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ORIGINAL RESEARCH

The Level of Apolipoprotein A-I Is Associated with a Prognosis in Patients with Chronic Heart Failure Especially in HFmrEF and HFpEF: A Retrospective Cohort Study

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Objective: The present study aimed to explore the predictive value and prognosis of apolipoprotein A-I (ApoA-I) in chronic heart failure (CHF) patients.

Methods: We recruited 4442 patients with CHF who were admitted to The First Affiliated Hospital of Xinjiang University Medical University with a period of ten years from July 2012, and the mean follow-up time was 22.75 months. The endpoints were defined as all-cause mortality (ACM), the patients divided into low and high ApoA-I groups according to the optimal cutoff value of the ROC curve from finally analyzed HF patients.

Results: In the whole follow-up periods, multivariate Cox regression analysis showed that total CHF patients in low ApoA-I groups had significantly increased risk of ACM as compared with patients in the high ApoA-I group (hazard ratio [HR]=0.702, 95% confidence interval [CI]: 0.603–0.817, P <0.001). This trend was consistent in patients with heart failure with mid-range (HFmrEF) (HR = 0.443, 95% CI: 0.298–0.658, P <0.001) and heart failure with preserved ejection fraction (HFpEF) (HR = 0.704, 95% CI: 0.539–0.919, P = 0.010), but not in heart failure with reduced ejection fraction (HFrEF) (HR = 0.806, 95% CI: 0.582–1.116, P = 0.194).

Conclusion: The Apolipoprotein A-I concentrations significantly associated with ACM of CHF especially in HFmrEF and HFpEF.

Keywords: apolipoprotein A-I, chronic heart failure, lipoprotein metabolism, all-cause mortality

Introduction

Chronic heart failure represents the final stage of various cardiac diseases, primarily characterized by systemic and/or pulmonary circulatory congestion and insufficient perfusion of tissues and organs.[1] The 5-year survival rate once CHF is diagnosed is statistically less than 50% and the prevalence of CHF is on the rise with the aging population and advances in healthcare measures, with the prevalence of heart failure(HF) predicted to rise to 46% by 2030.[2] CHF is the leading cause of hospitalization in the older age group of 65 years with about 30–40% of CHF patients having a history of hospitalization, and after the first hospitalization for CHF, about 6.1% of males and 5.6% of females will have a recurrence within 30 days.[3] With the highest rate of hospitalization and 30-day readmission among all diseases, CHF imposes a heavy burden on health-care costs.[4] Despite the existence of a plethora of medications and rehabilitation therapies for the management of patients diagnosed with CHF, certain treatments do not yield optimal outcomes, particularly in cases of HFpEF and HFmrEF and this variability can be attributed to the distinct pathogenesis and

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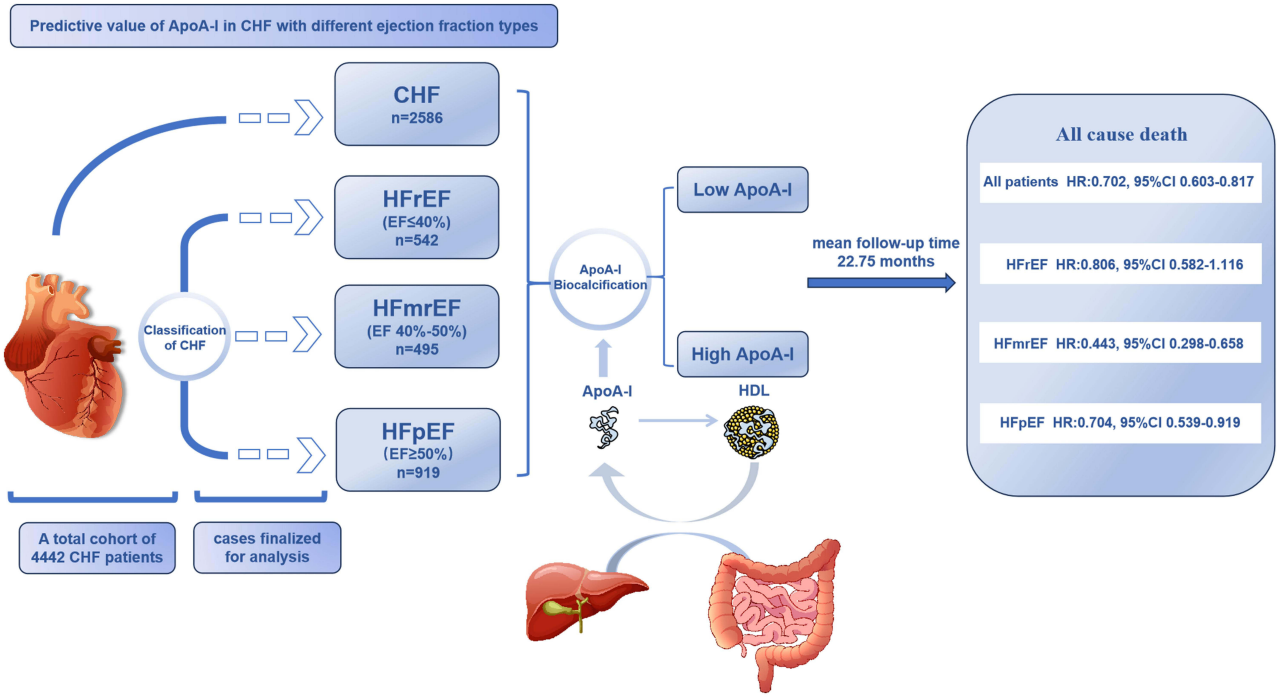
Graphical Abstract



clinical manifestations associated with different ejection fractions of CHF.[3,5] Indeed, the utility of conventional indicators such as B-type natriuretic peptide and cardiac troponin as prognostic assessment factors in CHF may be limited.[6] Furthermore, it is crucial to emphasize the necessity of identifying novel risk factors, as well as novel prognostic markers and therapeutic targets, and in addition, further substantiation is required to determine whether the same prognostic indicator can be equally useful in three different phenotypes of CHF types.

As one of the lipoproteins, High-density lipoprotein cholesterol (HDL-C) involved in the process of atherosclerosis based on the mechanisms such as the thrombogenicity, inflammation, and endothelial dysfunction.[7–9] In the preceding study of our team, it was demonstrated that HDL-C levels have been found to be associated with mortality in cases of CHF, with low concentrations of HDL-C frequently predicting higher mortality.[10] ApoA-I, the major protein component of HDL, accounting for approximately 70% of its protein content, facilitates reverse cholesterol transport (RCT),[11–13] and exhibits cardiovascular protective effects.[14,15] Clinical studies on the prognostic assessment of ApoA-I are mostly based on the population with atherogenic dyslipidemia.[16–18] However, research has identified that, in additions to its function in RCT, ApoA-I can elicit anti-inflammatory effects, inhibit the apoptosis of macrophages and vascular endothelial cells, and modulate this process either through or independently of the RCT pathway.[19–21] Early on, it was predicted that ApoA-I might have a beneficial effect on HF through an anti-inflammatory mechanism, while increasing circulating concentrations of ApoA-I has previously been shown to improve cardiac function and inhibit ventricular remodeling in mice.[22] In the research on the mechanism of ApoA-I in CHF summarized by the team of Mishra M, it was found that ApoA-I not only exerts anti-inflammatory effects by, for example, impeding the activation of CD11b, a member of the integrin family, to regulate leukocyte adhesion and migration, and modulating the activation of neutrophils in vitro and in vivo. It can also improve oxidative stress by reducing the oxidative modification of LDL. Moreover, it may stimulate angiogenesis and improve coronary microcirculation by promoting the proliferation of endothelial progenitor cells, thereby alleviating myocardial ischemia.[23] However, clinical studies on the relationship between ApoA-I and CHF remain scarce, especially in the different types of CHF classified by ejection fraction. Given our previous findings on

whether ApoA-I could also be evaluated as a factor fo long-term mortality in heart failure, we conducted a further investigation in the same cohort and examined the relationship between high and low ApoA-I levels and different types of long-term mortality in CHF.

Methods

This investigation represents a single-center, retrospective cohort study aimed at examining the association between ApoA-I levels and long-term mortality in patients diagnosed with CHF. The study adheres to the ethical principles outlined in the Declaration of Helsinki (ethics number 202207–019), with approval from the Ethics Committee of The First Affiliated Hospital of Xinjiang Medical University. The standard flow chart for discharge is depicted in Figure 1.

Patients Selection

The cohort consists of 4442 patients diagnosed with CHF who were admitted to The First Affiliated Hospital of Xinjiang Medical University between July 2012 and January 2022. The inclusion criteria encompassed patients with pre-existing, clinically managed CHF, and patients had to be aged 18 years or over and meet the diagnostic criteria for CHF, as specified in the 2018 Chinese Guidelines for the Diagnosis and Treatment of Heart Failure.[24] Their New York cardiac function was graded at stages II to IV. The exclusion criteria involved individuals with acute systemic conditions such as sepsis or shock upon admission, those with a history of malignancy, autoimmune disorders, significant organ impairment, acute or chronic inflammatory pathologies, or incomplete medical records. Further details pertaining to the study design can be accessed via the registry entry under the identifier NCT06092658 on ClinicalTrials.gov. This repository provides comprehensive information regarding the methodology, protocols, and regulatory considerations governing the study, ensuring transparency and accessibility for peer review and further scientific inquiry. Ultimately, 2586 patients were deemed eligible for inclusion in the analysis.

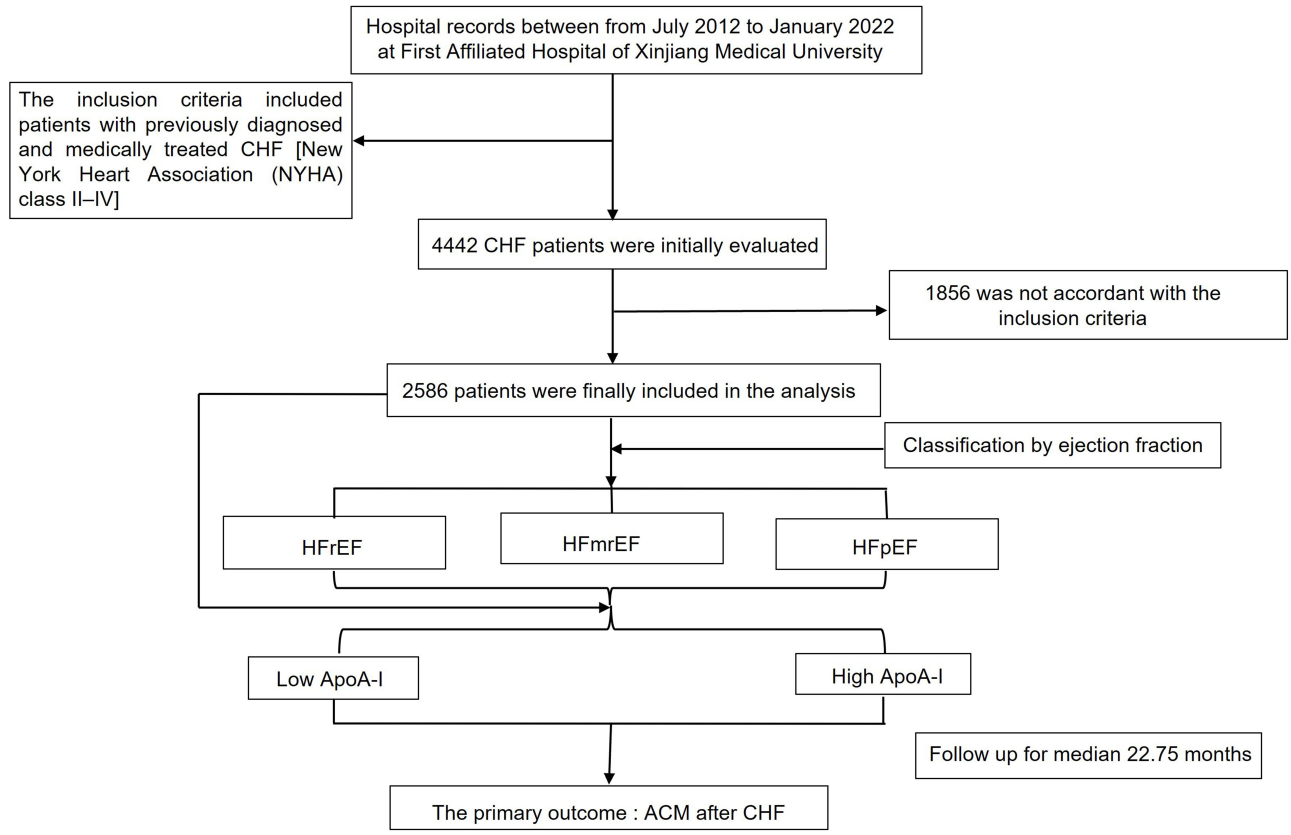


Figure 1 Flowchart of patient enrollment.

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Upon categorization based on left ventricular ejection fraction (LVEF), patients were stratified into three subgroups: HFrEF: LVEF≤40%, HFmrEF: LVEF40-50%, and HFpEF: LVEF≥50%. After excluding cases with missing data, the final distribution of participants across these groups was as follows: 542 patients with HFrEF, 495patients with HFmrEF, and 919 patients with HFpEF.

Data Collection

In this study, we collected information on patient demographics, laboratory measures, and relevant previous medical history. Demographic information such as age and gender was collected, alongside details of patients' medical history, was the risk factor related to CHF, including comorbidities such as diabetes mellitus, hypertension, coronary artery disease (CAD), valvular heart disease (VHD), congenital heart disease (CHD), and cardiomyopathy (CM), among others. Laboratory tests were carried out on peripheral blood samples. These were taken from fasting patients early in the morning on admission to hospital.

The laboratory measurements encompassed a comprehensive lipid analysis, N-terminal pro-brain-type natriuretic peptide (NT-proBNP) levels, and renal function parameters, as well as serum albumin. All measurements were analyzed by trained laboratory professionals following standardized protocols to ensure data accuracy and reliability.

Research Groups and Follow-Up

The Receiver-operating characteristic (ROC) curves were used to determine the best cutoff of ApoA-I (cutoff: 1.015g/L), and patients were divided into low or high ApoA-I groups. Comprehensive follow-up was ensured through outpatient counseling, telecommunication, and other contacts until an endpoint event occurred or the study ended. The median study duration was 22.75 months, with an interquartile range of 12.37 to 47.11 months, and the primary outcomes was ACM.

Statistics Analysis

Statistical analyses were performed utilising the SPSS 26.0 Windows software. Continuous variables were summarized as either means with standard deviations or medians accompanied by interquartile ranges, depending on the distribution of the data. Categorical variables were expressed as frequencies and percentages. To facilitate the comparison of baseline characteristics, normally distributed continuous variables were analysed using analysis of Student's *t*-test, while non-normally distributed data were assessed using the Kruskal–Wallis test or Mann–Whitney *U*-test. The Chi-squared test ($\chi 2$) was employed for comparisons of categorical data across groups. Kaplan-Meier survival analysis was used to evaluate the relationship between ApoA-I levels and long-term survival across all CHF patients and within specific subtypes. Furthermore, multivariable Cox proportional hazards regression models were employed to identify independent prognostic factors associated with patient outcomes. Hazard ratios and their corresponding 95% confidence intervals were calculated, with a P-value threshold of less than 0.05 considered indicative of statistical significance.

Results

Baseline Characteristics

Table 1 shows the baseline characteristics of the 2586 CHF patients. Lower levels of ApoA-I were significantly associated with a younger age ($P = 0.007$), a higher percentage of males ($P < 0.001$), lower rates of hypertension ($P < 0.001$), lower levels of serum albumin ($P < 0.001$) and a less favorable lipid profile (all P values < 0.001), including total cholesterol (TC), HDL-C, low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) levels. Additionally, lower ApoA-I levels correlated with higher creatinine (Cr) levels ($P < 0.001$), higher uric acid (UA) levels ($P < 0.001$), and elevated NT-proBNP levels ($P < 0.001$).

The baseline characteristics of patients with HFrEF, HFmrEF and HFpEF were then analyzed separately (Table 2). Across these three CHF subtypes, only besides the TG in HFmrEF (P=0.977), the other distribution including sex and laboratory indices showed significant differences between the two ApoA-I groups, resembling the overall CHF characteristics (all P values < 0.05). Age was significantly different between the two ApoA-I groups in the HFrEF subset, while cardiomyopathy (CM) and hypertension differences were noted in both HFmrEF and HFpEF groups.

Table 1 Baseline Characteristics of the All CHF Patients

Characteristic	Low ApoA-I(N=1222)	High ApoA-I(N=1364)	P value
Age, y	63.16±13.73	64.60±13.38	***0.007***
Male sex, n(%)	870 (71.2)	796 (58.4)	***<0.001***
Medical history, n(%)			
CAD	663 (54.3)	751 (55.1)	0.692
Hypertension	614 (50.2)	796 (58.4)	***<0.001***
VHD	259 (21.2)	298 (21.8)	0.702
CHD	31 (2.5)	25 (1.8)	0.226
CM	210 (17.2)	207 (15.2)	0.181
Diabetes	302 (24.7)	357 (26.2)	0.416
Arrhythmias	593 (48.5)	648 (47.5)	0.609
Neoplasms	45 (3.7)	45 (3.3)	0.068
Biochemical measures*			
Cr(μmol/L)	89.96 (75.35, 99.99)	83.00 (69.81, 98.00)	***<0.001***
UA (μmmol/L)	440.00 (335.40, 572.00)	393.07 (310.00, 505.20)	***<0.001***
Albumin(g/L)	37.13±5.00	39.55±4.72	***<0.001***
TG (mmol/L)	1.13 (0.83, 1.58)	1.35 (0.99, 1.95)	***<0.001***
TC (mmol/L)	3.22±0.95	4.12±1.11	***<0.001***
HDL-C (mmol/L)	0.80±0.21	1.18±0.34	***<0.001***
LDL-C (mmol/L)	2.17±0.90	2.65±0.93	***<0.001***
NT-proBNP (pg/mL)	3571.00 (999.50, 7515.00)	1318.50 (486.70, 4387.25)	***<0.001***

Notes: P value for the comparison among the two groups. The boldfaced and italicized P values are statistically different. *All measures are expressed as median (IQR), with the exception of TC, HDL-C, LDL-C and Albumin that are expressed as mean±SD.

Abbreviations: CAD, coronary artery disease; VHD, valvular heart disease; CHD, congenital heart disease; CM, cardiomyopathy; Cr, Creatinine; UA, Uric acid; TG, Triglyceride; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain-type natriuretic peptide.

Associations Between ApoA-I and ACM in CHF at Total and Different Types

In the overall cohort, a clear and significant association was observed between elevated ApoA-I levels and a reduction in long-term mortality. Specifically, patients with lower ApoA-I levels exhibited a substantially higher mortality rate compared to those with higher ApoA-I levels (48.9% vs 34.7%, P < 0.001). As demonstrated in Table 3, this trend was consistently observed within the heart failure subgroups. However, a statistical discrepancy was exclusively observed within the HFmrEF and HFpEF cohorts. Further substantiation of this finding is provided by the Kaplan-Meier survival curves depicted in Figures 2–5, which demonstrate that the cumulative mortality rate over the follow-up period was significantly higher in patients with lower ApoA-I levels. Statistical analysis using the Log rank test then confirmed statistically different associations in CHF, HFmrEF, HFpEF with a P value < 0.001.

To further explore the potential relationship between ApoA-I levels and long-term mortality in CHF patients, multivariate Cox proportional hazards regression models were employed. These models were adjusted for a comprehensive set of conventional clinical prognostic factors, including age, hypertension, Cr, serum albumin and NT-proBNP. We found that low ApoA-I showed a positive association with the risk of mortality. Specifically, in the overall population of CHF patients, those with lower ApoA-I levels exhibited a significantly higher risk of mortality compared to those with higher ApoA-I levels (low ApoA-I vs high ApoA-I: HR = 0.702, 95% CI 0.603–0.817, P <0.001). The same significant trend was observed in HFmrEF (low ApoA-I vs high ApoA-I: HR = 0.443, 95% CI 0.298–0.658, P <0.001) and HFpEF patients (low ApoA-I vs high ApoA-I: HR = 0.704, 95% CI 0.539–0.919, P=0.010). Interestingly, we did not find this association of ACM with ApoA-I in the HFrEF group (low ApoA-I vs high ApoA-I: HR = 0.806, 95% CI 0.582–1.116, P=0.194). The data are shown in Tables 4 and 5,

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Table 2 Baseline Characteristics in the Subgroups of Patients

Characteristic	HFrEF			HFmrEF			HFpEF		
	Low ApoA-I(N=309)	High ApoA-I(N=233)	P value	Low ApoA-I(N=208)	High ApoA-I(N=287)	P value	Low ApoA-I(N=370)	High ApoA-I(N=549)	P value
Age, y	59.40±12.98	63.41±13.08	***<0.001***	63.83±11.52	62.96±13.24	0.439	65.18±14.65	65.94±13.15	0.425
Male sex, n(%)	250 (80.9)	162 (69.5)	***0.002***	156 (75.0)	188 (65.5)	***0.029***	234 (63.2)	270 (49.2)	***<0.001***
Medical history, n(%)									
CAD	160 (51.8)	121 (51.9)	1.000	138 (66.3)	177 (61.7)	0.299	187 (50.5)	304 (55.4)	0.157
Hypertension	147 (47.6)	112 (48.1)	0.931	106 (51.0)	160 (55.7)	0.316	211 (57.0)	360 (65.5)	***0.010***
VHD	58 (18.8)	54 (23.2)	0.239	36 (17.3)	54 (18.8)	0.724	99 (26.8)	127 (23.1)	0.213
CHD	4 (1.3)	4 (1.7)	0.730	3 (1.4)	2 (0.7)	0.654	16 (4.3)	12 (2.2)	0.078
CM	115 (37.2)	79 (33.9)	0.469	22 (10.6)	52 (18.1)	**0.022**	14 (3.8)	28 (5.1)	0.422
Diabetes	77 (24.9)	53 (22.7)	0.612	70 (33.7)	83 (28.9)	0.279	85 (23.0)	146 (26.6)	0.245
Arrhythmias	182 (58.9)	143 (61.4)	0.596	107 (51.4)	139 (48.4)	0.525	154 (41.6)	234 (42.6)	0.786
Neoplasms	8 (2.6)	5 (2.1)	0.785	6 (2.9)	9 (3.1)	1.000	18 (4.9)	26 (4.7)	1.000
Biochemical measures*									
Cr(μmol/L)	91.00 (77.90, 100.94)	87.08 (74.00, 98.00)	***0.012***	89.18 (75.58, 114.19)	82.00 (69.00, 97.44)	***0.001***	90.52 (75.00, 99.30)	81.30 (68.93, 95.81)	***<0.001***
UA (μmmol/L)	513.00 (403.00, 636.40)	456.80 (362.00, 568.00)	***0.001***	428.50 (327.53, 539.19)	390.00 (315.00, 502.00)	***0.026***	406.65 (315.63, 531.73)	373.10 (298.00, 480.00)	***0.007***
Albumin(g/L)	38±4.55	40.45±4.40	***<0.001***	37.76±4.82	39.89±4.76	***<0.001***	37.09±5.00	39.22±4.46	***<0.001***
TG (mmol/L)	1.06 (0.83, 1.53)	1.38 (1.02, 2.00)	***<0.001***	1.30 (0.92, 1.70)	1.25 (0.96, 1.78)	*0.977*	1.14 (0.80, 1.735)	1.40 (1.00, 2.22)	***<0.001***
TC (mmol/L)	3.27±0.92	4.12±1.11	***<0.001***	3.32±1.09	3.86±0.96	***<0.001***	3.13±0.91	4.20±1.18	***<0.001***
HDL-C (mmol/L)	0.80±0.20	1.13±0.27	***<0.001***	0.82±0.20	1.14±0.29	***<0.001***	0.81±0.22	1.20±0.38	***<0.001***
LDL-C (mmol/L)	2.24±0.78	2.68±0.92	***<0.001***	2.22±1.00	3.23±0.83	***0.002***	2.06±0.76	2.69±1.00	***<0.001***
NT-proBNP (pg/mL)	5059.50 (2557.50, 8323.75)	3098.00 (1287.00, 6592.00)	***<0.001***	3146.00 (754.500, 7174.00)	1300.00 (500.50, 4110.50)	***0.006***	2199.00 (802.35, 6251.50)	754.90 (214.00, 2333.50)	***<0.001***

Notes: P value for the comparison among the two groups. The boldfaced and italicized P values are statistically different. *All measures are expressed as median (IQR), with the exception of TC, HDL-C, LDL-C and Albumin that are expressed as mean±SD.

Abbreviations: ACM, All-cause mortality, CAD, coronary artery disease; VHD, valvular heart disease; CHD, congenital heart disease; CM, cardiomyopathy; Cr, Creatinine; UA, Uric acid; TG, Triglyceride; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; HFpEF, Heart failure with preserved ejection fraction; HFmrEF, Heart failure with mid - range ejection fraction; HFrEF, Heart failure with reduced ejection fraction.

Table 3 Long-Term ACM in All Patients and in the Subgroups of Patients

Groups	ACM, n(%)		
	Low ApoA-I	High ApoA-I	P value
All patients	598 (48.9)	473 (34.7)	***<0.001***
HFrEF	143 (46.3)	95 (40.8)	0.221
HFmrEF	94 (45.2)	74 (25.8)	***<0.001***
HFpEF	177 (47.8)	175 (31.9)	***<0.001***

Note: The boldfaced and italicized P values are statistically different.
Abbreviations: ACM, All-cause mortality; HFpEF, Heart failure with preserved ejection fraction; HFmrEF, Heart failure with mid - range ejection fraction; HFrEF, Heart failure with reduced ejection fraction.

and the ACM risk comparison for low and high ApoA-I employed by multivariate Cox proportional hazards regression models depicted in Figures 6–9.

Discussion

This study investigates the relationship between ApoA-I and CHF, highlighting its potential as a straightforward and practical indicator for identifying high-risk CHF patients after admission.

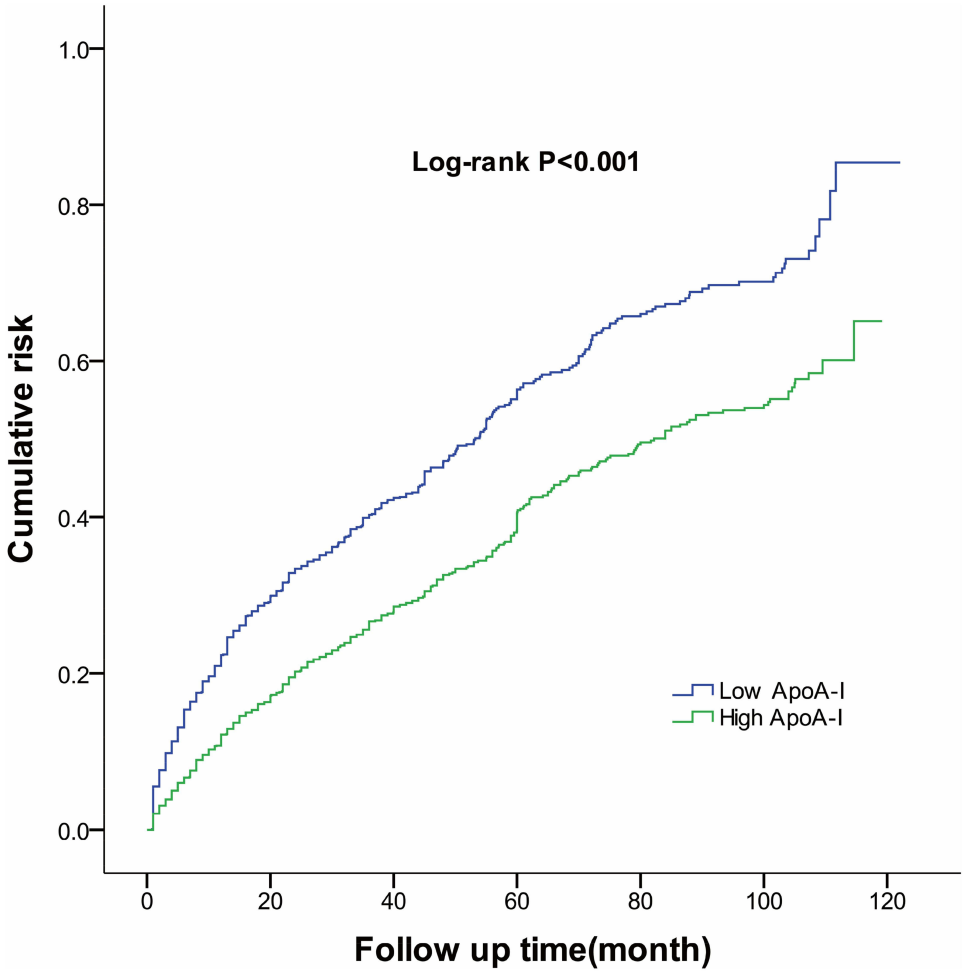

Figure 2 Kaplan-Meier curves for survival analysis of ACM in all CHF patients.

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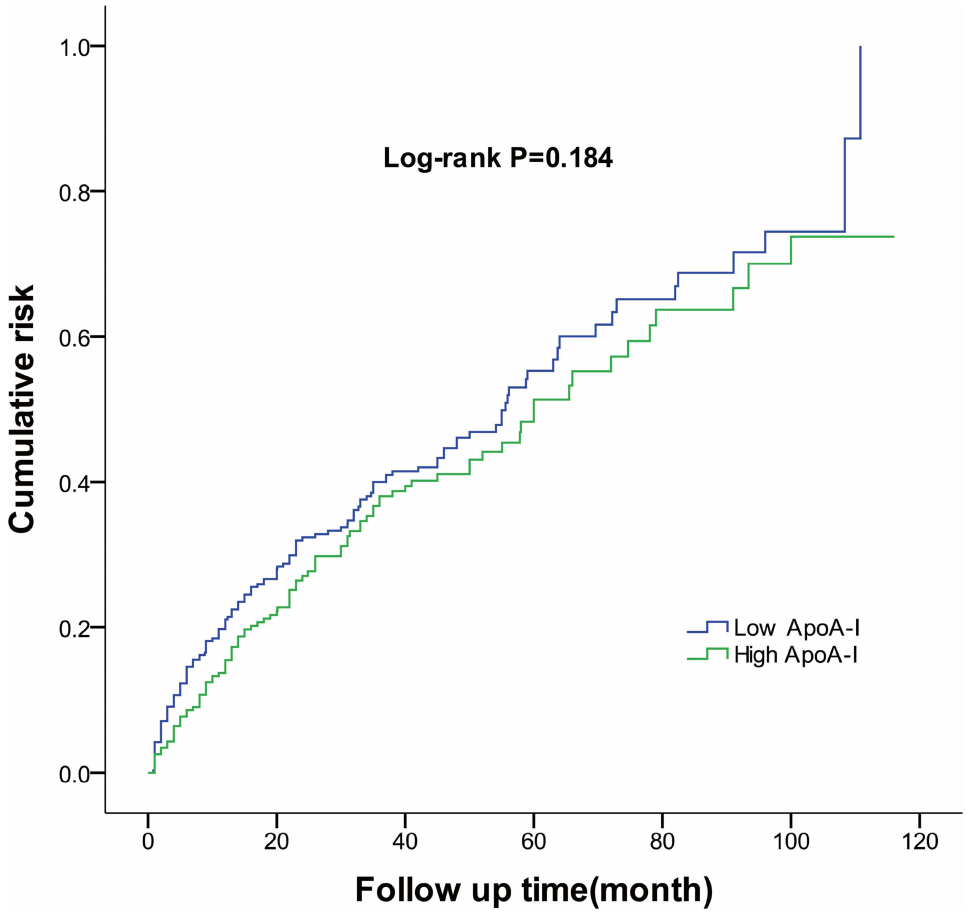

Figure 3 Kaplan-Meier curves for survival analysis of ACM in HFrEF patients.

Considering that the main protective mechanism of ApoA-I against cardiovascular disease is RCT, previous studies have largely focused on exploring cardiovascular diseases induced by prolonged myocardial ischemia caused by severe coronary artery lesions.[15,16,25,26] With regard to ischemic etiology, HFmrEF resembles HFrEF, with a higher frequency of underlying CAD compared to those with HFpEF,[5,27,28] while based on the most recent guidelines, it is evident that the three distinct classifications of CHF (HFpEF, HFmrEF, and HFrEF) exhibit varying pathophysiological underpinning.[1,29] Patients with HFpEF are typically older, predominantly female, and frequently present with comorbidities such as hypertension, atrial fibrillation, and non-cardiovascular conditions including chronic kidney disease and obesity.[30] Therefore we used the international classification, LVEF, to assess whether long-term prognosis differs with different plasma concentrations of ApoA-I in different categories of CHF, for which clinical data are lacking in the current study. The findings of the study indicated that CHF with low levels of ApoA-I exhibited a higher risk of ACM in comparison to those with high levels of ApoA-I, while the results observed in the HFmrEF and HFpEF subgroups were consistent with those of the total cohort.

The findings of this study imply that high plasma concentrations of ApoA-I may also be a protective factor for the kidneys in CHF,[31] which is similar to the results of the previous study. However, this did not reduce the ACM in CHF. In addition, previous studies have shown that serum albumin can be a strong prognostic indicator of chronic or acute HF and that low serum albumin levels are associated with adverse endpoint events.[32] Our results are in line with this especially in HFpEF. Conversely, plasma concentrations of TC, TG, HDL-C, and LDL-C were higher in the high-level ApoA-I group compared with the low-level group, and previous studies pointed out the "cholesterol and obesity paradox".[33] This suggests that lower cholesterol ester concentrations are associated with a poorer prognosis in CHF,

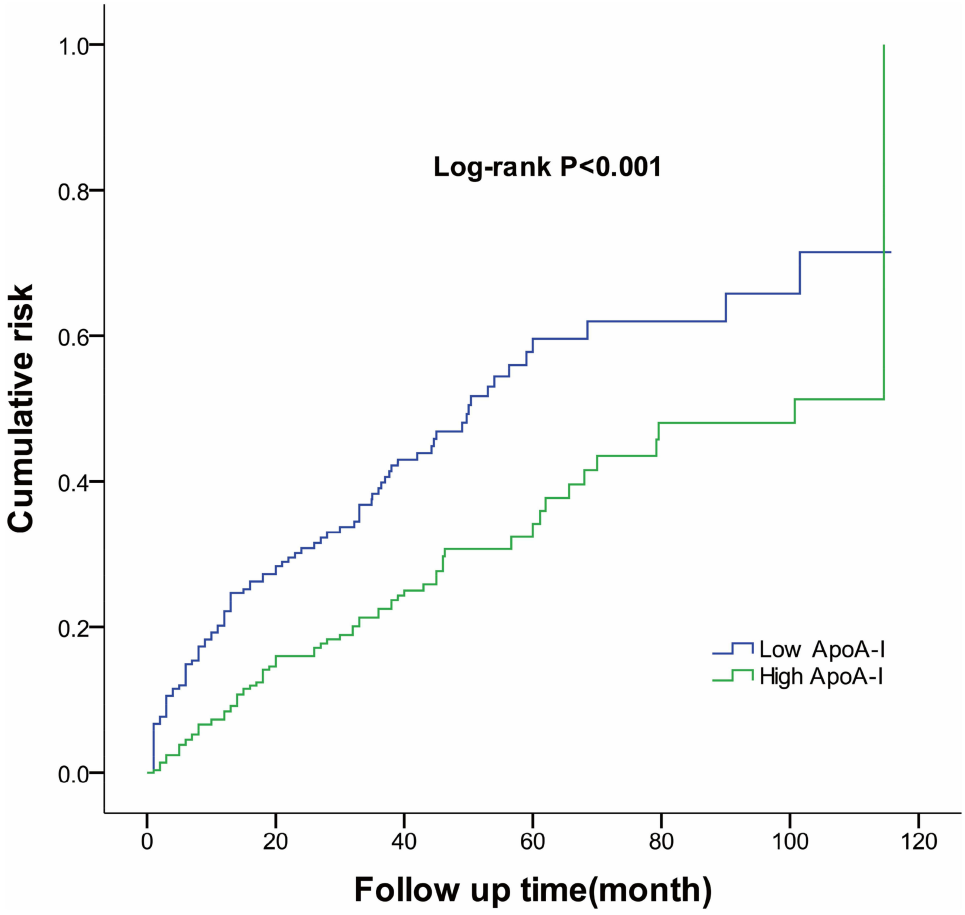

Figure 4 Kaplan-Meier curves for survival analysis of ACM in HFmrEF patients.

and the results of the present study are similar to those associated with this paradox. Higher plasma levels of NT-proBNP were observed in the group with low concentrations of ApoA-I. A previous study in a cohort of patients with suspected infarction demonstrated that both NT-proBNP and ApoA-I can be used as a prognostic predictor of major cardiovascular events within 1 year.[34] Furthermore, when combined with Multivariate Cox analysis results, the present study demonstrated that NT-proBNP and ApoA-I have the same predictive validity in the prediction of ACM events in CHF. This further reinforces the predictive value of ApoA-I for adverse outcomes in patients suffering from CHF.

As a relatively uncommon cardiovascular protective factor, our findings align with those of previous studies, indicating that HF patients with elevated ApoA-I levels tend to have a better prognosis.[35,36] This was found to be the same trend in the HFrEF, HFmrEF, and HFpEF subgroups, but the statistical significance was only in the latter two groups. It is imperative to recognize the distinguishing characteristics of the three clinical phenotype of CHF. HFpEF is primarily characterised by diastolic dysfunction and is typically precipitated by cardiac injury resulting from comorbidities.[29] Conversely, HFrEF is primarily characterised by systolic dysfunction, which is secondary to direct cardiac injury, particularly that resulting from ischemia.[37,38] Finally, HFmrEF is hypothesised to exhibit a clinical manifestation that is intermediate between HFpEF and HFrEF.[39] We adjusted for obvious confounding factors in the baseline and controlled for the confounding effects of risk factors on the final outcome as much as possible. The final results were consistent with the previous ones, so we speculate that differences in pathophysiological mechanisms are the fundamental cause of the different final outcomes.

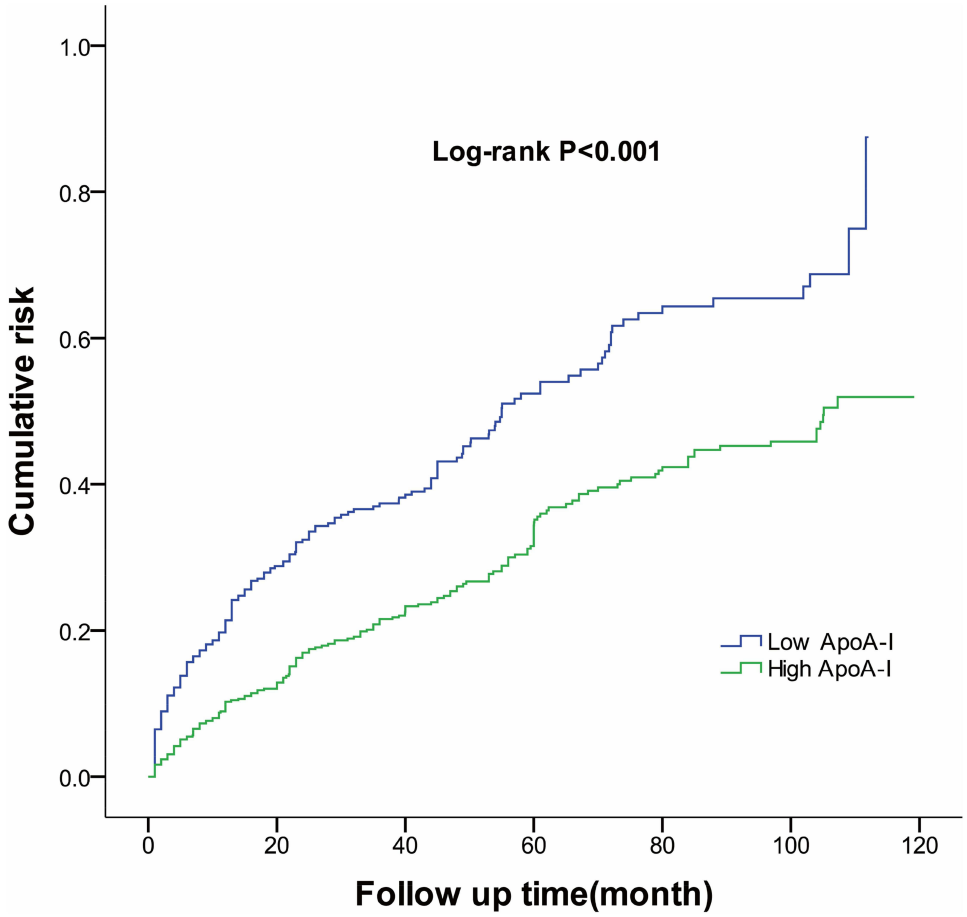

Figure 5 Kaplan-Meier curves for survival analysis of ACM in HFpEF patients.

Inflammation represents a critical component in the pathophysiological process associated with CHF,[40] wherein ApoA-I functions by virtue of its anti-inflammatory and antioxidant properties. Previous investigators showed that low levels of ApoA-I were independently associated with poor prognosis in patients with non-ischemic HF and hypothesized that ApoA-I may play a beneficial role in non-ischemic HF, in part through anti-inflammatory effects.[35] This hypothesis is supported by the results of several experiments on mice.[41,42] Low levels of ApoA-I tend to predict poorer metabolic status, and the functional role of ApoA-I is affected by changes in the internal

Table 4 Multivariate COX Regression Analysis in ACM of All CHF

Variable	B	SE	Wald	HR(95% CI)	P value
ApoA-I dichotomous variable	−0.354	0.078	20.815	0.702(0.603, 0.817)	***<0.001***
Age	0.032	0.003	109.280	1.032(1.026, 1.038)	***<0.001***
Hypertension	−0.139	0.075	3.400	0.871(0.751, 1.009)	0.065
Albumin	−0.032	0.008	14.951	0.969(0.954, 0.985)	***<0.001***
Cr	−0.007	0.026	0.063	1.000(0.994, 1.005)	0.802
NT-proBNP	0.036	0.004	72.573	1.036(1.028, 1.044)	***<0.001***

Note: The boldfaced and italicized P values are statistically different.
Abbreviations: Cr, Creatinine; NT-proBNP, N-terminal pro-brain-type natriuretic peptide.

Table 5 Multivariate COX Regression Analysis in ACM of the Subgroups of Patients

Variable	HFrEF					HFmrEF					HFpEF				
	B	SE	Wald	HR(95% CI)	P value	B	SE	Wald	HR(95% CI)	P value	B	SE	Wald	HR(95% CI)	P value
ApoA-I dichotomous variable	−0.216	0.166	1.686	0.806(0.582, 1.116)	0.194	−0.815	0.202	16.249	0.443(0.298, 0.658)	***<0.001***	−0.351	0.136	6.656	0.704(0.539, 0.919)	***0.010***
Age	0.026	0.006	17.613	1.027(1.014, 1.040)	***<0.001***	0.038	0.008	22.120	1.038(1.022, 1.055)	***<0.001***	0.038	0.006	48.071	1.039(1.028, 1.051)	***<0.001***
Hypertension	−1.141	0.160	0.780	0.868(0.635, 1.188)	0.377	0.289	0.203	2.030	1.335(0.897, 1.986)	0.154	−0.201	0.133	2.273	0.818(0.630, 1.062)	0.132
Albumin	−0.031	0.019	2.770	0.970(0.935, 1.006)	0.096	−0.019	0.022	0.775	0.981(0.940, 1.024)	0.981	−0.052	0.015	12.588	0.949(0.922, 0.977)	***<0.001***
Cr	0.006	0.004	2.318	1.062(0.982, 1.142)	0.128	−0.012	0.057	0.833	1.000(0.976, 1.010)	0.833	0.052	0.051	1.015	1.000(0.985, 1.005)	0.314
NT-proBNP	0.040	0.009	19.300	1.040(1.022, 1.058)	***<0.001***	0.049	0.013	14.909	1.050(1.024, 1.074)	***<0.001***	0.024	0.008	9.178	1.035(1.020, 1.049)	***0.002***

Note: The boldfaced and italicized P values are statistically different.
Abbreviations: Cr, Creatinine; NT-proBNP, N-terminal pro-brain-type natriuretic peptide.

environment,[43] whereas in contrast to the ischemic etiology as a major participant in HFrEF, which is predominantly based on focal inflammatory manifestations after myocardial ischemic necrosis, HFpEF has been suggested to be systemic inflammatory response-driven, which can trigger a cascade of profound pathophysiological alterations, encompassing oxidative stress imbalance, endothelial/microvascular dysfunction, and myocardial fibrosis,[44] leading to clinically complex syndromes. We considered that in poorer metabolic status and the combination of systemic inflammatory response-driven HFpEF,[45] the poor internal environment may further exacerbate the impaired ApoA-I

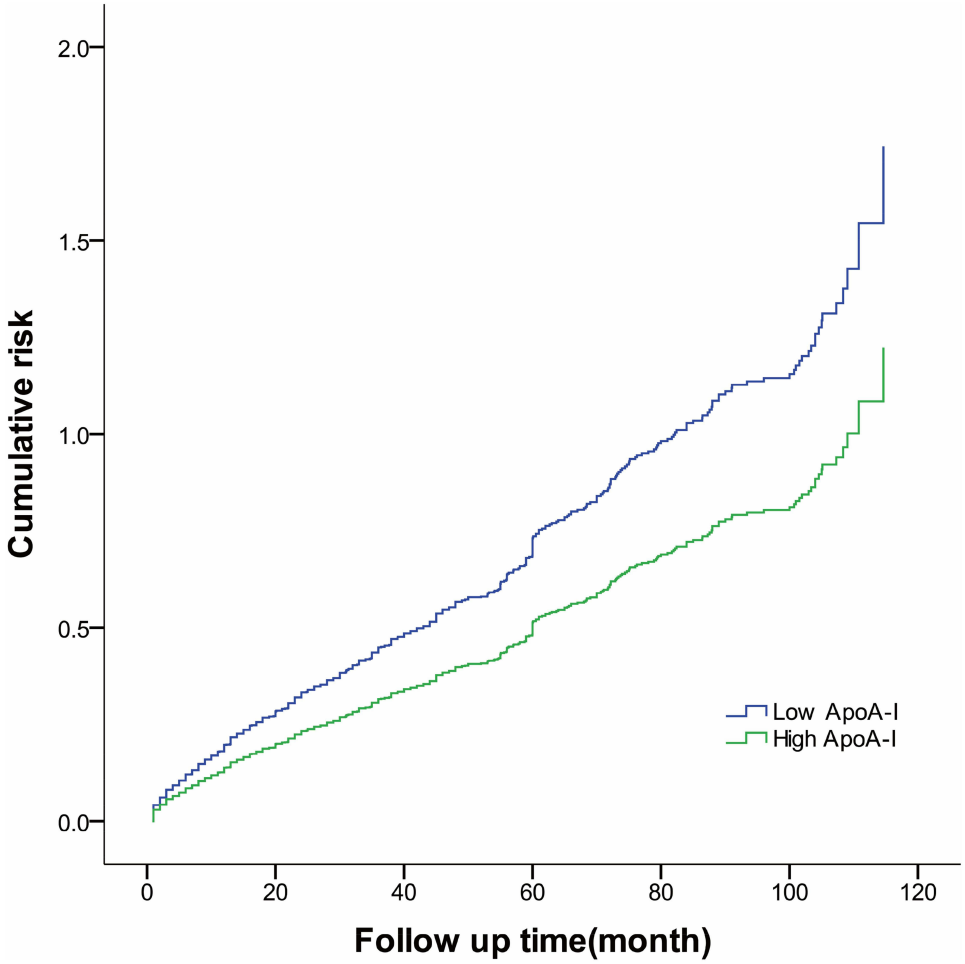

Figure 6 Multivariate Cox regression analysis for survival analysis of ACM in all CHF patients.

https://doi.org/10.2147/IJGM.S531156

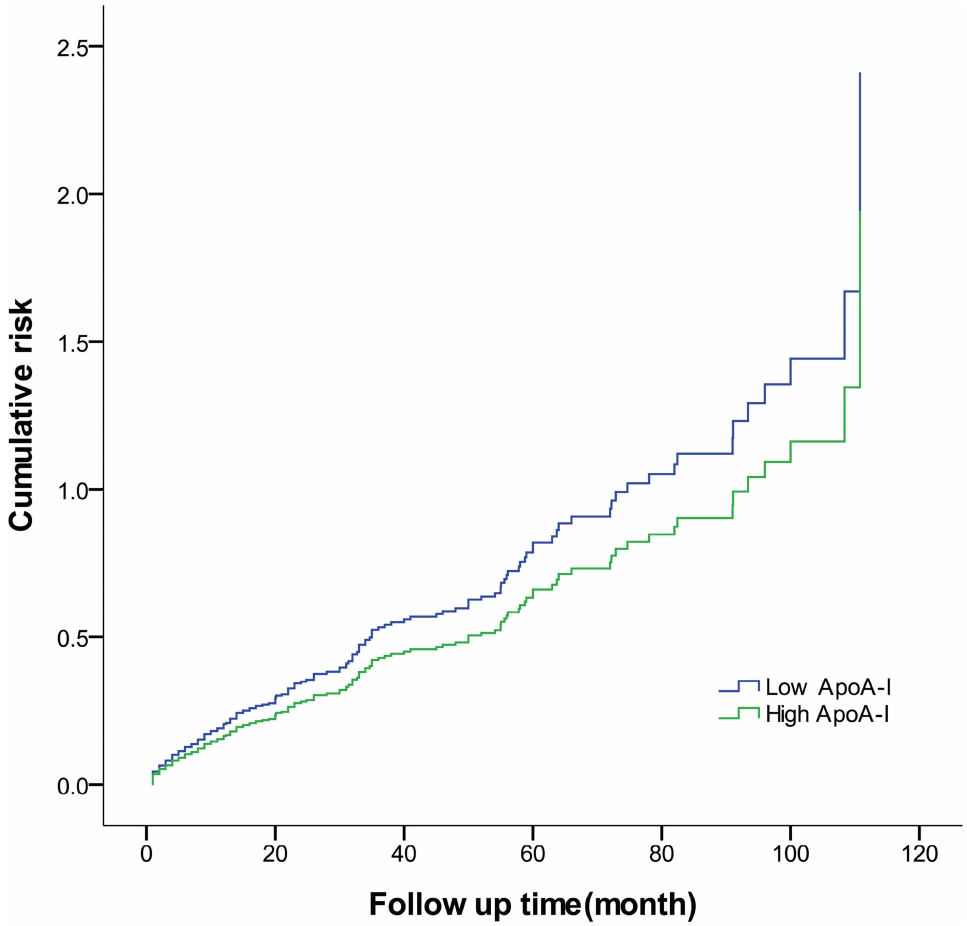

Figure 7 Multivariate Cox regression analysis for survival analysis of ACM in HFrEF patients.

function,[46] heralding a further decline in the protective effect of ApoA-I in patients with low ApoA-I levels, leading to a worse prognosis in the low ApoA-I group, so we can more clearly observe the differences in outcomes of different ApoA-I levels in the HFpEF and HFmrEF groups. Current research has substantiated that ApoA-I facilitates insulin secretion,[47] modulates oxidative stress, mitigates endothelial/microvascular dysfunction, and ameliorates myocardial fibrosis.[23] These mechanisms may collectively contribute to the observed superior prognosis in HFrEF patients with elevated ApoA-I levels compared to those with lower levels. However, this protective effect is not as pronounced in comparison to HFpEF, which may account for the absence of statistically significant differences observed in HFrEF patients. In addition, high plasma levels of ApoA-I have been shown to be associated with improved skeletal muscle mitochondrial function,[48] and improving skeletal muscle mitochondrial function has been shown to improve symptoms and prognosis in HFpEF,[49] a mechanism that may further up-regulate the protective effect of high plasma levels of ApoA-I in patients with HFpEF.

From our results it can be concluded that ApoA-I is a good prognostic indicator for long-term ACM in CHF. However, subsequent to the publication of the results of CSL112 (AEGIS-II trial), a human plasma-derived ApoA-I, it was observed that the high-risk CAD groups did not demonstrate a benefit from the drug.[50] In light of the lack of success observed with previous HDL-C treatments, Professor Ballantyne et al have proposed a moratorium on further studies of HDL-C therapies. They advocate for a more thorough investigation into the genetics, proteomics and metabolomics of HDL-C to identify more precise targets.[51] However, the protective role of ApoA-I in several types of diseases has been clarified,[52–54] and it may be possible to go beyond the treatment of atherosclerotic diseases and conduct clinical trials of ApoA-I in other non-atherosclerotic diseases to provide some new therapies. Combined with the results of our study,

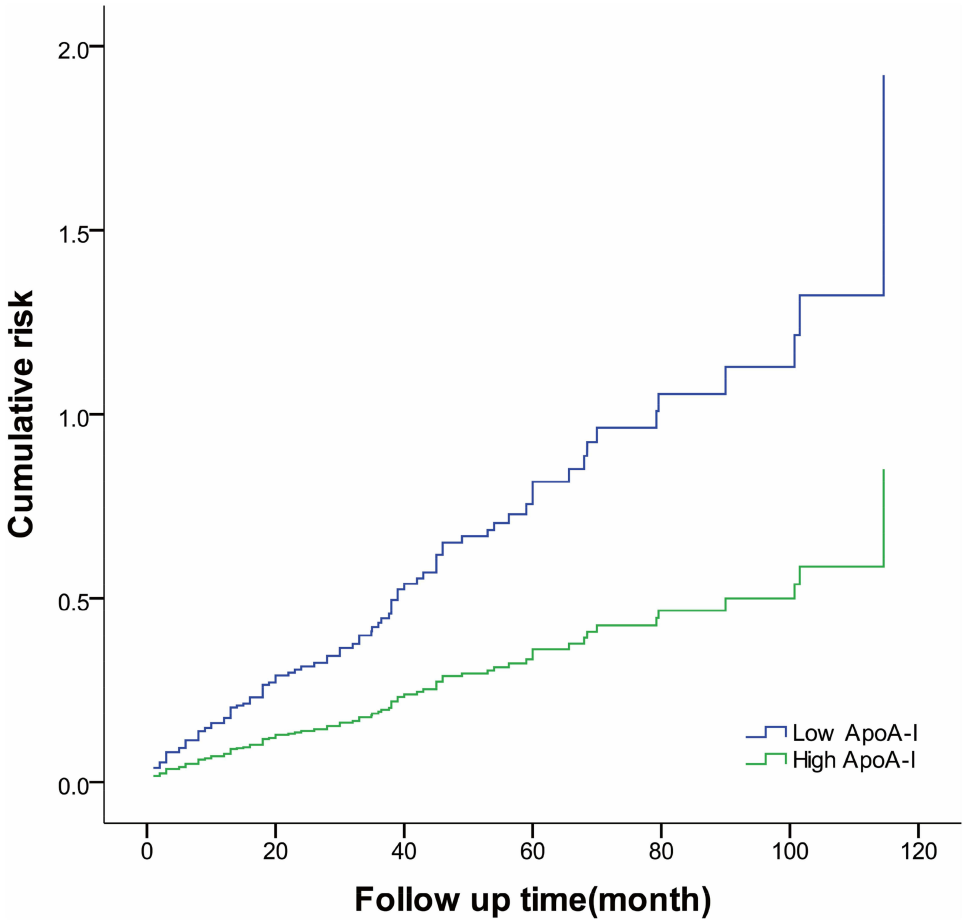

Figure 8 Multivariate Cox regression analysis for survival analysis of ACM in HFmrEF patients.

ApoA-I infusion therapy may become a good improvement for CHF, especially in patients with HFpEF and HFmrEF who lack effective treatment.

The limitations of our study should be considered. First, the function of ApoA-I can be influenced by variations in the internal environment, which means its role may differ based on the severity of HF. We did not assess cardiac function gradations and therefore cannot determine whether pro- or anti-inflammatory effects of ApoA-I are more pronounced in severe cases of CHF and we have not yet conducted a more detailed evaluation of CHF based on hemodynamic phenotype classification, which offers a more precise stratification for prognostic assessment.[55] Therefore, additional research is necessary to elucidate the prognostic value of ApoA-I in predicting outcomes for each hemodynamic phenotype. Additionally, previous research has demonstrated a U-shaped relationship between plasma HDL concentrations, atherosclerotic cardiovascular disease (ASCVD), and ACM,[13,56] and this is a conclusion that is also in line with our study.[10] As one of the key functional proteins, the dichotomous analysis of ApoA-I alone is inherently limiting. In addition, we only recorded plasma ApoA-I levels at enrolment without following their changes over time, while different medications and patient compliance may have a bias on ApoA-I levels, so the impact of dynamic fluctuations in this biomarker could not be analysed, and the optimal timing of sampling to estimate risk stratification could not be determined. Finally, this study was a single-centre study, which led to limited results due to local geographical and cultural specificities. Therefore, the role of ApoA-I in the prognosis and management of CHF disease should be further explored through prospective, large-scale, multicentre studies.

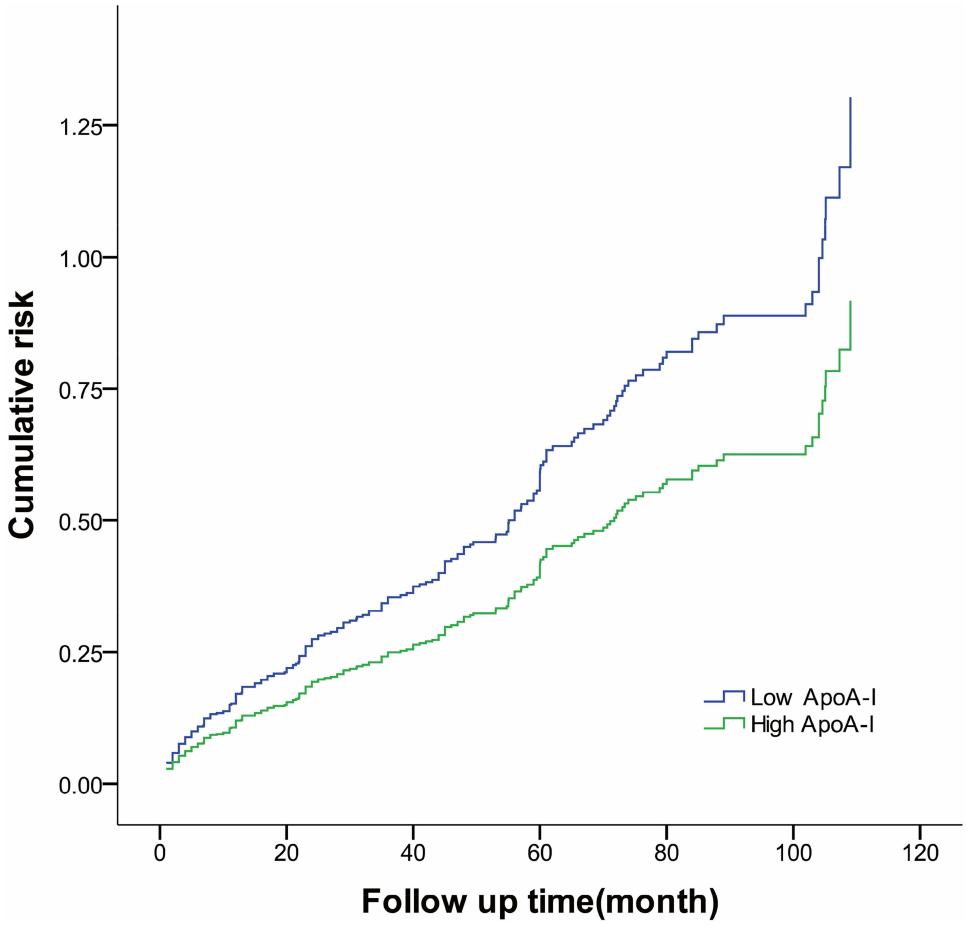

Figure 9 Multivariate Cox regression analysis for survival analysis of ACM in HFpEF patients.

Conclusions

High plasma levels of ApoA-I are inversely associated with ACM in CHF, particularly in HFmrEF and HFpEF. ApoA-I serves as a valuable biomarker for assessing long-term prognosis in patients with CHF, aiding clinicians in identifying those at high risk. This could enable the development of more aggressive management plans and close monitoring strategies. Furthermore, our findings strongly advocate for expanding research into the roles of ApoA-I beyond its established functions in athero-protection and treatment.

Abbreviations

ACM, All-cause mortality; CHF, Chronic heart failure; HF, Heart failure; HFrEF, Heart failure with reduced ejection fraction; HFmrEF, Heart failure with mid-range ejection fraction; HFpEF, Heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; CAD, Coronary artery disease; CVD, Cardiovascular disease; VHD, Valvular heart disease; CHD, Congenital heart disease; CM, cardiomyopathy; Cr, creatinine; UA, uric acid; TG, Triglyceride; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol.

Data Sharing Statement

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Ethics Committee of The First Affiliated Hospital of Xinjiang Medical University. Due to the retrospective nature of our study, the requirement for written informed consent was waived by the ethics committee. The authors ensured that the data was anonymized and maintained with confidentiality Consent for publication.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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