Research Article

Association Between the Lipid Profile and Renal Dysfunction in the Heart Failure Patients

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Key Words

Lipid • HDL-C • Renal dysfunction • EGFR • Heart failure

Abstract

Background/Aims: In heart failure patients with high prevalence of chronic renal disease (CKD), hospitalization and mortality, whether the lipid profile was associated with renal dysfunction remained unknown. The present study intended to clarify the association between the lipid profile and renal dysfunction in the heart failure patients. **Methods:** 336 hospitalized heart failure patients with left ventricle ejection fraction (LVEF) $\leq 45\%$ and New York Heart Association (NYHA) class II-IV were enrolled. The estimated glomerular filtration rate (eGFR) $< 90 \text{ mL/min} \cdot 1.73 \text{ m}^2$ was defined as renal dysfunction. The demographic, clinical data, blood samples and echocardiography were documented. The Pearson simple linear correlation was performed to evaluate the confounding factors correlated with eGFR. The significantly correlated factors were enrolled in Logistic regression as confounding factors to determine the association between the lipid profile and renal dysfunction in the heart failure patients. **Results:** 182 patients (54.2%) had renal dysfunction and 154 patients (45.8%) did not have renal dysfunction. The waist circumference, platelet counts, platelet distribution width (PDW), high density lipoprotein-cholesterol (HDL-C), apolipoprotein A1 (apoA1), albumin and left ventricular ejection fraction (LVEF) are positively correlated with eGFR (all $P < 0.05$). Meanwhile, the age, mean platelet volume (MPV), neutrophilic granulocyte percentage (NEUT%), urea nitrogen (BUN), creatinine and total bilirubin (TBIL) are negatively correlated with eGFR (all $P < 0.05$). The total cholesterol (TC), triglyceride, low density lipoprotein-cholesterol (LDL-C) and apolipoprotein B (apoB) show no correlation with eGFR. After the adjustment of sex, hypertension, diabetes mellitus, age, waist circumference, platelet counts, MPV, PDW, NEUT%,

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TBIL, albumin and LVEF, HDL-C is the only lipid factor still significantly associated with renal dysfunction in hospitalized heart failure patients ($OR=0.119$, $P=0.003$). **Conclusion:** Among the lipid profile of TC, triglyceride, LDL-C, HDL-C, apo A1 and apo B, the HDL-C is the only lipid factor significantly associated with renal dysfunction in hospitalized heart failure patients.

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Introduction

Heart failure (HF) is often accompanied with renal dysfunction, and the relationship between heart and kidney has been discussed in a variety of studies [1–3]. Cole RT et al. [4] reviewed that 20% to 57% patients with chronic, stable HF and 30% to 67% patients with acutely decompensated HF had certain levels of renal dysfunction. According to a recent large sample UK study based on the 50, 114 heart failure patients, the prevalence of CKD in the HF community was 63%, it brought an 11% increase in hospitalization and 17% in mortality in heart failure patients [5]. The pathophysiological features have demonstrated that heart failure may cause the reduction in cardiac output and decrease in renal perfusion, which have become the primary driver for renal dysfunction in HF [6–8].

The shocking results have driven us to pay more attention to the renal dysfunction in heart failure patients, the associated risk factors should be intervened to decrease the prevalence, hospitalization and mortality. Among the various confounding factors for renal dysfunction in heart failure, the dyslipidemia has become an important element according to recent studies [9, 10]. One recent study based on 188, 577 chronic kidney disease (CKD) patients (defined as estimated glomerular filtration rate (eGFR) <60 mL/min·1.73 m²) demonstrated that a 17-mg/dL increase in HDL cholesterol concentration was associated with a 0.8% increase in eGFR ($P=0.004$) and lower risk for eGFR <60 mL/min·1.73 m² ($OR=0.85$, $P<0.001$) [11]. There was no evidence for a causal relationship between LDL cholesterol, triglyceride concentration and any kidney disease measure.

In heart failure patients with high CKD prevalence and also with high CKD induced hospitalization and mortality, whether the lipid profile was associated with renal dysfunction remained unknown. The present study intended to clarify the association between the lipid profile and renal dysfunction in the heart failure patients.

Materials and Methods

Subjects

We performed this present cross-sectional study in 1st Cardiology Department of People's Hospital of Shaanxi Province from January 2017 to June in 2018. We enrolled hospitalized patients with left ventricular ejection fraction (LVEF) $\leq 45\%$ and New York Heart Association (NYHA) class II–IV. NYHA class II is defined as mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity. NYHA class III is defined as marked limitation in activity due to symptoms, even during less-than-ordinary activity, comfortable only at rest. NYHA class IV is defined as severe limitations in activity, even while at rest, who are mostly bedbound patients [12]. Heart failure was confirmed by clinical heart failure specialists and cardiologists after consulting with the symptoms and the echocardiography report. The main exclusion criteria included significant cognitive impairment, life-threatening comorbidity, and unwillingness for cooptation [13].

336 hospitalized patients with heart failure were enrolled, 188 patients (56.0%) were male and 148 patients (44.0%) were female. The patients were divided into two groups according to renal function, the renal dysfunction is defined as eGFR < 90 mL/min·1.73 m² [14]. 182 patients (54.2%) had renal dysfunction and 154 patients (45.8%) did not have renal dysfunction.

eGFR calculation

eGFR is calculated using Modification of Diet in Renal Disease-Isotope Dilution Mass Spectrometry (MDRD-IDMS) equation, which is considered as the most appropriate calculation method in Chinese population [15].

Demographic and clinical data

Demographic data and cardiovascular risk factors were obtained from the medical records. Body weight was measured with a double balance placed on a firm surface while the shoes were taken off. Height was measured with a Frankfort plane positioned at a 90° angle against a wall-mounted metal tape. The waist circumference was measured from the narrowest point between the lower borders of the rib cage and the iliac crest at the end of normal expiration and to the nearest 0.1 cm [16].

Blood samples and echocardiography

Peripheral blood was sampled from patients in a fasting state in the morning following the admission day. Venous blood samples were sent to Clinical Laboratory Department of People's Hospital of Shaanxi Province for red blood cells (RBC) counts, hemoglobin, platelet counts, plateletcrit, mean platelet volume (MPV), platelet distribution width (PDW), white blood cells (WBC) counts, neutrophilic granulocyte percentage (NEUT%), total cholesterol (TC), triglyceride, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), urea nitrogen (BUN), creatinine, total bilirubin (TBIL) and albumin detection using standard biochemical techniques. Echocardiographic data (left ventricular ejection fraction [LVEF]) was obtained using Doppler echocardiography conducted within 3 days of admission [17].

Definition of risk factors

Hypertension was defined as an average systolic blood pressure ≥ 140 mm Hg, or an average diastolic blood pressure ≥ 90 mm Hg, or both, or self-reported use of antihypertensive medication, or a self-reported history of hypertension.

Diabetes was defined as fasting plasma glucose ≥ 7.0 mmol/L, or random plasma glucose ≥ 11.1 mmol/L, or 2 hour plasma glucose in oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L, or use of insulin or oral hypoglycemic agents, or a self-reported history of diabetes.

Smoking index was defined as number of cigarettes smoked per day $\times$ years of smoking. Body mass index (BMI) was calculated as weight in kg divided by height in m^2 [18].

Statistical analysis

The statistical analysis was conducted using SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean $\pm$ standard deviations and the differences between the renal dysfunction group and the without renal dysfunction group were analyzed using the Mann-Whitney U-test. Categorical variables were expressed as proportions and the differences in categorical variables were analyzed using chi-square test and fisher exact test. Pearson correlation analysis was conducted to determine the correlation between eGFR and lipid and other clinical and laboratory factors. Logistic regression was performed to determine whether the lipids factors were associated with renal dysfunction after the adjustment of each confounding factor. Statistical significance was established at $P < 0.05$.

Results

Baseline characteristics of heart failure patients with and without renal dysfunction are shown in Table 1. A total of 182 patients have renal dysfunction, counting for 54.2% of all 336 heart failure patients. The Mean $\pm$ S.D. of eGFR is 66.14 ± 16.01 mL/min $\cdot$ 1.73 m^2 in patients with renal dysfunction and 120.68 ± 22.20 mL/min $\cdot$ 1.73 m^2 in patients without renal dysfunction. The percentage of women in patients with renal dysfunction is significantly higher than that in patients without renal dysfunction. 242 patients (72.0%) have NYHA classification of class II, 70 (20.8%) patients have NYHA classification of class III and 24

Table 1. Baseline characteristics of heart failure patients with and without renal dysfunction. Note: NYHA, New York Heart Association; BMI, Body Mass Index; RBC, Red Blood Cells; MPV, Mean Platelet Volume; PDW, Platelet Distribution Width; WBC, White Blood Cells; NEUT%, neutrophilic granulocyte percentage; TC, Total Cholesterol; HDL-C, High-Density Lipoprotein-Cholesterol; LDL-C, Low-Density Lipoprotein-Cholesterol; apoA1, apolipoprotein A1; apoB, apolipoprotein B; BUN, Urea Nitrogen; eGFR, estimated glomerular filtration rate; TBIL, Total Bilirubin; LVEF, left ventricular ejection fraction; * $P < 0.05$

Factors	With renal dysfunction (n=182)	Without renal dysfunction (n=154)	P value
Sex			<0.001*
Men	82 (45.1%)	106 (68.8%)	
Women	100 (54.9%)	48 (31.2%)	
NYHA classification			<0.001*
II	108 (59.3%)	134 (87.0%)	
III	52 (28.6%)	18 (11.7%)	
IV	22 (12.1%)	2 (1.3%)	
Hypertension	116 (63.7%)	78 (50.6%)	0.016*
Diabetes mellitus	52 (28.6%)	26 (16.9%)	0.011*
Age (years)	63.47±11.08	60.96±10.16	0.013*
BMI (kg/m ²)	23.66±3.49	24.10±3.03	0.205
Waist circumference (cm)	84.08±9.77	86.98±9.16	0.003*
Smoking index	85.33±180.10	98.96±218.92	1.000
RBC counts (×10 ¹² /L)	4.31±0.58	4.24±0.56	0.095
Hemoglobin (g/L)	134.08±17.79	131.73±17.67	0.220
Platelet counts (×10 ⁹ /L)	184.15±49.39	184.30±60.50	0.748
Plateletcrit (%)	0.19±0.05	0.18±0.05	0.013*
MPV (fL)	10.55±1.19	10.06±1.54	<0.001*
PDW (fL)	15.72±2.30	17.00±1.78	<0.001*
WBC counts (×10 ⁹ /L)	6.77±1.91	6.58±4.85	0.001*
NEUT% (%)	57.15±22.41	40.59±31.09	<0.001*
TC (mmol/L)	4.34±1.07	4.38±1.14	0.685
Triglyceride (mmol/L)	1.63±0.97	1.64±1.11	0.694
HDL-C (mmol/L)	1.11±0.31	1.26±0.32	<0.001*
LDL-C (mmol/L)	2.11±0.71	2.06±0.75	0.481
apoA1 (g/L)	1.09±0.24	1.20±0.24	0.001*
apoB (g/L)	1.23±3.73	0.79±0.22	0.191
BUN (mmol/L)	7.31±3.80	5.10±1.37	<0.001*
Creatinine (umol/L)	98.50±38.59	59.67±11.50	<0.001*
eGFR (mL/min·1.73 m ²)	66.14±16.01	120.68±22.20	<0.001*
TBIL (umol/L)	20.29±16.50	16.02±7.43	0.130
Albumin (g/L)	36.69±4.91	39.43±5.21	<0.001*
LVEF (%)	34.34±7.06	40.05±4.58	<0.001*

patients (7.1%) have NYHA classification of class IV. The distribution of NYHA classification shows significant difference between the patients with or without renal dysfunction. A more severe NYHA classification (class III and IV) is noticed in patients with renal dysfunction when compared with patients without renal dysfunction (40.7% vs 13.0%, $P < 0.001$). The incidences of hypertension and diabetes mellitus are significantly higher in patients with renal dysfunction than those in patients without renal dysfunction (both $P < 0.05$). The age, plateletcrit, MPV, WBC counts, NEUT%, BUN, creatinine and eGFR in patients with renal dysfunction are significantly higher than those in patients without renal dysfunction (all $P < 0.05$). The waist circumference, PDW, HDL-C, apoA1, albumin and LVEF in patients with renal dysfunction are significantly lower than those in patients without renal dysfunction (all $P < 0.05$). The BMI, smoking index, RBC counts, hemoglobin, platelet counts, TC, triglyceride, LDL-C, apoB and TBIL showed no significant difference between the patients with renal dysfunction and the patients without renal dysfunction.

The Pearson correlation analysis between eGFR and lipid, clinical, laboratory factors in heart failure patients are showed in Table 2. The waist circumference, platelet counts, PDW, HDL-C, apoA1, albumin and LVEF are positively correlated with eGFR (all $P < 0.05$). Meanwhile, the age, MPV, NEUT%, BUN, creatinine and TBIL are negatively correlated with eGFR (all $P < 0.05$). The BMI, smoking index, RBC counts, hemoglobin, plateletcrit, TC, triglyceride, LDL-C and apo B show no correlation with eGFR.

Since the HDL-C and apoA1 are the only two lipid indicators correlated with eGFR, we have built the Logistic regressions for renal dysfunction using HDL-C and apoA1 simultaneously. The Logistic regression analyses are showed in Table 3. In Table 3, we have enrolled all the factors significantly correlated with eGFR except creatinine, BUN, since the two renal function factors are highly correlated with eGFR. Meanwhile, we have also enrolled the significantly varied categorical factor sex, hypertension and diabetes mellitus in the Logistic regression, the NYHA classification is not in the regression since it is closely related with LVEF. After the adjustment of sex, hypertension, diabetes mellitus, age, waist circumference, platelet counts, MPV, PDW, NEUT%, TBIL, albumin and LVEF, HDL-C is still significantly associated with renal dysfunction in hospitalized heart failure patients ($OR=0.119$, $P=0.003$), the apoA1 is not significantly associated with renal dysfunction in hospitalized heart failure patients ($OR=0.204$, $P=0.235$).

Discussion

Heart and kidney are tightly connected organs in heart failure. Previous studies have demonstrated high prevalence of renal dysfunction in heart failure patients [6–8]. A recent UK national study has documented the prevalence of CKD (eGFR<60 ml/min·1.73m²) in the HF community is 63% [5]. Whilst the high prevalence of CKD in the community HF population is consist with that in hospital [19] and other specialist care settings [20]. In this present study, 8 patients (2.4%) has eGFR of 15–30 mL/min·1.73 m², 46 patients (13.7%) has eGFR of 30–59 mL/min·1.73 m², 128 patients (38.1%) has eGFR of 60–89 mL/min·1.73 m², 154 patients (45.8%) has eGFR ≥90 mL/min·1.73 m². When compared with 63% in UK, the prevalence of CKD (eGFR<60 ml/

Table 2. Pearson correlation analysis between eGFR and lipid and other clinical and laboratory factors in heart failure patients. Note: eGFR, estimated glomerular filtration rate; BMI, Body Mass Index; RBC, Red Blood Cells; MPV, Mean Platelet Volume; PDW, Platelet Distribution Width; WBC, White Blood Cells; NEUT%, neutrophilic granulocyte percentage; TC, Total Cholesterol; HDL-C, High-Density Lipoprotein-Cholesterol; LDL-C, Low-Density Lipoprotein-Cholesterol; apoA1, apolipoprotein A1; apoB, apolipoprotein B; BUN, Urea Nitrogen; TBIL, Total Bilirubin; LVEF, Left Ventricular Ejection Fraction; * $P<0.05$

Table 3. Logistic regression analysis for renal dysfunction using lipid and confounding factors in heart failure patients. Note: CI, Confidence Interval; MPV, Mean Platelet Volume; PDW, Platelet Distribution Width; NEUT%, Neutrophilic Granulocyte Percentage; HDL-C, High-Density Lipoprotein-Cholesterol; apoA1, apolipoprotein A1; TBIL, Total Bilirubin; LVEF, Left Ventricular Ejection Fraction; * $P<0.05$

Factors	Odd ratios	95% CI	P value
Male	0.082	0.026–0.257	<0.001*
Hypertension	3.731	1.309–10.632	0.014*
Diabetes mellitus	1.006	0.269–3758	0.993
Age	1.006	0.962–1.053	0.782
Waist circumference	0.969	0.915–1.026	0.278
Platelet counts	1.003	0.994–1.011	0.540
MPV	1.962	1.227–3.138	0.005*
PDW	0.650	0.477–0.888	0.007*
NEUT%	0.989	0.941–1.040	0.666
HDL-C	0.064	0.010–0.420	0.004*
apoA1	0.204	0.015–2.809	0.235
TBIL	1.011	0.954–1.070	0.715
Albumin	0.840	0.741–0.951	0.006*
LVEF	0.942	0.897–0.989	0.017*

Factors	r	P value
Age	-0.212	<0.001*
BMI	0.082	0.132
Waist circumference	0.177	0.001*
Smoking index	-0.050	0.365
RBC counts	-0.106	0.056
Hemoglobin	-0.104	0.059
Platelet counts	0.130	0.019*
Plateletcrit	-0.005	0.933
MPV	-0.235	<0.001*
PDW	0.243	<0.001*
WBC counts	-0.040	0.477
NEUT%	-0.266	<0.001*
TC	0.054	0.338
Triglyceride	-0.029	0.600
HDL-C	0.249	<0.001*
LDL-C	-0.015	0.793
apoA1	0.262	<0.001*
apoB	-0.065	0.243
BUN	-0.507	<0.001*
Creatinine	-0.744	<0.001*
TBIL	-0.127	0.022*
Albumin	0.237	<0.001*
LVEF	0.314	<0.001*

min/1.73m²) is 16.1% in our population. The reasons for the difference may come from the difference in EF and NYHA classification since the previous UK study lacked data of ejection fraction or NYHA classification. Our results were consistent with the results from the DALYOUTCOMES study, it reported that 11% of all participants had an eGFR < 60 mL/min/1.73 m², indicating that CKD is highly prevalent in patients with CAD patients, especially in heart failure patients [21]. Löfman I et al. [22] reported increasing mortality with decreasing kidney function regardless of age, presence of diabetes, NYHA class, duration of heart failure and haemoglobin levels in 47,716 Swedish HF patients. It was also documented that when the kidney damage appeared, mortality and morbidity significantly increased in heart failure patients [23, 24], an 11% increase in hospitalization and 17% in mortality were noticed in the CKD patients.

The mechanisms of renal dysfunction in heart failure patients can be complicated and multifactorial, the reduced renal perfusion and venous congestion may come as the most important elements [25]. A variety of other mechanisms such as inflammatory and cellular immune-mediated mechanisms; stress-mediated and neuro-hormonal responses; metabolic and nutritional alteration including bone and mineral disorders, altered haemodynamic and acid-base or fluid status; development of anaemia and intrinsic tubular damage also play important roles in the process [26–30]. Among the various reasons, dyslipidemia may also be one of them for renal dysfunction in heart failure patients [31]. Dyslipidemia is often characterized with elevated plasma triglycerides and LDL-C and reduced HDL-C concentrations [32]. In epidemiologic studies based on humans, the presence of dyslipidemia is significantly associated with a higher risk of suffering from renal dysfunction in the CKD population [33–35]. The studies based on animals have shown that the development and progression of kidney damage is associated with increased glomerulosclerosis and tubulointerstitial damage caused by hyperlipidemia [36].

This present study reveals that after adjustments of confounding factors, HDL-C is still associated with renal dysfunction in heart failure patients, but the LDL-C, TG, TC, apoA1 and apoB show no association with renal dysfunction. Whether HDL-C levels can be used as predictors of kidney function decline is still controversial in previous cohort studies. Some studies showed that low HDL-C levels were associated with a faster rate of progression of kidney disease [37]. One recent randomization analysis demonstrated that genetically higher HDL cholesterol concentration was associated with better kidney function based on large samples from the largest lipid and CKD cohorts [11]. Visconti L et al. [38] also reported lipid disorders in CKD were characterized by reduced HDL-C, high triglycerides and normal or slightly reduced LDL-C level. The mechanism for the association is not entirely clear, previous studies showed that the HDL-C had the antioxidant, anti-inflammatory and antithrombotic functions, which would reduce atherosclerosis in renal arteries and other arteries, it may serve as the protector of the renal functions [39]. Second, the decreased apoA1 and lecithin cholesterol acyltransferase deficiency were often documented in patients with kidney dysfunction, they could lead to lower plasma HDL-C [40, 41]. On the contrary, in a large cohort of 3939 patients with CKD, the total cholesterol, triglycerides, VLDL-C, LDL-C, HDL-C, apoA1, and apoB were not independently associated with progression of kidney disease [42]. The reason may be that the HDL particle is highly complicated and over 80 proteins and several hundred lipids are carried within it. Simple cholesterol measurement might not allow us to obtain the biologic functions of the specific HDL particles [39, 40]. Therefore, functional studies of each HDL component in the cholesterol efflux capacity and the reverse cholesterol transport, would be needed in the future [43].

In this present study, we also found that some other confounding factors were also associated with renal function after adjustments in heart failure patients. The albumin, LVEF and PDW showed the protective effects on renal function and the female, hypertension and MPV showed the opposite effects on renal function. It is easy to understand that the improve of heart function (LVEF) [44] and nutrition status (albumin) [45] may lead to better kidney perfusion and less kidney damage, which could result in better renal function.

Meanwhile, female sex [46] and hypertension [47] were traditional risk factors responsible for the deterioration of renal function. Interestingly, MPV was found to be a risk factor for renal function with $OR=1.992$ ($P=0.005$). Some studies have documented the association between MPV and inflammation [48]. The mechanism may be as follows, the heart failure process is also a process of inflammatory, increased inflammatory mediators may affect MPV, then it might induce larger and more reactive platelets [49]. Since the bone marrow might be exposed to chronic inflammation caused by heart failure for a period of long time, the inflammatory mediators would have enough time to make changes on MPV [50]. The documented association of PDW and renal function is rare, interestingly, PDW has been added as a novel prognostic marker of cardiovascular death in some researches [51]. Further study may focus on the mechanism of association of PDW and renal function in heart failure patients.

The strength of the study is that the association between the lipids profile and renal function is first established in specific population, the heart failure patients. The population has unique feature of lipids profile and renal function. The association between the HDL-C and eGFR could be used as evidence for modulation of HDL-C for better kidney function in heart failure patients. The study has also several limitations, the cross-section study could not determine the causal relationship between HDL-C declination and renal dysfunction. Second, the urine samples were not collected in this study, therefore, the incidence of renal dysfunction may be under-estimated.

Conclusion

In conclusion, in this cross-sectional study based on patients with heart failure, HDL-C is still significantly associated with renal dysfunction in hospitalized heart failure patients after the adjustment of sex, hypertension, diabetes mellitus, age, waist circumference, platelet counts, MPV, PDW, NEUT%, TBIL, albumin and LVEF. Further researches are needed to determine the subtype of HDL-C associated with renal dysfunction and clarify whether mandatory elevation of the specific subtype of HDL-C may improve the kidney function in heart failure patients.

Abbreviations

apoA1 (apolipoprotein A1); apoB (apolipoprotein B); BMI (body mass index); CI (confidence interval); BUN (urea nitrogen); eGFR (estimated glomerular filtration rate); CKD (chronic kidney disease); HDL-C (high density lipoprotein-cholesterol); HF (heart failure); LDL-C (low-density lipoprotein-cholesterol); LVEF (left ventricular ejection fraction); MPV (mean platelet volume); NEUT%, neutrophilic (granulocyte percentage); NYHA (New York Heart Association); PDW (platelet distribution width); RBC (red blood cells); SD (standard deviation); TBIL (total bilirubin); TC (total cholesterol); WBC (white blood cells).

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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