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The prognostic role of high-density lipoprotein cholesterol/C-reactive protein ratio in idiopathic pulmonary fibrosis

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Abstract

Background: The prognosis of idiopathic pulmonary fibrosis (IPF) patients is highly heterogeneous. Abnormalities in lipids and their metabolism play an important role in the development of IPF.

Aim: To investigate the value of lipid parameters, C-reactive protein (CRP) and high-density lipoprotein cholesterol/C-reactive protein (HDL-C/CRP) ratio levels in the prognosis of IPF patients.

Design: An observational cohort study.

Methods: We collected baseline data of non-IPF controls and IPF patients, and IPF patients were followed up for 4 years. All-cause death or lung transplantation and IPF-related death were the outcome events. Receiver operating characteristic curves and Cox proportional hazards models were used to analyze the predictive effect of lipid parameters, CRP and HDL-C/CRP ratio on the prognosis of IPF patients.

Results: IPF patients had lower HDL-C, HDL-C/CRP ratio and higher CRP compared to non-IPF controls. IPF patients who died or underwent lung transplantation were older and had worse pulmonary function, lower HDL-C, HDL-C/CRP ratio and higher CRP compared with surviving patients. HDL-C/CRP ratio was better than HDL-C and CRP in predicting all-cause death or lung transplantation. IPF patients with low HDL-C/CRP ratio had shorter survival times. The HDL-C/CRP ratio and diffusing capacity for carbon monoxide (DLCO)% of predicted were independent protective factors for all-cause death or lung transplantation and IPF-related death in IPF patients, while age and gender-age-physiology (GAP) Stage ≥ 2 (HR = 4.927) were independent risk factors for all-cause death or lung transplantation. Age $>$ 65 years (HR = 3.533) was an independent risk factor for IPF-related death.

Conclusion: HDL-C/CRP ratio was a valid predictor of clinical outcomes in IPF patients, including all-cause death or lung transplantation and IPF-related death.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial lung disease (ILD) of unknown etiology. IPF patients have a high mortality rate and a poor prognosis, with a median survival time of only 2.5–3.5 years after diagnosis.[1]

Dysregulation of lipid metabolism is one of the major metabolic alterations in IPF and has a significant effect on pathogenesis.[2] High-density lipoprotein (HDL) or its components may play a protective role in IPF. Lower plasma high-density lipoprotein cholesterol (HDL-C) is associated with greater serum MMP-7 and SP-A levels,[3] and MMP-7 and SP-A levels are thought to be associated with lung inflammation and extracellular matrix remodeling. Serum levels of small HDL particles (S-HDLP) are inversely associated with GAP index, mortality or lung transplantation in IPF patients.[4]

C-reactive protein (CRP) is considered an important marker of acute and chronic inflammation, and inflammation is also involved in the development and progression of pulmonary fibrosis.[5] For patients with IPF, fibrotic hypersensitivity pneumonitis, rheumatoid arthritis-associated ILD and systemic sclerosis-associated ILD, after adjusting for age, gender, smoking history, immunosuppressant therapy and baseline disease severity, higher CRP levels were associated with shorter 5-year survival.[6]

No study combines CRP and HDL-C as an indicator of prognosis in patients with IPF. Results of a multicenter clinical study involving 796 heart failure with preserved ejection fraction (HFpEF) patients in Japan showed that HFpEF patients with low HDL-C/CRP ratio had a higher risk of all-cause death and cardiac death, and HDL-C/CRP ratio was an independent predictor of all-cause

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death and cardiac death in HFpEF patients.[7] Due to the value of HDL-C and CRP in the prognosis of IPF patients mentioned above, we speculate that the HDL-C/CRP ratio may also have a good prognostic effect on IPF patients.

This study aims to compare lipid parameters, CRP and HDL-C/CRP ratio levels in IPF patients and non-IPF controls, and investigate their prognostic role in IPF patients.

Materials and methods

Study design and subjects

This was an observational cohort study. In this study, we collected the clinical data of IPF patients hospitalized in the Second Xiangya Hospital of Central South University from January 2011 to March 2019. The diagnosis of IPF was determined according to official ATS/ERS/JRS/ALAT clinical practice guidelines of IPF.[8,9] The inclusion criteria were (i) definite diagnosis of IPF; (ii) age > 18 years and (iii) CRP and lipid parameters measured during hospitalization. The exclusion criteria were a combination of lung or other organ tumors and unstable cardiac, vascular or nervous system diseases. The enrolled IPF patients were followed up at 48 months after discharge by inpatient, outpatient or telephone follow-up. All-cause death and unilateral or bilateral lung transplantation within 48 months after discharge was considered the primary outcome. The secondary outcome was IPF-related death.

Non-IPF controls were from the general population who underwent routine physical examinations at the Health Management Center of the Second Xiangya Hospital of Central South University from January 2023 to March 2023, and physical examination data of non-IPF controls were collected. The inclusion criteria for non-IPF controls were (i) age >18 years and (ii) CRP and lipid parameters were measured. The exclusion criteria were the combination of lung disease, tumors and unstable cardiac, vascular or nervous system diseases based on physical examination reports.

Data collection

CRP and lipid profile were measured in all subjects in this study by the clinical laboratory of the Second Xiangya Hospital of Central South University. Fasting venous blood was drawn from subjects via venipuncture, and serum lipid parameters [including total cholesterol (TC), HDL-C, low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG)] were measured by the automatic biochemical analyzer (ABBOTT ARCHITECT C8000, America), and serum CRP was measured by the specific protein analyzer (BECKMAN COULTER IMAGE 800, America). Clinical data of IPF patients including age, gender, body mass index (BMI), smoking status, pulmonary function (including forced vital capacity (FVC)% of predicted, forced expiratory volume in 1 s (FEV1)% of predicted, FEV1/FVC and diffusing capacity for carbon monoxide (DLCO)% of predicted), lipid parameters, CRP, pulmonary infection and the use of anti-fibrotic drugs were collected. The judgment of the GAP Stage was based on the criteria developed by Ley *et al.*[10] For non-IPF controls, data on age, gender, BMI, pulmonary function, lipid parameters and CRP were collected. At follow-up, it was determined whether the patient survived, died or had a lung transplant and the time of death or lung transplant and the cause of death were recorded.

Statistical analysis

Continuous variables were tested for normality, and variables conforming to the normal distribution were described by mean ± SD, and variables not conforming to the normal distribution were described by median (interquartile range, IQR). Student's *t*-test was used to compare differences between two groups for continuous variables that followed a normal distribution with equal variance, otherwise Mann–Whitney *U* test was used. Categorical variables were presented as *n* (%), and Pearson's chi-square test was used to compare differences between the two groups. Receiver operating characteristic (ROC) curves were plotted to determine the predictive value of the variable based on the area under the curve (AUC). The Youden index (Sensitivity + Specificity − 1) takes the maximum value to obtain the optimal operating point and the sensitivity and specificity of this cut-off value in predicting a 4-year prognosis in IPF patients. Factors associated with the prognosis of IPF patients were identified by Cox proportional hazard models. Kaplan–Meier survival curve and log-rank tests were used to compare cumulative survival rates between the two groups. The significance level of all tests was 0.05, and statistical analysis was conducted by statistical software IBM SPSS Statistics (Version 26) and MedCalc.

Results

The enrollment and follow-up results of IPF patients are shown in Figure 1. A total of 123 IPF patients entered the study, 11 were lost to follow-up and 112 IPF patients completed 48 months of follow-up, of which 30 patients survived, 2 patients underwent lung transplantation, 80 patients died (all-cause), 60 of whom died related to IPF. Forty-five non-IPF controls who met the criteria were recruited.

Baseline characteristics of IPF patients and non-IPF controls

Demographic data, CRP and lipid profile of the IPF patients and non-IPF controls included in this study were presented in Table 1. The age, gender and BMI of non-IPF controls in the analysis were consistent with those of IPF patients, whereas the proportion of smokers was higher in IPF patients ($P = 0.001$). FVC% of predicted and FEV1% of predicted were worse in IPF patients than in non-IPF controls. Patients with IPF had lower HDL-C, HDL-C/TC ratio and HDL-C/CRP ratio and higher CRP compared to non-IPF controls ($P < 0.001$). 112 patients who completed 48 months of follow-up were divided into the survival group ($n = 30$, median survival time: 48.0 months) and the all-cause death or lung transplantation group ($n = 82$, median survival time: 27.5 months), as shown in Table 2. IPF patients in the survival group were younger. IPF patients in the all-cause death or lung transplantation group had significantly worse pulmonary function than those in the survival group, including FVC% of predicted, FEV1% of predicted and DLCO% of predicted ($P < 0.05$). Similarly, the proportion of IPF patients with GAP Stage ≥ 2 was higher in the all-cause death or lung transplantation group than in the survival group. In addition, patients in the all-cause death or lung transplantation group had lower TC, HDL-C and HDL-C/CRP ratio, but their CRP levels were higher. However, there was no statistical difference in the proportion of patients using anti-fibrotic drugs between the two groups.

Prognostic value of baseline lipid parameters, CRP and HDL-C/CRP ratio in IPF patients

To evaluate the prognostic value of baseline lipid profile parameters, CRP and HDL-C/CRP ratio in IPF patients, we plotted ROC curves, only the ROC curves for TC, HDL-C, CRP and HDL-C/CRP ratio were statistically significant ($P < 0.05$) in predicting the all-cause death or lung transplantation, as shown in Table 3 and Figure 2. Of these, AUC was better for CRP and HDL-C/CRP ratio,

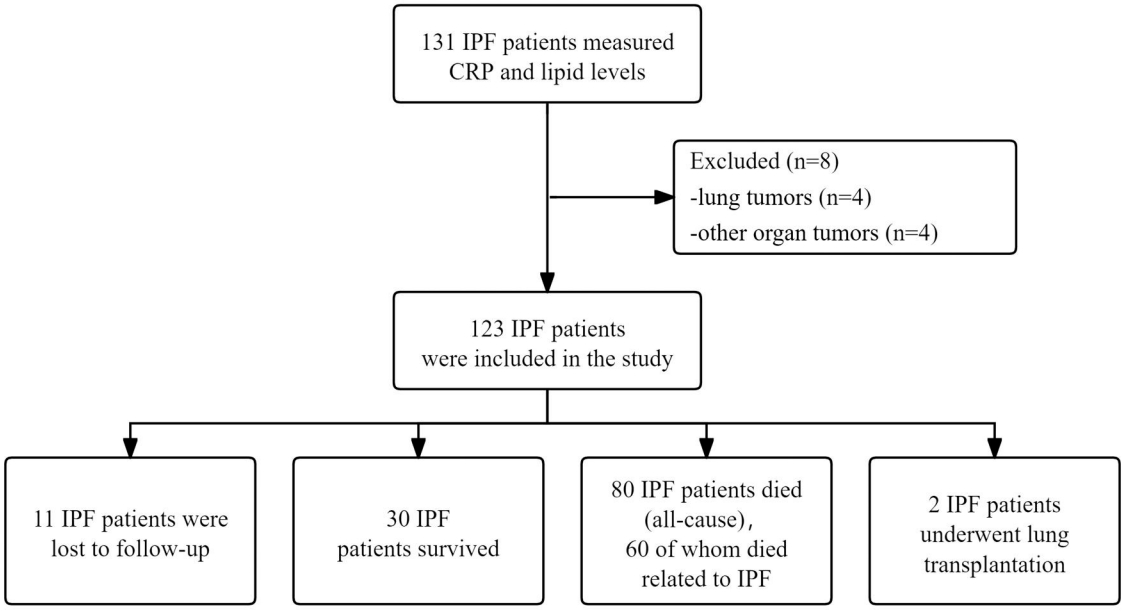

Figure 1. The enrollment and follow-up results of IPF patients.

Table 1. Demographic characteristics, CRP and lipid profile of non-IPF controls and IPF patients[a]

	Non-IPF controls (N = 45)	IPF patients (N = 123)	P
Age (years)	65.0 ± 12.0	65.1 ± 9.5	0.632
<60	13 (28.9)	30 (24.4)	
60–74	23 (51.1)	71 (57.7)	
≥75	9 (20.0)	22 (17.9)	0.742
Gender			
Male (*n*, %)	32 (71.1)	88 (71.5)	
Female (*n*, %)	13 (28.9)	35 (28.5)	0.956
BMI (kg/m^2)			
<18.5	2 (4.4)	5 (4.1)	
18.5–23.9	20 (44.4)	62 (50.4)	
24.0–27.9	19 (42.2)	41 (33.3)	
≥28.0	4 (9.0)	15 (12.2)	0.729
Smoking	19 (42.2)	85 (69.1)	0.001
Pulmonary function test			
FVC% of predicted	109.3 ± 14.4	78.9 ± 21.6	<0.001
FEV1% of predicted	112.9 ± 7.4	82.0 ± 20.7	<0.001
FEV1/FVC (%)	84.6 ± 8.5	90.2 ± 11.1	0.002
Lipid profile			
TC (mg/dl)	4.5 (3.9–4.7)	4.3 (3.7–4.9)	0.269
HDL-C (mg/dl)	1.3 (1.2–1.5)	1.0 (0.8–1.2)	<0.001
LDL-C (mg/dl)	2.7 (2.3–3.1)	2.7 (2.2–3.2)	0.555
TG (mg/dl)	1.3 (0.7–1.9)	1.5 (1.0–1.8)	0.118
HDL-C/TC ratio	0.3 (0.3–0.4)	0.2 (0.2–0.3)	<0.001
CRP (mg/l)	0.8 (0.3–2.0)	4.7 (2.6–9.9)	<0.001
HDL-C/CRP ratio	1.6 (0.6–4.2)	0.2 (0.1–0.4)	<0.001

[a] Data are presented as the mean ± SD, *n* (%) or median (IQR). Student's t-test, Pearson's chi-square test and Mann–Whitney *U* test were used to compare differences between groups.

compared these two ROC curves we found that the ROC curve of HDL-C/CRP ratio was better than that of CRP, and the difference was statistically significant ($P = 0.048$). The baseline HDL-C/CRP ratio had an optimal operating point of 0.22 for predicting all-cause death or lung transplantation within 4 years in IPF patients, providing a sensitivity of 65.43% and a specificity of 76.19%. Kaplan–Meier Survival Curve was plotted by dividing IPF patients into low HDL-C/CRP ratio and high HDL-C/CRP ratio groups using the cut-off point of 0.22, as shown in Figure 3. The survival time of IPF patients in the low HDL-C/CRP ratio group was shorter than that in the high HDL-C/CRP ratio group. Only CRP (AUC = 0.636, optimal operating point = 4.14 mg/l) and HDL-C/CRP ratio (AUC = 0.658, optimal operating point = 0.23) could predict the risk of IPF-related death in IPF patients (Table 3 and Figure 4), and there was no statistical difference in AUC between them ($P = 0.185$). Kaplan–Meier Survival Curve was plotted using IPF-related death as the outcome, with IPF patients in the low HDL-C/CRP ratio group having a shorter survival time ($P < 0.001$), and the results are shown in Figure 5.

Predictors of all-cause death or lung transplantation and IPF-related death at 4 years in IPF patients

From Table 4, we found that BMI, FVC% of predicted, DLCO% of predicted, TC and HDL-C/CRP ratio were protective factors for all-cause death or lung transplantation in IPF patients in univariate Cox proportional hazard models analyses, while age, CRP and GAP Stage ≥ 2 were risk factors. Multivariate Cox proportional hazard models analyses were performed for these indicators to construct Model 1 and Model 2. Both multivariate models had good discrimination on the all-cause death or lung transplantation of IPF patients. HDL-C/CRP ratio was a protective factor for all-cause death or lung transplantation in IPF patients (Model 1 HR = 0.191, Model 2 HR = 0.196). For every 1.00 increase in the HDL-C/CRP ratio, the risk of all-cause death or lung transplantation in IPF patients will be reduced by 80.9% and 80.4%, respectively. In Model 1, age and DLCO% of predicted were also factors influencing all-cause death or lung transplantation in IPF patients. Model 2 showed that the HR for GAP Stage ≥ 2 was 4.927, suggesting that patients with IPF who had GAP Stage ≥ 2 at baseline had a 4.927-fold higher risk of all-cause death or lung transplantation than patients with GAP Stage 1. In addition, HDL-C/CRP ratio (HR = 0.120, $P = 0.015$) and DLCO% of predicted (HR = 0.959, $P < 0.001$) were also the protective factors in the multivariate Cox proportional hazard models analyses with IPF-related death as the outcome event, and age > 65 years (HR = 3.533, $P < 0.001$) was a risk factor (Table 5).

Table 2. Baseline characteristics of IPF patients in the survival and death (all-cause) or lung transplantation groups[a]

	Survival ($N = 30$)	Death (all-cause) or lung transplantation ($N = 82$)	P
Age (years)	59.7 ± 10.5	67.4 ± 8.4	<0.001
Gender			
Male (*n*, %)	19 (63.3)	61 (74.4)	
Female (*n*, %)	11 (36.7)	21 (25.6)	0.251
BMI (kg/m^2)	24.7 ± 2.9	23.5 ± 3.5	0.101
Smoking	21 (70.0)	56 (68.3)	0.863
Pulmonary function test			
FVC% of predicted	87.5 ± 22.5	74.2 ± 19.9	0.006
FEV1% of predicted	89.9 ± 22.6	78.2 ± 19.7	0.015
FEV1/FVC (%)	88.8 ± 10.6	91.4 ± 11.0	0.298
DLCO% of predicted	67.4 ± 18.1	51.5 ± 18.5	0.001
GAP Stage ≥ 2	0(0.0)	29(51.8)[b]	<0.001
Lipid profile			
TC (mg/dl)	4.6 (4.1–5.1)	4.2 (3.6–4.9)	0.028
HDL-C (mg/dl)	1.1 (0.9–1.2)	0.9 (0.8–1.2)	0.027
LDL-C (mg/dl)	2.8 (2.5–3.2)	2.7 (2.1–3.2)	0.249
TG (mg/dl)	1.5 (1.1–1.8)	1.4 (1.0–1.8)	0.446
HDL-C/TC ratio	0.2 (0.2–0.3)	0.2 (0.2–0.3)	0.678
CRP (mg/l)	3.0 (1.9–4.5)	5.7 (3.3–11.6)	<0.001
HDL-C/CRP ratio	0.4 (0.2–0.6)	0.2 (0.1–0.3)	<0.001
Pulmonary infection (*n*, %)	3 (10.0)	18 (22.0)	0.151
Anti-fibrotic therapy (*n*, %)	12 (40.0)	24 (29.3)	0.282
Median survival time (month)	48.0 (48.0–48.0)	27.5 (18.0–36.0)	<0.001

[a] Data are presented as the mean ± SD, *n* (%) or median (IQR). Student's *t*-test, Pearson's chi-square test and Mann–Whitney *U* test to compare differences between groups. GAP: gender, age, and 2 lung physiology variables (FVC% of predicted and DLCO% of predicted).
[b] Of the 82 patients in the death or lung transplantation group, only 56 patients had a complete GAP score.

Table 3. ROC curves of baseline lipid profile, CRP and HDL-C/CRP ratio predicted 48-month clinical outcome in IPF patients[a]

	AUC	P	95% CI	Optimal operating point	Sensitivity (%)	Specificity (%)
Primary outcome (all-cause death or lung transplantation)						
TC (mg/dl)	0.613	0.036	0.521–0.699	3.97	45.68	76.19
HDL-C (mg/dl)	0.615	0.031	0.523–0.701	0.94	53.09	71.43
LDL-C (mg/dl)	0.563	0.249	0.471–0.652	2.38	43.21	76.19
TG (mg/dl)	0.551	0.352	0.458–0.640	3.30	93.83	16.67
HDL-C/TC ratio	0.519	0.734	0.427–0.610	0.25	65.43	42.86
CRP (mg/l)	0.686	<0.001	0.596–0.767	4.39	66.67	71.43
HDL-C/CRP ratio	0.719	<0.001	0.631–0.797	0.22	65.43	76.19
Secondary outcome (IPF-related death)						
TC (mg/dl)	0.555	0.290	0.463–0.645	5.10	88.33	25.40
HDL-C (mg/dl)	0.561	0.241	0.496–0.650	0.89	38.33	76.19
LDL-C (mg/dl)	0.526	0.618	0.434–0.617	2.35	40.00	69.84
TG (mg/dl)	0.559	0.264	0.467–0.648	1.29	51.67	66.67
HDL-C/TC ratio	0.513	0.801	0.421–0.604	0.33	93.33	15.87
CRP (mg/l)	0.636	0.007	0.544–0.721	4.14	68.33	57.14
HDL-C/CRP ratio	0.658	0.001	0.567–0.741	0.23	66.67	60.32

[a] 95% CI: 95% confidence interval.

Discussion

The study found that IPF patients had lower HDL-C, HDL-C/TC ratio, HDL-C/CRP ratio and higher CRP compared to non-IPF controls. IPF patients who died (all-cause) or underwent lung transplantation within 4 years of diagnosis were older and had worse pulmonary function, lower TC, HDL-C, HDL-C/CRP ratio and higher CRP compared with surviving patients. The survival time of IPF patients with low HDL-C/CRP ratio was shorter than that of patients with high HDL-C/CRP. HDL-C/CRP ratio and DLCO% of predicted were protective factors for all-cause death or lung transplantation in IPF patients, while age and GAP Stage ≥ 2 were risk factors. HDL-C/CRP ratio and DLCO% of predicted were also protective factors for IPF-related death, and age > 65 years was a risk factor.

The lung is rich in lipids and has active lipid metabolism, which is involved in and regulates a variety of pathophysiological processes.[11] In addition to being a major component of pulmonary surfactant, lipids are involved in shaping the extracellular matrix.[11] Abnormalities in lipids and their metabolic pathways play an important role in pulmonary fibrosis.[12–15] Cholesterol was converted into 25-hydroxycholesterol (25-HC) by cholesterol 25-hydroxylase, and 25-HC participated in lung tissue remodeling by promoting fibroblast expression of TGF-β, α-smooth muscle actin, collagen I and extracellular matrix deposition.[16] HDL binds free cholesterol and transports it to the liver where it is metabolized and eventually excreted via the bile. Aihara *et al.*[17] found that HDL levels were lower in patients with chronic interstitial pneumonia/fibrosis than in controls. A study in a population of IPF patients also found that serum S-HDLP concentrations were associated with disease severity and mortality risk in IPF patients.[4] Similar to previous studies, our results showed that patients with IPF had a lower level of HDL-C than non-IPF controls. Among 112 IPF patients who completed the 4-year follow-

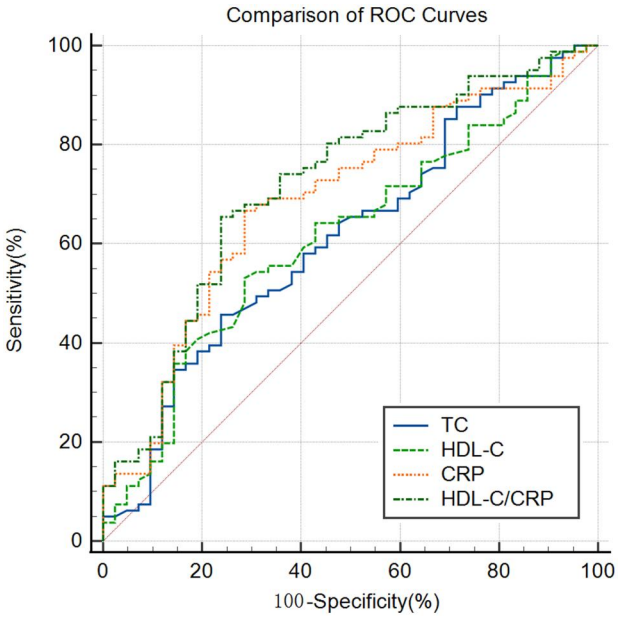

Figure 2. Comparison of ROC curves for TC, HDL-C, CRP and HDL-C/CRP ratio in predicting all-cause death or lung transplantation in IPF patients.

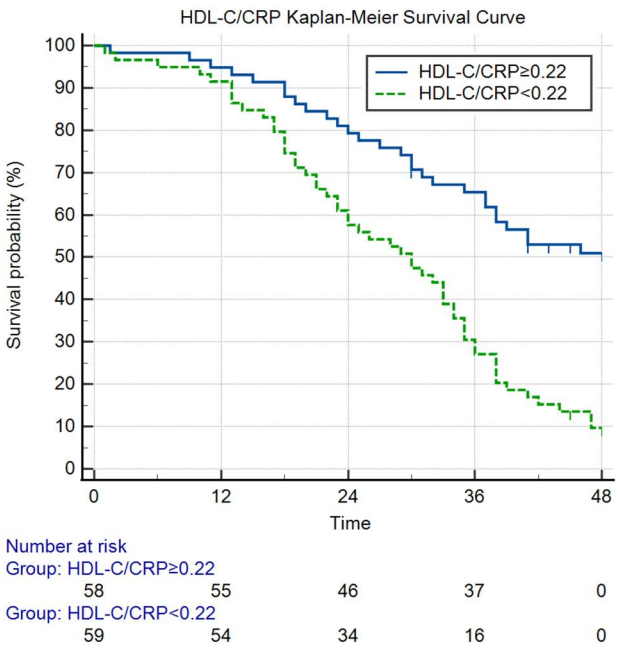

Figure 3. Kaplan–Meier survival curve of low HDL-C/CRP ratio and high HDL-C/CRP ratio groups, and all-cause death or lung transplantation was the outcome event. Log-rank test $P < 0.001$, HR = 3.004, 95% CI: 1.904–4.740.

up, patients in the all-cause death or lung transplantation group also had lower HDL-C and TC levels than patients in the survival group. Combined with the results of other published studies, we suggest that baseline lipid levels in patients with IPF may be related to the development and prognosis of the disease.

CRP is associated with a variety of fibrotic diseases and is an important mediator in the development of fibrosis; CRP promotes fibrosis in the heart and kidney by activating the TGF-β/Smad signaling pathway.[18–21] The two-sample Mendelian randomization analysis of GWAS analysis data of 1028 IPF patients and 196 986

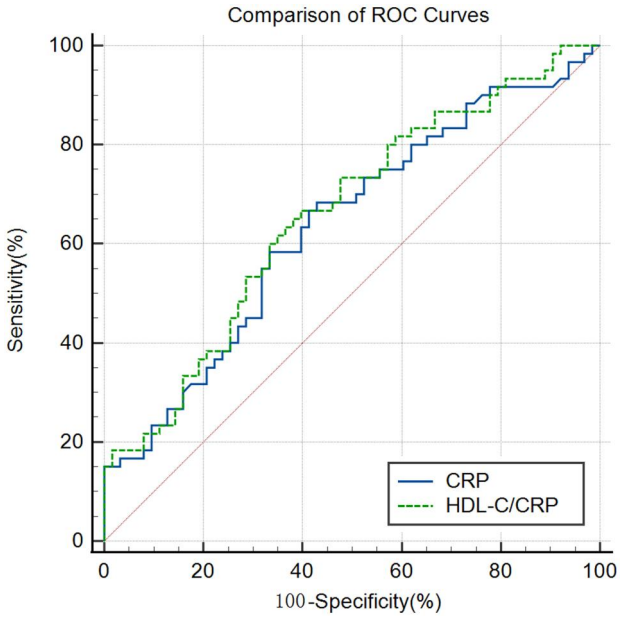

Figure 4. Comparison of ROC curves for CRP and HDL-C/CRP ratio in predicting IPF-related death in IPF patients.

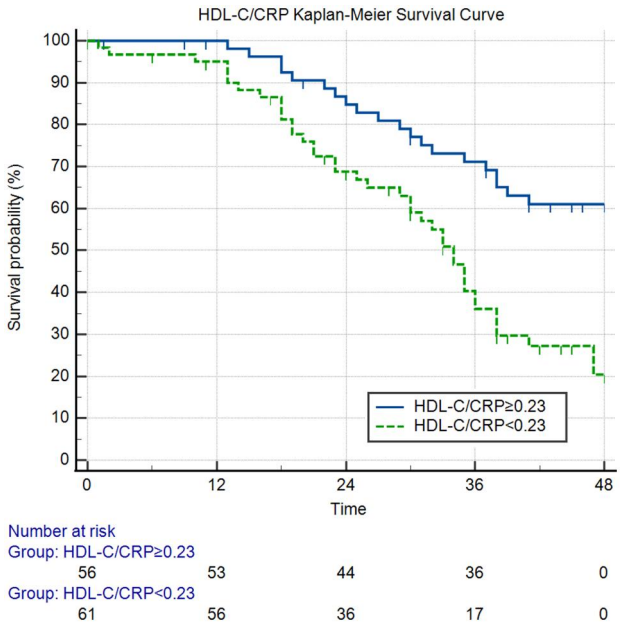

Figure 5. Kaplan–Meier survival curve of low HDL-C/CRP ratio and high HDL-C/CRP ratio groups, and IPF-related death was the outcome event. Log-rank test $P < 0.001$, HR = 2.794, 95% CI: 1.655–4.717.

controls from FinnGen Biobank showed that elevated circulating CRP levels increased the risk of IPF in the population.[5] However, another Mendelian randomization analysis of GWAS data from the UK Biobank showed a negative correlation between CRP and ILD and IPF.[22] There are currently few causal studies on circulating CRP and the risk of IPF, and more clinical studies are needed for further confirmation. Differential expression protein analysis after proteomic testing of blood samples from IPF patients and healthy subjects showed that CRP expression was up-regulated in IPF patients. ELISA was used to validate CRP levels in patients with IPF, sarcoidosis and hypersensitivity pneumonia, and it was found that CRP levels in all three groups were higher than in healthy subjects.[23] We compared CRP levels between IPF patients

Table 4. Results of the univariate and multivariate Cox proportional hazard models analyses for death or lung transplantation as the outcome in IPF patients[a]

	HR	95% CI	P
Univariate COX proportional hazard model			
Age (years)	1.072	1.043–1.102	<0.001
BMI (kg/m^2)	0.920	0.859–0.985	0.016
FVC% of predicted	0.984	0.971–0.996	0.008
DLCO% of predicted	0.970	0.956–0.985	<0.001
TC (mg/dl)	0.784	0.623–0.986	0.037
CRP (mg/l)	1.012	1.005–1.020	0.006
HDL-C/CRP ratio	0.112	0.035–0.356	<0.001
GAP Stage ≥ 2	5.431	3.044–9.692	<0.001
Multivariate COX proportional hazard Model 1			
Age (years)	1.096	1.056–1.138	<0.001
DLCO% of predicted	0.965	0.950–0.981	<0.001
HDL-C/CRP ratio	0.191	0.049–0.742	0.017
Multivariate COX proportional hazard Model 2			
HDL-C/CRP ratio	0.196	0.048–0.801	0.023
GAP Stage ≥ 2	4.927	2.738–8.868	<0.001

[a] Multivariate COX proportional hazard Model 1: including age, BMI, FVC% of predicted, DLCO% of predicted, TC, CRP, HDL-C/CRP ratio. Harrell's C-index: 0.757, 95% CI: 0.698–0.815. Multivariate COX proportional hazard Model 2: including BMI, TC, CRP, HDL-C/CRP ratio, GAP Stage ≥ 2. Harrell's C-index: 0.741, 95% CI: 0.683–0.800.

Table 5. Results of the univariate and multivariate Cox proportional hazard models analyses for IPF-related death as the outcome in IPF patients[a]

	HR	95% CI	P
Univariate COX proportional hazard model			
Age > 65 years	2.383	1.423–3.991	0.001
BMI (kg/m^2)	0.919	0.849–0.995	0.036
FVC% of predicted	0.980	0.966–0.995	0.007
DLCO% of predicted	0.958	0.940–0.976	<0.001
CRP (mg/l)	1.015	1.007–1.023	<0.001
HDL-C/CRP ratio	0.106	0.027–0.410	0.001
GAP Stage ≥ 2	6.464	3.370–12.397	<0.001
Multivariate COX proportional hazard model			
Age > 65 years	3.533	1.846–6.759	<0.001
DLCO% of predicted	0.959	0.941–0.976	<0.001
HDL-C/CRP ratio	0.120	0.021– 0.667	0.015

[a] Multivariate COX proportional hazard model: including age > 65 years, BMI, FVC% of predicted, DLCO% of predicted, CRP, HDL-C/CRP ratio. Harrell's C-index: 0.779, 95% CI: 0.715–0.842.

and non-IPF controls, with higher CRP levels in IPF patients. In addition, patients with IPF who died (all-cause) or underwent lung transplantation within 4 years of diagnosis also had higher CRP levels than surviving patients. Hachisu *et al.*[24] found that CRP, lactate dehydrogenase and TC were predictors of in-hospital mortality in patients with acute exacerbation of IPF after adjustment for age, sex and BMI. CRP is also a risk factor for death in polymyositis/dermatomyositis-associated ILD patients.[25] CRP is an easily accessible serological marker and may be a potential biomarker that can predict the prognosis of IPF patients.

The prognosis of IPF patients is very heterogeneous, so it is very important to find reliable biomarkers to estimate the prognosis of IPF patients and select the best treatment. As mentioned above, both lipid level and CRP have certain predictive values for the prognosis of IPF. HDL-C/CRP ratio was found to be significantly associated with left ventricular diastolic function and right ventricular systolic function in HFpEF patients and was an independent predictor of all-cause and cardiac death in HFpEF patients.[7] However, there are no studies of HDL-C/CRP ratio in IPF. As a combination of anti-fibrotic and pro-fibrotic factors, the HDL-C/CRP ratio was better than HDL-C and CRP in predicting all-cause death in IPF patients, although there was no statistical difference in predicting IPF-related death between HDL-C/CRP ratio and CRP. IPF patients in the low HDL-C/CRP ratio group had shorter survival time than those in the high HDL-C/CRP ratio group, and the HDL-C/CRP ratio remains a protective factor for all-cause death and IPF-related death in IPF patients after adjustment for age, BMI, FVC% of predicted, DLCO% of predicted or GAP Stage. Obtaining HDL-C/CRP is easier and more economical than pulmonary function and lung high-resolution CT, and can be detected in almost all hospitals. Therefore, HDL-C/CRP is a simple and effective auxiliary indicator for predicting the prognosis of IPF patients.

IPF is more prevalent in the elderly population, with all-cause mortality being higher in IPF patients aged ≥ 75 years than in those aged < 75 years.[26] We also confirmed that age is a risk factor for all-cause death and IPF-related death in patients with IPF. Several systematic reviews of the effectiveness of anti-fibrotic therapies in patients with IPF have shown that anti-fibrotic therapies reduce the risk of mortality as well as the risk of acute exacerbations in patients with IPF.[27,28] However, in our study, the proportion of patients using anti-fibrotic therapy in IPF in the all-cause death or lung transplantation group was not statistically different from that in the survival group. Whether patients with IPF received anti-fibrotic therapy was influenced by a variety of factors such as disease severity and quality of life,[29] which in part affected the analysis of the prognosis of patients with IPF treated with anti-fibrotic therapy. In addition, anti-fibrotic drugs are expensive and some patients may stop halfway for financial reasons. IPF patients who had been treated with nintedanib or pirfenidone were assigned to the anti-fibrotic treatment group, and it was not clear whether the patients took the drug regularly and for which period they took the drug, which may also have contributed to the result that anti-fibrotic treatment was not associated with the prognosis of IPF patients in this study.

This study also has limitations. First, this study was a single-center study with a limited number of samples, and data from a larger sample size of patients are needed to validate the predictive effect of the HDL-C/CRP ratio on the prognosis of IPF patients. Second, only 72.4% of the 123 IPF patients included in this study had complete pulmonary function data, which may have some impact on our results.

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Author contributions

Xiaoli Ouyang contributed to the design of the study and the writing of the manuscript; Yijin Qian, Yuexin Tan and Qing Zhang contributed to the collection, reduction and analysis of the data; Qinxue Shen and Min Song contributed to the revision of the manuscript; Jingcheng Shi contributed to the audit of statistical methods; and Hong Peng contributed to the design of the study, revision and final approval of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

None declared.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval

The study was approved by the Medical Ethics Committee of the Second Xiangya Hospital of Central South University (Approval Number LYF2022147). The study was retrospective and therefore informed written consent could be waived from the study subjects.

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