA1 levels had a 2.836-fold risk of comorbid CpcPH compared with patients with higher ApoA1 levels (Table 4).

## Association between ApoA1 and outcomes of patients with HF-PH

During the 1-year follow-up period, 54 (31%) patients had composite clinical events. The patients with lower ApoA1 levels had 23 (41.1%) events during follow-up, whereas the patients without lower ApoA1 levels had 31 (26.1%) events ($p < 0.005$, by Chi-square test) (Table 5).

However, there were no significant differences in HF hospitalization or cardiac death between the two groups of patients. Finally, we analyzed the all-cause death of the two groups of patients by log-rank test during the continued follow-up. Lower ApoA1 levels had a lower survival rate during follow-up than patients with higher ApoA1 levels (Figure 2).

## DISCUSSION

The present prospective study demonstrated that lipid metabolism and inflammation are the main differences in the biological activity of plasma proteins between CpcPH patients and IpcPH patients. Levels of ApoA1, a lipoprotein, were lower in CpcPH patients than in IpcPH patients. Furthermore, we first reported that ApoA1 levels were negatively correlated with PVR in patients with HF-PH. In addition, lower ApoA1 levels were an effective predictor of pulmonary vascular remodeling and adverse outcomes in patients with HF-PH.

Inflammation plays an important role in promoting HF-PH and pulmonary vascular remodeling.[17,18] The reasons include pulmonary vascular endothelial cell injury and pulmonary arterial muscle cell proliferation caused by inflammation.[19] On the other hand, myocardial damage related to inflammation results in deterioration of heart function and subsequent backward transmission of pressure. Our plasma proteomics data also showed that CpcPH patients have more proteins that are involved in inflammation than do IpcPH patients. ApoA1 exerts a cardioprotective effect by inhibiting interleukin-1 and tumor necrosis factor-alpha (TNFa).[20] Lower ApoA1 levels were strongly associated with adverse outcomes in congestive HF patients in a TNFa-308 polymorphism-dependent manner.[13] However, there was no difference in pulmonary capillary wedge pressure (PCWP) levels

**TABLE 4** Univariate and multivariate logistic regression analysis of HF patients with Cpc-pH
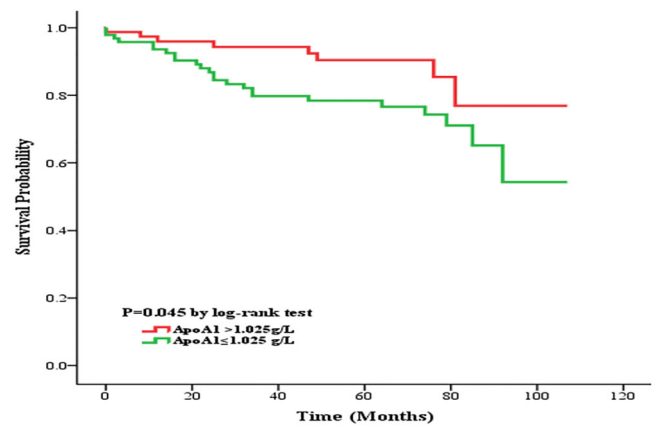
|  | Hazard ratio | 95% CI | p value |
|---|---|---|---|
| Univariate logistic regression analysis | | | |
| Male gender | 0.671 | 0.362–1.242 | 0.204 |
| Age | 1.005 | 0.984–1.026 | 0.646 |
| BMI | 1.017 | 0.954–1.085 | 0.600 |
| Hypertension | 1.187 | 0.654–2.153 | 0.573 |
| Diabetes | 1.332 | 0.634–2.798 | 0.449 |
| NT-proBNP | 1.000 | 1.000–1.000 | 0.004 |
| SCr | 1.002 | 1.000–1.003 | 0.095 |
| Uric acid | 1.003 | 0.995–1.011 | 0.427 |
| eGFR | 0.997 | 0.988–1.006 | 0.544 |
| EF | 0.994 | 0.974–1.014 | 0.550 |
| NYHA (I, II) | 0.507 | 0.266–0.965 | 0.039 |
| ApoA1 (≤1.025 g/L) | 3.290 | 1.646–6.578 | 0.001 |
| ApoB | 0.580 | 0.172–1.949 | 0.378 |
| TG | 0.791 | 0.595–1.053 | 0.108 |
| TC | 0.841 | 0.618–1.146 | 0.273 |
| HDL | 0.572 | 0.247–1.325 | 0.193 |
| LDL-C | 0.795 | 0.559–1.131 | 0.202 |
| Lp(a) | 0.999 | 0.998–1.001 | 0.358 |
| Multivariate logistic regression analysis | | | |
| Constant | 0.563 |  | 0.017 |
| ApoA1 (≤1.025 g/L) | 2.836 | 1.393–5.775 | 0.004 |
| NT-proBNP | 1.000 | 1.000–1.000 | 0.013 |

Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BMI, body mass index; CO, cardiac output; DCM, dilated cardiomyopathy; DPG, diastolic pressure gradient; EF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HDL, high-density lipoprotein; HHD, hypertensive heart disease; ICM, ischemic cardiomyopathy; LDL-C, low-density lipoprotein cholesterol; Lp (a), lipoprotein a; MI, myocardial infarction; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal-pro B-type natriuretic peptide; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention; PCWP, pulmonary capillaries wedge pressure; RHD, rheumatic heart disease; ROC, receiver operating characteristic; RVR, pulmonary vascular resistance; SCr, serum creatinine; TC, total cholesterol; TG, total triglycerides.



**FIGURE 2** Log-rank test for death by subgroups with lower or higher ApoA1 level. ApoA1, apolipoprotein A1

between patients with lower ApoA1 levels and patients with higher ApoA1 levels. In addition, lower ApoA1 levels were an independent factor impacting CpcPH. Therefore, we believe that ApoA1 has a direct relationship with pulmonary vascular remodeling in the course of HF-PH. Previous studies have shown that apolipoprotein A1 mimetic peptides attenuate inflammatory and oxidant levels in lung disease[21–23] and have protective effects against PH.[15] Similar to previous studies, this study revealed that HF-PH patients with lower ApoA1 levels (≤1.025 g/L) usually had higher PVR and DPG levels, which indicates severe pulmonary vascular remodeling.

ApoA1 is an important component of HDL that facilitates the transport of cholesterol, triglycerides, and phospholipids between plasma and cells.[24] Higher cholesterol levels were associated with better survival in advanced HF patients, which is called the "cholesterol paradox".[25] The possible mechanism of this phenomenon is cardiogenic cachexia combined with more severe catabolism and inflammation and intestinal edema.[26] In our study, HF-PH patients with lower ApoA1 levels had lower cholesterol levels, meaning a higher probability of pulmonary vascular remodeling and a worse prognosis.

PH is an independent risk factor for adverse clinical outcomes in patients with HF. If combined with

**TABLE 5** Frequency of heart failure hospitalization, cardiac death and composed clinical events according to ApoA1 levels

|  | ApoA-I ≤1.025 mmol/L (n = 56) | ApoA-I >1.025 mmol/L (n = 119) | p value |
|---|---|---|---|
| Rehospitalization with heart failure | 23 (41.1%) | 31 (26.1%) | 0.045 |
| Cardiac death | 20 (35.7%) | 30 (25.2%) | 0.151 |
| Composed clinical events | 8 (14.3%) | 10 (8.4%) | 0.232 |

Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B.

pulmonary vascular remodeling, HF has an increased mortality rate.[27] However, there is a lack of optimal indicators for assessing pulmonary vascular remodeling in patients with HF, other than PVR and DPG obtained by RHC. RHC is invasive and therefore used only in selected patients with severe disease. In the present research, lower ApoA1 levels were an independent risk factor for CpcPH and even affected the prognosis of HF-PH patients after adjusting for CpcPH. The ApoA1 level can be easily obtained, and incorporating it as a biomarker of pulmonary vascular remodeling to evaluate the prognosis of HF-PH patients may be a good choice. This study is preliminary and is considerably limited by the small number of study patients, which may lead to a lack of power for statistical analyses. Further analyses are needed in HF-PH patients to confirm the prognostic role of ApoA1.

In conclusion, according to our results, lower ApoA1 levels appear to be associated with higher PVR and adverse outcomes in patients with HF-PH, which correlate with activating inflammation. ApoA1 is a better biomarker for evaluating pulmonary vascular remodeling in HF patients.

## CONFLICT OF INTEREST
The authors declare no conflict of interest.

## ETHICS STATEMENT
The study protocol was approved by the Human Ethics Review Committee of Nanjing First Hospital.

## ORCID
*Wande Yu* https://orcid.org/0000-0001-5379-2169

## REFERENCES
1. Murphy SP, Ibrahim NE, Januzzi JJ. Heart failure with reduced ejection fraction: a review. JAMA. 2020;324(5): 488–504.
2. Maron BA, Kovacs G, Vaidya A, Bhatt DL, Nishimura RA, Mak S, Guazzi M, Tedford RJ. Cardiopulmonary hemodynamics in pulmonary hypertension and heart failure: JACC review topic of the week. J Am Coll Cardiol. 2020;76(22): 2671–81.
3. Vanderpool RR, Saul M, Nouraie M, Gladwin MT, Simon MA. Association between hemodynamic markers of pulmonary hypertension and outcomes in heart failure with preserved ejection fraction. JAMA Cardiol. 2018;3(4):298–306.
4. Assad TR, Hemnes AR, Larkin EK, Glazer AM, Xu M, Wells QS, Farber-Eger EH, Sheng Q, Shyr Y, Harrell FE, Newman JH, Brittain EL. Clinical and biological insights into combined post- and pre-capillary pulmonary hypertension. J Am Coll Cardiol. 2016;68(23):2525–36.
5. Leopold JA. Biological phenotyping of combined post-capillary and pre-capillary pulmonary hypertension: focus on pulmonary vascular remodeling. J Am Coll Cardiol. 2016;68(23):2537–39.
6. Ghio S, Crimi G, Temporelli PL, Traversi E, La Rovere MT, Cannito A, Vizza D, Scelsi L, Raineri C, Guazzi M, Oltrona Visconti L. Haemodynamic effects of an acute vasodilator challenge in heart failure patients with reduced ejection fraction and different forms of post-capillary pulmonary hypertension. Eur J Heart Fail. 2018;20(4):725–34.
7. Mishra M, De Geest B. High-density lipoprotein-targeted therapies for heart failure. Biomedicines. 2020;8(12):620.
8. Mishra M, Muthuramu I, De Geest B. HDL dysfunction, function, and heart failure. Aging (Albany NY). 2019;11(2): 293–94.
9. Sirtori CR, Ruscica M, Calabresi L, Chiesa G, Giovannoni R, Badimon JJ. HDL therapy today: from atherosclerosis, to stent compatibility to heart failure. Ann Med. 2019;51(7–8):345–59.
10. Holme I, Aastveit AH, Hammar N, Jungner I, Walldius G. Lipoprotein components and risk of congestive heart failure in 84,740 men and women in the Apolipoprotein MOrtality RISk study (AMORIS)[J]. Eur J Heart Fail. 2009;11(11):1036–42.
11. Wedel H, Mcmurray JJ, Lindberg M, Wikstrand J, Cleland JG, Cornel JH, Dunselman P, Hjalmarson A, Kjekshus J, Komajda M, Kuusi T, Vanhaecke J, Waagstein F, CORONA Study G. Predictors of fatal and non-fatal outcomes in the controlled rosuvastatin multinational trial in heart failure (CORONA): incremental value of apolipoprotein A-1, high-sensitivity C-reactive peptide and N-terminal pro B-type natriuretic peptide. Eur J Heart Fail. 2009;11(3):281–91.
12. Iwaoka M, Obata JE, Abe M, Nakamura T, Kitta Y, Kodama Y, Kawabata K, Takano H, Fujioka D, Saito Y, Kobayashi T, Hasebe H, Kugiyama K. Association of low serum levels of apolipoprotein A-I with adverse outcomes in patients with nonischemic heart failure. J Card Fail. 2007;13(4):247–53.
13. Gombos T, Förhécz Z, Pozsonyi Z, Jánoskuti L, Prohászka Z, Karádi I. Long-term survival and apolipoprotein A1 level in chronic heart failure: interaction with tumor necrosis factor alpha −308 G/A polymorphism. J Card Fail. 2017;23(2): 113–20.
14. Gordon EM, Figueroa DM, Barochia AV, Yao X, Levine SJ. High-density lipoproteins and apolipoprotein A-I: potential new players in the prevention and treatment of lung disease. Front Pharmacol. 2016;7:323.
15. Sharma S, Umar S, Potus F, Iorga A, Wong G, Meriwether D, Breuils-Bonnet S, Mai D, Navab K, Ross D, Navab M, Provencher S, Fogelman AM, Bonnet S, Reddy ST, Eghbali M. Apolipoprotein A-I mimetic peptide 4F rescues pulmonary hypertension by inducing microRNA-193-3p. Circulation. 2014;130(9):776–85.
16. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland J, Coats A, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA,

Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano G, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document G. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27): 2129–200.

17. Marra AM, Benjamin N, Cittadini A, Bossone E, Grünig E. When pulmonary hypertension complicates heart failure. Heart Fail Clin. 2020;16(1):53–60.

18. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013;62(4):263–71.

19. van der Feen DE, Bartelds B, de Boer RA, Berger R. Pulmonary arterial hypertension in congenital heart disease: translational opportunities to study the reversibility of pulmonary vascular disease. Eur Heart J. 2017;38(26):2034–41.

20. Tang C, Liu Y, Kessler PS, Vaughan AM, Oram JF. The macrophage cholesterol exporter ABCA1 functions as an anti-inflammatory receptor. J Biol Chem. 2009;284(47):32336–43.

21. Choi SH, Wallace AM, Schneider DA, Burg E, Kim J, Alekseeva E, Ubags ND, Cool CD, Fang L, Suratt BT, Miller YI. AIBP augments cholesterol efflux from alveolar macrophages to surfactant and reduces acute lung inflammation. *JCI Insight*. 2018;3(16):e120519.

22. Yao X, Gordon EM, Figueroa DM, Barochia AV, Levine SJ. Emerging roles of apolipoprotein E and Apolipoprotein A-I in the pathogenesis and treatment of lung disease[J]. Am J Respir Cell Mol Biol. 2016;55(2):159–69.

23. Gordon EM, Figueroa DM, Barochia AV, Yao X, Levine SJ. High-density lipoproteins and apolipoprotein A-I: potential new players in the prevention and treatment of lung disease. Front Pharmacol. 2016;7:323.

24. Nilsson O, Lindvall M, Obici L, Ekström S, Lagerstedt JO, Del Giudice R. Structure dynamics of ApoA-I amyloidogenic variants in small HDL increase their ability to mediate cholesterol efflux. J Lipid Res. 2020;62:100004.

25. Cunha FM, Pereira J, Ribeiro A, Silva S, Araújo JP, Leite-Moreira A, Bettencourt P, Lourenço P. The cholesterol paradox may be attenuated in heart failure patients with diabetes. Minerva Med. 2019;110(6):507–14.

26. Velavan P, Huan Loh P, Clark A, Cleland JG. The cholesterol paradox in heart failure. Congest Heart Fail. 2007;13(6):336–41.

27. Guazzi M, Naeije R. Pulmonary hypertension in heart failure: pathophysiology, pathobiology, and emerging clinical perspectives. J Am Coll Cardiol. 2017;69(13):1718–34.

## SUPPORTING INFORMATION

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