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Original Article

Clinical significance of sFRP5, RBP-4 and NT-proBNP in patients with chronic heart failure

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Abstract: Objective: This study was designed to investigate the levels and clinical significance of secretory frizzled-related protein 5 (sFRP5), retinol binding protein 4 (RBP-4) and N-terminal (NT)-pro hormone BNP (NT-proBNP) in patients with chronic heart failure (CHF). Methods: Eighty-nine patients with CHF treated in our hospital were included as the observation group. Seventy-five healthy volunteers who underwent physical examination in our hospital during the same period were selected as the control group. The subjects in the observation group were divided into NYHA class II (n=23), NYHA class III (n=34) and NYHA class IV (n=32) according to NYHA classification, and the levels of sFRP5, RBP-4 and NT-proBNP as well as left ventricular end-diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF) were compared in the three groups. Spearman correlation was used to analyze the relationship between sFRP5, RBP-4, NT-proBNP and LVEDD, LVEF. The ROC curves of sFRP5, RBP-4 and NT-proBNP for the diagnosis of CHF were plotted. Patients in the observation group were divided into a death group (n=30) and a survival group (n=59) according to the 1-year follow-up outcome, and the levels of sFRP5, RBP-4, and NT-proBNP were compared between the two groups. Results: The observation group showed significantly higher levels of sFRP5, RBP-4, NT-proBNP and LVEDD, and a significantly lower level of LVEF than the control group. Spearman's correlation analysis showed that sFRP5, RBP-4, NT-proBNP were correlated with LVEDD and LVEF in CHF patients ($P < 0.05$). The ROC curve showed that the AUC of sFRP5, RBP-4 and NT-proBNP for CHF diagnosis were 0.9378, 0.9133, and 0.9375, respectively. sFRP5, RBP-4, and NT-proBNP in the death group were all higher than those in the survival group ($P < 0.05$). Conclusion: sFRP5, RBP-4, and NT-proBNP showed a close correlation with CHF. It is worthy of using this method as a clinical index for the diagnosis and prognosis of CHF.

Keywords: Chronic heart failure, sFRP5, RBP-4, NT-proBNP, clinical significance

Introduction

Heart failure is a compilation of pathological changes caused by myocardial infarction, cardiomyopathy, hemodynamic overload, and inflammation, which are characterized by myocardial injury, structural changes, myocardial functional changes and left ventricular dysfunction [1, 2]. The typical symptoms of patients with chronic heart failure (CHF) include dyspnea, fatigue, and fluid retention, making it one of the most serious cardiovascular diseases [3]. CHF is a state of persistent heart failure, and is the final stage of various cardiovascular diseases. It has high prevalence, high rate of re-hospitalization, and high mortality rate, and is considered as one of the most serious public health challenges of the 21st century [4, 5]. With the changes of peoples' lifestyle and dietary habits, the incidence of CHF also shows an increasing annual trend. According to epidemiological data, there are 4.2 million patients with CHF in China, and the incidence rate of CHF among 35-74 years old is about 0.9%. Although the diagnosis and treatment of CHF are improving, CHF remains a leading cause of death, with a mortality rate similar to that of cancer. About 50% of CHF patients will die within 5 years [6-8].

Accurate diagnosis and timely and effective intervention are important prerequisites for improving the prognosis of CHF. The current diagnostic method of CHF lacks sensitivity and specificity. Rapid detections based on serum biomarkers have attracted more and more

attention of medical workers because of their reproducibility and short detection time [9, 10]. Studies have found that biomarkers can provide information for early diagnosis, risk stratification, and prognosis assessment in CHF patients [11]. Secretory frizzled-related protein 5 (sFRP5) is an anti-inflammatory adipocytokine, and retinol binding protein 4 (RBP-4) is an adipose-derived protein. Studies have shown that these factors are closely related to atherosclerosis and metabolic diseases, and are positively correlated with the degree of cardiomyocyte hypertrophy [12, 13]. N-terminal (NT)-pro hormone BNP (NT-proBNP) is a common clinical heart failure marker, with the advantages of having a long half-life and good stability, and it is often used in the detection of early or mild heart failure [14]. A clinical study of 90 patients with heart failure indicated that serum NT-proBNP levels are abnormally elevated in CHF patients and that levels of this factor are strongly associated with the prognosis of CHF patients [15].

The aim of this study was to investigate the correlation between sFRP5, RBP-4 and NT-proBNP with the prognosis of CHF patients, so as to provide clinical references for improving the prognosis of CHF patients.

Materials and methods

Baseline data

Eighty-nine patients with CHF treated in the Cardiology Department of Chengde Medical College Affiliated Hospital from May 2018 to September 2019 were included as the observation group, and 75 healthy individuals who underwent physical examination were enrolled as the control group.

Inclusion criteria: (1) patients enrolled in the study all met the diagnostic criteria for heart failure [16] established by the Chinese Society of Cardiovascular Medicine (2014); (2) patients who were conscious, had some self-care ability, and were able to cooperate with the implementation of the study; (3) patients who clearly understood the procedures and principles of the study and signed an informed consent form; (4) the study was approved by the hospital's ethics committee; (5) the data of the enrolled subjects were complete; and (6) those with NYHA class II-IV were included.

Exclusion criteria: (1) patients comorbid with serious organ diseases such as renal failure; (2) patients comorbid with mental illness; (3) patients comorbid with liver and kidney dysfunction; (4) patients who were unable to take care of themselves; (5) patients comorbid with heart disease such as myocarditis and heart valve disease; (6) patients comorbid with serious infectious diseases, immune system diseases or blood system diseases; and (7) patients comorbid with malignant tumors were excluded.

Intervention methods

Serological markers: All subjects were required to fast for 10-12 h, and venous blood was drawn early in the morning. The serum was quickly centrifuged for testing, followed by determination of sFRP5, RBP-4 and NT-proBNP levels. Among them, the kits produced by Shanghai Enzyme Linked Biotechnology Co., Ltd. were used to detect sFRP5, the enzyme-linked immunosorbent assay kit produced by Shanghai RD Company was used to determine serum RBP4, and the German Roche detector was used to determine serum NT-proBNP by electrochemiluminescence. The above indicators were tested 3 times, and the average value was taken as the final result.

Cardiac function evaluation: The E8 color Doppler ultrasound diagnostic instrument (General Motors of the United States) was used to evaluate the cardiac function [left ventricular end-diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF)] of the enrolled patients. Similarly, each indicator was tested 3 times to obtain the average value.

Grouping criteria: Patients in the observation group were divided according to the criteria proposed by the New York Heart Association (NYHA) in 1928, namely, NYHA class II (n=23), NYHA class III (n=34) and NYHA class IV (n=32).

Evaluation criteria: The levels of sFRP5, RBP-4 and NT-proBNP, LVEDD and LVEF in patients with different NYHA grading were compared with those in the control group. The correlation between sFRP5, RBP-4, NT-proBNP, and LVEDD, LVEF was investigated using Spearman's correlation analysis. The ROC curves of sFRP5, RBP-4 and NT-proBNP levels for CHF diagnosis

Table 1. Comparison of baseline data between two groups ($X \pm SD$)/[n (%)]

Clinical information		Observation group (n=89)	Control group (n=75)	t/X^2	P
Gender	Male	59	45	0.003	0.957
	Female	30	30		
Smoking history	Yes	29	15	3.283	0.07
	No	60	60		
Hypertension	Yes	19	11	1.216	0.27
	No	70	64		
Leukocyte ($\times 10^9$/L)		7.44 ± 2.11	6.12 ± 1.98	4.105	< 0.001
Average age (years)		45.98 ± 4.33	46.01 ± 4.29	0.044	0.965
Average weight (kg)		64.29 ± 3.91	64.34 ± 3.89	0.082	0.935

were plotted and the area under the curve (AUC) was respectively calculated.

Statistical methods

SPSS 22.0 software was used for data analysis, and the experimental data were measurement data. Statistical software was used to perform two tests on all of the data, namely normality and homogeneity of variance tests. $P > 0.10$ indicated that the data met the criterial for normality. The data were expressed as (mean ± standard deviation) and examined using one-way ANOVA. If the data did not meet the normality test, the data were expressed as median ± QR, rank sum test was used, and the LSD-t test was used for comparison of two groups. Pearson's correlation analysis was used to calculate the regression coefficients using the principles of bivariate and correlation principles in the statistical software, and hypothesis tests were conducted on the regression coefficients. Figure illustration in this study was implemented using Graphpad Prism software [17]. $P < 0.05$ suggested a significant difference.

Results

Comparison of clinical data

A total of 164 patients were included in this study, including 104 males and 60 females, aged 40-60 years, with an average age of (46.00 ± 3.98) years. The general clinical data including gender, average age, average weight, smoking history, hypertension, leucocyte levels, *etc*. did not differ significantly between the two groups ($P > 0.05$), and were comparable (**Table 1**).

Comparison of the differences in serological parameters

The sFRP5, RBP-4 and NT-proBNP of CHF patients in the observation group were significantly higher than those in the control group ($P < 0.05$) (**Figure 1A**), and the sFRP5, RBP-4 and NT-proBNP of CHF patients in NYHA class IV were significantly higher than those in NYHA class II ($P < 0.05$) (**Figure 1B**).

Comparison of cardiac function indices

The observation group exhibited significantly higher LVEDD and significantly lower LVEF than the control group ($P < 0.05$) (**Figure 2A**). Meanwhile, the patients with NYHA IV showed significantly higher LVEDD and significantly lower LVEF than the patients with NYHA II ($P < 0.05$) (**Figure 2B**).

Correlation analysis of serological and cardiac function parameters in CHF patients

sFRP5, RBP-4, and NT-proBNP showed positive associations with LVEDD (r=0.9878, r=0.7675, r=0.7449, $P < 0.05$) (**Figure 3**) and negative associations with LVEF (r=-0.9874, r=-0.7377, r=-0.7342, $P < 0.05$) (**Figure 4**).

Value of serological parameters for CHF diagnosis

The AUCs of sFRP5, RBP-4, and NT-proBNP for CHF diagnosis were 0.9378 (95% CI 0.8480-1.000), 0.9133 (95% CI 0.8185-1.000) and 0.9375 (95% CI 0.8473-1.000), respectively ($P < 0.05$), suggesting that sFRP5, RBP-4, and NT-proBNP all had good diagnostic value for CHF (**Figure 5**).

Comparison of serum blood markers in patients with different clinical outcomes

Patients in the observation group were divided into the death group (n=30) and the survival group (n=59) according to their clinical out-

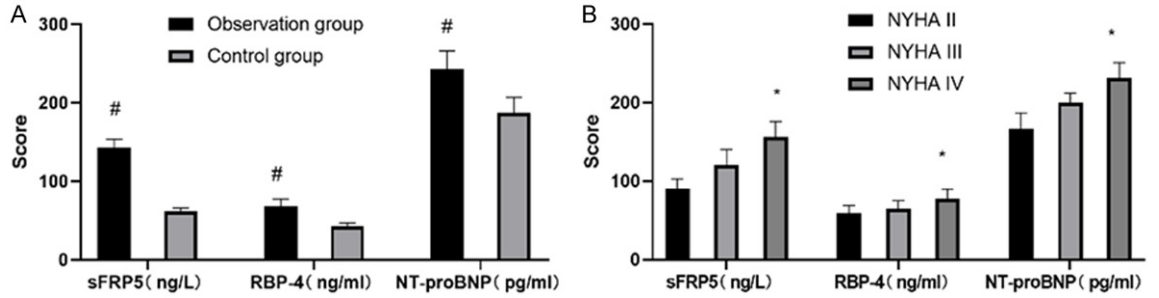

Figure 1. Comparison of the differences in serological indices between different groups of patients. sFRP5, RBP-4, and NT-proBNP levels in the observation group were significantly higher than those in the control group ($P < 0.05$) (A); sFRP5, RBP-4, and NT-proBNP levels in patients with NYHA IV were significantly higher than those in patients with NYHA II ($P < 0.05$) (B). #$P < 0.05$, compared to control group; *$P < 0.05$, compared to NYHA II patients.

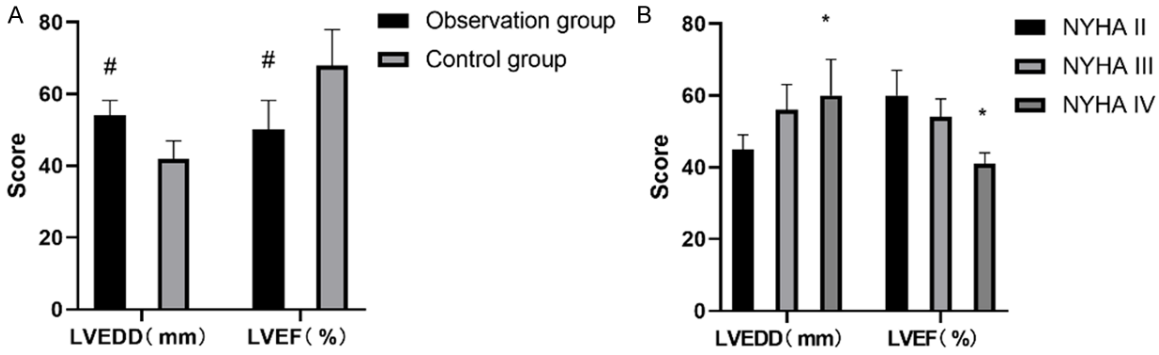

Figure 2. Comparison of the differences in cardiac function indices between different groups of patients. The observation group showed a significantly higher LVEDD and a significantly lower LVEF than the control group (A) ($P < 0.05$); patients with NYHA class IV showed a significantly higher LVEDD and a significantly lower LVEF than patients with NYHA class II (B) ($P < 0.05$). #$P < 0.05$, compared to control group; *$P < 0.05$, compared to NYHA II patients.

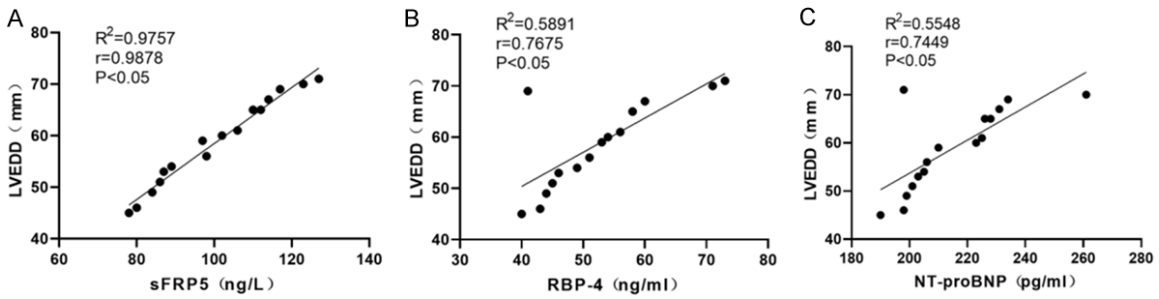

Figure 3. Correlation analysis between serological parameters and LVEDD in CHF patients. sFRP5 (A), RBP-4 (B), and NT-proBNP (C) showed a positive association with LVEDD (r=0.9878, r=0.7675, r=0.7449, $P < 0.05$).

come. The sFRP5, RBP-4 and NT-proBNP levels of the survival group were significantly lower than those of the death group ($P < 0.05$) (**Figure 6**).

Discussion

Heart failure has become the focus of medical research [18], and with the increasing prevalence of cardiovascular and cerebrovascular diseases in China, heart failure has been a leading factor affecting the quality of life of Chinese residents. The diagnosis and treatment protocols and follow-up process of heart failure have been improved, and heart failure treatment centers have been established to facilitate timely diagnosis, standardized treatment and follow-up intervention [19, 20]. Results from clinical practice has indicated that CHF is not induced by a single factor, but it is a

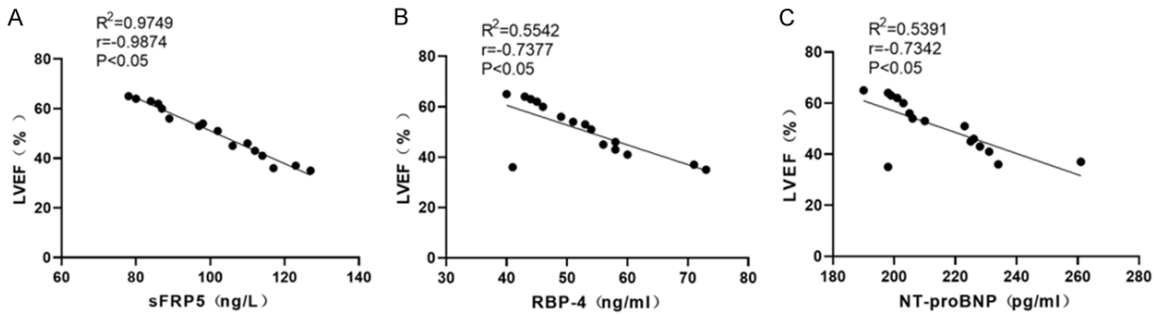

Figure 4. Correlation analysis between serological parameters and LVEF in CHF patients. sFRP5 (A), RBP-4 (B), and NT-proBNP (C) showed a negative association with LVEF (r=-0.9874, r=-0.7377, r=-0.7342, $P < 0.05$).

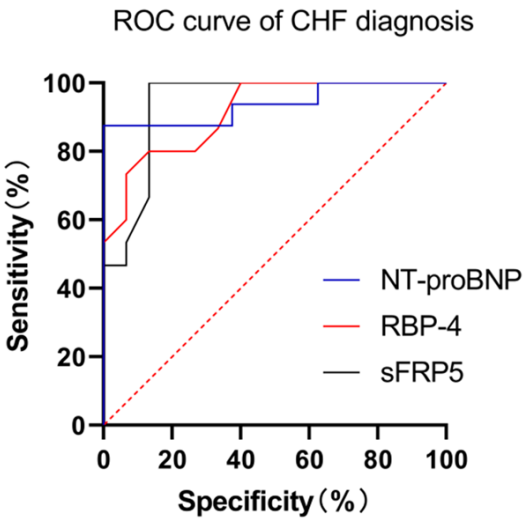

Figure 5. The diagnostic value of serological indices for CHF. The AUC of sFRP5, RBP-4, and NT-proBNP were 0.9378 (95% CI 0.8480-1.000), 0.9133 (95% CI 0.8185-1.000), and 0.9375 (95% CI 0.8473-1.000), respectively ($P < 0.05$). These indicated that all the above indicators had good diagnostic value for CHF.

vicious cycle of multiple factors interrelated with each other, and early intervention plays a key role in slowing the progression of CHF and improving patient prognosis [21].

In this study, different subgroups were established to investigate the diagnostic and prognostic value of sFRP5, RBP-4 and NT-proBNP in CHF. The serum sFRP5, RBP-4 and NT-proBNP levels in CHF patients were significantly higher than those in healthy controls. With the increase of NYHA grade of CHF patients, the levels of sFRP5, RBP-4, and NT-proBNP also increased significantly, suggesting that sFRP5, RBP-4, and NT-proBNP may be related to the condition of CHF patients. A clinical study on patients with coronary artery disease found that the serum sFRP5 and RBP-4 levels of patients with acute myocardial infarction were significantly higher than those of patients with chronic coronary artery disease, and correlation analysis showed that the sFRP5 and RBP-4 levels of patients with acute myocardial infarction were significantly correlated with their coronary SYNTAX scores. Scholars believe that the levels of sFRP5 and RBP-4 in patients with coronary heart disease are significantly higher than those in healthy controls [22]. It has also been noted that RBP-4 levels are positively correlated with stenotic degree of coronary arteries in patients with coronary artery disease, and more severe coronary artery stenosis represents higher serum RBP-4 level [23]. We speculated that sFRP5 belongs to a family of secreted curl-related proteins that can regulate the pathological process of atherosclerosis, post-myocardial infarction myocardial injury and heart failure through the Wnt pathway. Evidence has shown that sFRP5 is positively correlated with cardiac function grading and LVEDD in CHF patients, which is consistent with the results of this study.

The correlation between RBP-4 and coronary heart disease has been confirmed. It has been found that the level of RBP-4 in patients with coronary heart disease is significantly higher than that in healthy individuals, and the level of RBP-4 may be related to the severity of coronary heart disease [24]. It has also been shown that the level of RBP-4 in patients with coronary heart disease is 48% higher than that in healthy individuals, and more branching of the diseased vessels in patients with

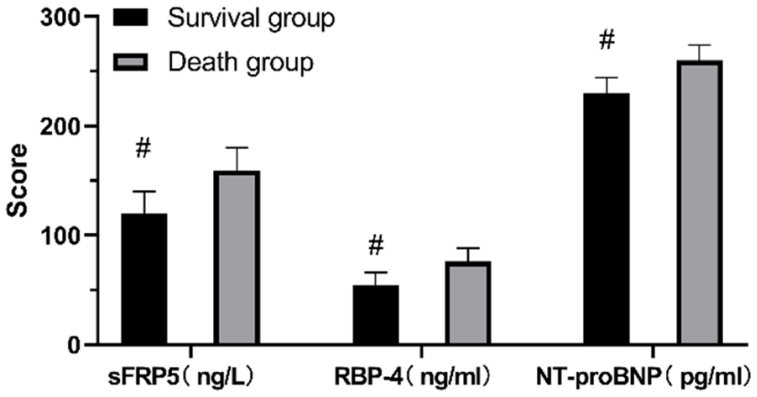

Figure 6. Comparison of the differences in serum blood parameters between patients with different clinical outcomes of CHF. sFRP5, RBP-4, and NT-proBNP levels in the survival group were significantly lower than those in the death group ($P < 0.05$). #$P < 0.05$, compared to the death group.

coronary heart disease indicates higher serum levels of RBP-4 [25]. In this study, we concluded that RBP-4 is widely involved in lipid metabolism and is closely associated with dyslipidemia, and its serum concentration is positively correlated with triglyceride level and negatively correlated with HDL. The reason for this may be related to the fact that the abnormal expression of RBP-4 affects insulin receptor signaling and thus energy metabolism. Studies have found that RBP-4 is also one of the inflammatory response markers, and that abnormal expression of RBP-4 aggravates endothelial cell damage and promotes chronic inflammatory responses in the vasculature, which is a crucial part of the pathological changes in CHF, which are all evidence for the correlation of sFRP5, RBP-4, and NT-proBNP with LVEDD and LVEF [26, 27].

Finally, sFRP5, RBP-4 and NT-proBNP had good diagnostic value for CHF, and were significantly higher in patients with poor prognosis. This suggested that sFRP5, RBP-4, and NT-proBNP can be used as the basis for primary diagnosis and prognosis of CHF.

In summary, sFRP5, RBP-4 and NT-proBNP show a close correlation with CHF and can be considered as clinical indicators for CHF diagnosis and prognosis. The innovation of this study is that the feasibility of sFRP5, RBP-4 and NT-proBNP in the diagnosis of CHF was demonstrated through Spearman's correlation analysis and ROC curves, taking LVEDD and LVEF, the commonly used indicators of CHF, as the starting point. The data are detailed and reliable, which can provide reference for subsequent studies. The limitation of this study is that no detailed research on the mechanism of sFRP5, RBP-4, and NT-proBNP was performed, which is proposed to be improved in the next step.

Disclosure of conflict of interest

None.

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