Increased Plasma Soluble Fractalkine in Patients with Chronic Heart Failure and Its Clinical Significance

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Summary
Fractalkine has been reported to play an important role in the pathophysiology of various cardiovascular disorders. This research aims to study the change of soluble fractalkine (sFKN) in plasma level of patients with chronic heart failure (CHF) and evaluate its prognostic value.

A total of 96 patients with CHF and 45 healthy subjects were included in this study. The plasma levels of sFKN, brain natriuretic peptide (BNP), and Interleukin-18 (IL-18) were determined by ELISA kits when they were first admitted to the hospital. Left ventricular ejection fraction (LVEF) was measured by echocardiogram. Rehospitalization status within 1 year after the first hospitalization was also recorded.

The plasma levels of sFKN, BNP, and IL-18 in patients with CHF were significantly higher than in the control group (P < 0.05). The concentrations of sFKN and BNP were increased with the severity of heart failure classified by NYHA classification (P < 0.05). Plasma sFKN level in CHF group was positively correlated with BNP (r = 0.441, P < 0.001) and IL-18 (r = 0.592, P < 0.001). Receiver operating characteristic curve analysis showed that area under the curve values of FKN, BNP, and IL-18 were 0.885 (95%CI: 0.810 to 0.960, P < 0.001), 0.889 (95%CI: 0.842 to 0.956, P < 0.001), and 0.878 (95%CI: 0.801-0.954, P < 0.001), respectively. The concentrations of sFKN and BNP were increased in patients readmitted more than once within 1 year (P < 0.05).

Key words: Bain natriuretic peptide, Inflammatory immune

CHF is a terminal phase of various cardiovascular diseases caused by changes in cardiac structure and function, affecting the quality of life and threatening the life of patients. The incidence rate of CHF is increasing steeply with the acceleration of aging process, changes in lifestyle, and advancement of clinical diagnosis. Patients with CHF have a poor prognosis and an increased risk of mortality. It is reported that 1 year mortality of patients with heart failure is 30% to 40%, and thereafter the mortality is less than 10% per year.1,2 Although the prognosis has been improved in the past 10 years, the mortality of heart failure is still high. Therefore, accurate risk prediction is significant for clinicians and patients to select appropriate management measures of patients with CHF.

It has been demonstrated that the physiopathologic mechanism of CHF is complex. Myocardial remodeling is considered to be the initiating factor in the development processes of CHF.3,4 Increased level of inflammatory cytokines contributes to change in heart contractility by promoting hypertrophy and inducing myocardial remodeling, which plays an important role in CHF.5,6,7 Fractalkine (FKN) is the only known member of the CX3C chemokine family, which is primarily expressed in multiple cells. FKN is a unique dual-function chemokine, acting as a chemoattractant in its soluble form and as an adhesion molecule in its membrane-bound form.8 FKN seems to play an essential role in the pathogenesis of vascular injury, and emerging evidence has demonstrated that it is important in the pathophysiology of various cardiovascular disorders, including atherosclerosis, coronary artery disease, myocardial infarction, and hypertension.8-11 Elevated FKN protein level was found in the failing human myocardium in patients with CHF.12 Basic research showed that FKN plays an important role in the promotion of myocardial fibrosis and cardiac remodeling.11 However, the precise role in biological function of myocardial cells is not fully understood. FKN was recently considered to be a potential predictor for various kinds of cardiovascular disorders.

Hence, this study aims to analyze the alteration of soluble FKN (sFKN) in plasma levels of patients with...
CHF as well as the prognostic value of CHF. Furthermore, the correlations between plasma sFKN with other predictable markers (BNP and IL-18) were also investigated.

Methods

Subjects: A total of 96 patients with CHF admitted to the Affiliated Hospital of Jining Medical University were enrolled from June 2016 to February 2017. The patients with CHF were diagnosed according to the CHF diagnosis standard. All patients had a history of CHF more than 6 months and New York Heart Association (NYHA) functional class II-IV. The value of left ventricular ejection fraction (LVEF) less than 0.45 was defined to have heart failure. The patients with circulatory system, hematology, digestive system, respiratory system, endocrinology and other related diseases were excluded. A total of 45 healthy subjects were randomly enrolled from hospital health examination center and acted as control group. All healthy participants received normal general physical examination, electrocardiograph, x-ray, blood biochemistry analysis, cardiac ultrasound, and other auxiliary examinations, excluding respiratory, circulatory, digestive, urinary, and hematological diseases. For the use of materials for research purposes, written informed consent was obtained from each patient. Human beings study has been approved by Ethics Committee of The Affiliated Hospital of Jining Medical University.

Sample collection: A volume of 5 mL fasting venous blood after a 12-hour fast was collected from median cubital vein from patients when they were first admitted to the hospital and placed in EDTA-K2 anticoagulant test tubes. The blood was centrifuged at the speed of 3000 rpm for 5 minutes, and plasma was extracted and stored at -80°C.

Clinical data collection: Demographic information including age, sex, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were recorded. Detailed smoking history, alcohol consumption, diabetes, hyperlipidemia, hypertension, cerebral vascular disease, lung disease, liver and kidney disease, heart disease and other medical history was documented. The blood biochemical indexes including lipid parameters, fasting plasma glucose, as well as liver, kidney and cardiac function indexes, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-c), and low-density lipoprotein-cholesterol (LDL-c), and other biochemical indexes including fasting plasma glucose (Glucose), alanine aminotransferase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), Hematocrit, high-sensitivity C reactive protein (HSCRP) were detected by Beckman CX-7 automatic biochemical Analyzer (Beckman Coulter, Inc., USA). LVEF was measured by echocardiogram.

Measurement of sFKN, BNP, and IL-18: The plasma concentrations of sFKN, BNP, and IL-18 in all participants were determined by corresponding ELISA kits (Green Byrd biotechnology limited company, Beijing, China). BNP cut-off value of 100 pg/mL is routinely used for diagnosing CHF in the general population.

Statistical method: All statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 13.0, IBM Corporation). Categorical data and measurement data were compared with chi-square test and two-sample independent t-test, respectively. One-way analysis of variance was used to compare means among 3 or more groups. Pearson’s or Spearman’s correlation coefficients were used to evaluate the correlation between sFKN and BNP (or IL-18). The diagnostic accuracies of sFKN, BNP, and IL-18 for CHF were assessed by performing receiver operating characteristic (ROC) curve. Multiple linear regression analysis was used to explore whether sFKN levels were affected by other factors, and the level of BUN, Cr, ALT, AST, and HSCRP were defined as independent variables. A value of \( P < 0.05 \) was regarded as statistically significant. Only (time to) the first hospitalization for CHF was included in the analysis.

Results

Clinical characteristics: The demographic information of participants was presented in Table I. The gender, age, and body weight in CHF group had no significant difference with the control group (\( P > 0.05 \)). There was also no significant difference between 2 groups in plasma lipid levels, including TC, TG, HDL-c, and LDL-c (\( P > 0.05 \)). The patients in CHF group had elevated levels of SBP, HR, Glu, ALT, BUN, Cr, UA, Hematocrit, HBDH, LDH, and HSCRP compared with the controls (\( P < 0.05 \)).

Increased plasma sFKN, BNP, and IL-18 concentrations in CHF patients: Plasma concentrations of sFKN, BNP, and IL-18 were detected in both CHF and control patients. BNP levels of 4 patients in the control group were measured above 500 ng/L. They could not rule out cardiac disease, so they were excluded from this group. As shown in Figure 1, plasma concentrations of sFKN, BNP, and IL-18 in CHF patients were significantly elevated compared with the controls (\( P < 0.01 \)).

Plasma sFKN, BNP, and IL-18 concentrations in different etiology of CHF subgroups: In this study, 96 patients were divided into 4 groups according to etiology: 35 cases with ischemic heart disease (IHD), 28 cases with dilated cardiomyopathy (DCM), 18 cases with valvular heart disease, and 15 cases with hypertensive heart disease. Plasma sFKN, BNP, and IL-18 concentrations in CHF subgroups were also compared. As shown in Table II, there was no statistical difference among different etiology of CHF subgroups (\( P > 0.05 \)).

Increasing plasma sFKN and BNP with progressive cardiac function in CHF patients: The patients with CHF were classified into 3 groups according to the degree of cardiac function: 22 cases with NYHA II, 35 cases with NYHA III, and 39 cases with NYHA IV. Data shown in Table III indicated that plasma sFKN, BNP, and IL-18 concentrations were increased in NYHA II group compared with the control group (\( P < 0.05 \)). The levels of sFKN and BNP were elevated significantly further in NYHA III group than in NYHA II group (\( P < 0.05 \)). In addition, NYHA IV group had higher plasma concentra-
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FIGURE 1. Plasma concentrations of sFKN (A), BNP (B), and IL-18 (C) in CHF patients and controls. The data were shown as mean ± SD. A value of $P < 0.05$ was considered statistically significant.

Table I. Clinical Data of CHF Patients and Controls

|                | CHF group  | Control group | $\chi^2$ | $P$  |
|----------------|------------|---------------|---------|------|
| Gender (F/M)   | 64/32      | 30/15         | 0.000   | 1.000|
| Age (years)    | 63.60 ± 12.30 | 42.73 ± 11.90 | 9.486   | 0.904|
| Body weight (kg)| 63.10 ± 12.41 | 58.98 ± 8.67  | 2.011   | 0.080|
| SBP (mmHg)     | 113.43 ± 25.40 | 118.27 ± 10.84 | 3.332   | 0.000|
| DBP (mmHg)     | 75.92 ± 18.23 | 72.71 ± 7.31  | 1.136   | 0.000|
| HR (times/minute)| 80.35 ± 20.02 | 69.93 ± 6.79  | 3.396   | 0.000|
| TC (mmol/L)    | 6.49 ± 20.31 | 3.82 ± 0.84   | 0.880   | 0.102|
| TG (mmol/L)    | 1.17 ± 1.04  | 1.24 ± 0.31   | 0.030   | 0.140|
| HDL-c (mmol/L) | 0.96 ± 0.33  | 1.34 ± 0.32   | -6.409  | 0.811|
| LDL-c (mmol/L) | 2.49 ± 2.58  | 2.92 ± 0.46   | -1.101  | 0.160|
| Glu (mmol/L)   | 6.78 ± 3.42  | 4.90 ± 0.54   | 3.675   | 0.000|
| ALT (u/L)      | 67.15 ± 218.25 | 21.46 ± 7.86  | 1.401   | 0.039|
| AST (u/L)      | 77.81 ± 304.47 | 22.11 ± 6.22  | 1.225   | 0.076|
| BUN (mmol/L)   | 11.17 ± 7.05 | 4.87 ± 0.79   | 4.896   | 0.001|
| Cr (umol/L)    | 130.37 ± 100.47 | 67.13 ± 20.86 | 1.401   | 0.039|
| UA (umol/L)    | 395.24 ± 156.51 | 149.11 ± 55.50 | 10.235  | 0.000|
| Hematoidin (umol/L)| 22.39 ± 27.47 | 2.47 ± 1.08   | 4.661   | 0.000|
| HBDH (u/L)     | 262.00 ± 157.77 | 144.93 ± 39.90 | 4.461   | 0.000|
| LDH (u/L)      | 311.93 ± 164.60 | 164.60 ± 47.13 | 4.888   | 0.001|
| HSCR (mg/L)    | 22.39 ± 27.47 | 2.47 ± 1.08   | 4.853   | 0.000|

A value of $P < 0.05$ was considered statistically significant.

Table II. Plasma Concentrations of FKN, BNP, and IL-18 in Different Etiology of CHF Subgroups

| Subgroups | Cases | LVEF (%) | sFKN (pg/ml) | BNP (pg/ml) | IL-18 (ng/L) |
|-----------|-------|----------|--------------|-------------|--------------|
| IHD group | 35    | 41 ± 9.12| 1428.57 ± 1245.17 | 1506.34 ± 1166.45 | 175.64 ± 119.20 |
| DCM group | 28    | 37 ± 10.37| 1623.12 ± 1585.23 | 1770.46 ± 1527.04 | 141.99 ± 77.34  |
| VHD group | 18    | 47 ± 8.78*| 1401.20 ± 1247.81 | 1759.78 ± 1634.71 | 146.14 ± 136.43 |
| HHD group | 15    | 33 ± 10.9*#| 1274.88 ± 668.38 | 1579.47 ± 1500.95 | 155.68 ± 84.95  |
| F         | 4.773 | 0.271    | 0.233        | 0.598        |              |
| P         | 0.004 | 0.846    | 0.873        | 0.620        |              |

F and P were measured by ANOVA. $F > 1$ and $P < 0.05$ represented significant differences between at least two groups among the four groups. A value of $P < 0.05$ was considered statistically significant. *$P < 0.05$ versus IHD group. **$P < 0.05$ versus DCM group. ***$P < 0.05$ versus VHD group.

Correlation between plasma sFKN and BNP/IL-18: The correlation analysis showed that plasma sFKN concentration was positively correlated with plasma BNP level in patients with CHF ($r = 0.441$, $P < 0.001$). Plasma sFKN concentration was also positively correlated with IL-18 level in patients with CHF ($r = 0.592$, $P < 0.001$) as shown in Figure 2.

ROC curve analysis: The ROC curve analysis of sFKN, BNP, and IL-18 for the diagnosis of CHF in all participants is presented in Figure 3. The results showed that the area under the curve (AUC) values of sFKN, BNP, and IL-18 were 0.885 (95%CI: 0.810 to 0.960, $P < 0.001$), 0.889 (95%CI: 0.842 to 0.956, $P < 0.001$), and 0.878...
Figure 2. Plasma FKN level correlated with BNP (A) and IL-18 (B) in patients with CHF.

Table III. Plasma Concentrations of sFKN, BNP, and IL-18 in CHF Patients with Different NYHA Classifications

| Subgroups | Cases | LVEF (%) | sFKN (pg/mL) | BNP (pg/mL) | IL-18 (ng/L) |
|-----------|-------|----------|--------------|-------------|--------------|
| Control   | 41    | 58 ± 3.03| 234.69 ± 457.48| 125.03 ± 139.26| 61.25 ± 60.10 |
| NYHA II   | 22    | 40 ± 8.43*| 666.94 ± 174.07*| 585.36 ± 389.90*| 151.79 ± 86.69* |
| NYHA III  | 35    | 41 ± 10.80*| 1572.38 ± 1118.76**| 1532.54 ± 1439.49**| 158.75 ± 97.22*   |
| NYHA IV   | 39    | 39 ± 10.03*| 1797.08 ± 1562.24**| 2431.95 ± 1349.16**| 158.80 ± 125.94*  |
| F        | 38.562| 23.342  | 28.562       | 13.366      |
| P        | 0.000 | 0.000   | 0.000        | 0.000       |

F and P were measured by ANOVA. F > 1 and P < 0.05 represented significant differences between at least two groups among the four groups. A value of P < 0.05 was considered statistically significant. *P < 0.05 versus control. **P < 0.05 versus NYHA II. ***P < 0.05 versus NYHA III.

Figure 3. The ROC curve of sFKN (A), BNP (B), and IL-18 (C) for the diagnosis of CHF.

Table IV. ROC Curve Analysis of sFKN in All Participants

| Cut-off (pg/mL) | Sensitivity | Specificity | Accuracy |
|----------------|-------------|-------------|----------|
| 174.38         | 100%        | 31.8%       | 78.0%    |
| 326.02         | 99.0%       | 54.5%       | 85.1%    |
| 358.41         | 97.9%       | 61.4%       | 86.5%    |
| 415.34         | 97.9%       | 70.5%       | 89.4%    |

(95%CI: 0.801-0.954, P < 0.001), respectively. For better application of sFKN in the clinical diagnose of CHF, different cut-offs were chosen, and the corresponding sensitivity, specificity, and accuracy were analyzed (Table IV). For example, when the cut-off of sFKN was set at 326.02 pg/mL, the sensitivity, specificity, and accuracy were 99.0%, 54.5%, and 85.1%, respectively.

sFKN levels were not affected by inflammatory status: CHF patients in NYHA III or IV may present renal dys-
function and inflammatory state. However, it is not clear whether the increased sFKN was caused by the worsening of heart failure or acute inflammation. To explore whether sFKN levels were affected by inflammation, we used SPSS to perform multiple linear regression analysis. BUN, Cr, ALT, AST, and HSCRP levels of NYHA III and IV patients (n = 74) were defined as independent variables. Data shown in Table V demonstrated that sFKN concentrations were not related to BUN, Cr, ALT, AST, and HSCRP levels (P > 0.05), which indicated that sFKN concentration was an independent factor for detecting CHF at NYHA III and IV patients.

**Concentrations of sFKN for predicting CHF prognosis:**
To elucidate prognosis of CHF patients by concentrations of sFKN, we followed up those patients after sample collection for 1 year and recorded their rehospitalization status. Thirty-seven in 96 patients (38.54%) were rehospitalized within 1 year. Data were analyzed by independent sample t-test, and the results shown in Table VI indicated that the concentrations of sFKN, IL-18, and BNP in the death within 1 year. But there was no statistical difference of increased level of sFKN was detected in patients with CHF who were readmitted more than once within 1 year.

**Discussion**
Our data demonstrated that plasma level of sFKN was significantly increased in patients with CHF compared with healthy controls, and its level was elevated with the severity of heart failure. ROC curve analysis also showed that AUC value of sFKN was 0.885, which implies it is a potential predictor of CHF. In addition, increased level of sFKN was detected in patients with CHF who were readmitted more than once within 1 year.

CHF is the end stage of many cardiovascular diseases, manifesting as the alteration of cardiac structure and function. The pathogenesis of CHF is very complex, which includes oxidative stress, neural and humoral response, cell apoptosis, and sustained inflammatory responses with immune system activation. The mechanism may be related to the excessive activation of damaged immune system of cardiomyocytes, immune cells function disorder, alterations of myocardial extracellular matrix, and the myocardial fibrosis. Although the knowledge of the mechanism in CHF has been updated and the treatment of CHF has been advanced, the morbidity and mortality are still high, which brings significant burden on families and society worldwide.

There is a growing interest in chemokines and cytokines and their essential role in the process of occurrence and development of CHF. Animal models of CHF have demonstrated that inflammatory cytokine production is not only as a phenomenon of excessive activation of the inflammatory response but also plays a direct or indirect role in the pathophysiology of CHF, including systolic dysfunction and ventricular dilatation and myocardial cell apoptosis.

Chemokine FKN, also known as CX3CL1, is a newly discovered chemokine, which is expressed in various cells including inflammatory cells, epithelial cells, cardiomyocytes, endothelial cells, and smooth muscle cells. FKN possesses leukocyte-chemotactic and vasoconstrictive properties, which plays an important role in cardiovascular diseases. FKN elicits its chemotaxis and adhesion functions by interacting with the chemokine receptor CX3CR1. FKN/CX3CR1 axis has been proved to take part in many inflammatory disorders. Husberg et al. first raised that FKN protein was increased in cardiac tissue from patients with heart failure using western blot analysis. They also found that serum FKN was increased in patients with heart failure, which is in line with our result. We also found that sFKN level was raised in pa-

### Table V. Multiple Linear Regression Analysis of sFKN Levels Affected by Inflammatory Status

| Independent variable | Non-standardized coefficient | Standard error | Standard coefficient | T value | P value |
|----------------------|-----------------------------|---------------|---------------------|--------|--------|
| BUN                  | 340.412                     | 71.270        | -0.092              | 4.776  | 0.000  |
| Cr                   | -3.375                      | 5.557         | 0.092               | 0.607  | 0.546  |
| ALT                  | -0.487                      | 0.392         | -0.188              | -1.241 | 0.219  |
| AST                  | -0.068                      | 0.498         | -0.071              | -0.136 | 0.893  |
| HSCRP                | -0.027                      | 0.357         | -0.040              | -0.077 | 0.939  |

A value of P < 0.05 was considered statistically significant.

### Table VI. Plasma Concentrations of sFKN, BNP, and IL-18 in CHF Patients with Different Rehospitalized Status

| Rehospitalization status | Cases   | LVEF (%) | sFKN (pg/mL) | BNP (pg/mL) | IL-18 (ng/L) |
|--------------------------|---------|----------|--------------|-------------|--------------|
| Rehospitalization frequency = 0 | 52 (54.17%) | 41 ± 8.52 | 1132.35 ± 848.62 | 1719.04 ± 1419.19 | 136.01 ± 80.31 |
| Rehospitalization frequency ≥ 1 | 37 (38.54%) | 40 ± 11.92 | 1746.21 ± 1488.79* | 1453.73 ± 1358.41* | 187.44 ± 133.50* |
| Death                    | 7 (7.29%) | 34 ± 9.79 | 1295.27 ± 767.40 | 2287.03 ± 1850.21 | 180.93 ± 106.24 |

A value of P < 0.05 was considered statistically significant. *P < 0.05 versus Rehospitalized = 0.
patients with CHF in accordance with diseases severity. Richter et al. reported FKN as an independent predictor of mortality in patients with advanced heart failure. Previous studies have confirmed that FKN could depress myocyte contractility. It was also reported that the addition of FKN to neonatal cardiomyocytes contributed to the increased levels of cardiac hypertrophic markers. Researchers presented that the inhibition or neutralization of FKN might be an effective therapeutic strategy of heart failure. Gu et al. employed 2 myocardial infarction-induced heart failure models and found that the treatment of FKN neutralizing antibody could significantly improve the survival rate of mice. They also addressed that FKN neutralizing antibody treatment prevented cardiac hypertrophy and remodeling after myocardial infarction. However, Perge et al. recently found that plasma FKN level remained statistically unaltered in patients with heart failure after 6 months of cardiac resynchronization therapy (CRT) [29580749]. More detailed knowledge about FKN should be further studied.

BNP, which secreted by cardiomyocytes, is the most powerful neurohormonal predictor of left ventricular function. It has been introduced exhibiting various bioactivities, including diuresis, natriuretic function, vasodilatation, and resisting renin-angiotensin-aldosterone system caused by vasoconstrictive effect. The determination of BNP and its N-terminal proB-type (NT-proBNP) is considered valuable for the diagnosis and prognosis of heart failure. In patients with heart failure, the levels of BNP are increased in accordance with diseases severity, which is also observed in this study. We also found that the level of sFKN was positively correlated with BNP concentration in patients with CHF. In addition, increased sFKN level was believed to increase the frequency of rehospitalization rather than BNP. These results further suggested the advantage of sFKN in the diagnosis and prognosis of CHF.

As addressed previously, the pathogenesis of CHF is very complex, and it is also a result of chronic inflammatory immune responses, involving a variety of inflammatory cells and inflammatory factors. FKN has an anti-inflammatory role partly through regulating inflammatory cytokines production. IL-18 is also known as INF-γ inducing factor, is mainly composed of macrophage and monocyte immune-regulating factor secreted by the cells. Research shows that IL-18 can promote cardiac hypertrophy and eventually lead to CHF. In this study, we found that plasma IL-18 level in patients with CHF was significantly increased compared with healthy controls, whereas there was no statistical difference with disease severity. However, concentrations of sFKN were increased with disease severity in patients with CHF. Both increased sFKN and IL-18 levels added the frequency of rehospitalization in our study.

In summary, increased plasma sFKN, BNP, and IL-18 levels were observed in patients with CHF, sFKN level was raised in accordance with diseases severity of CHF. Increased sFKN level raised the frequency of rehospitalization as well. Therefore, sFKN might be a potential biomarker for the evaluation of CHF and a useful tool for the diagnosis and prognosis of CHF. However, larger sample size of patients from different regions and serial change of sFKN in plasma level should be further studied in future research.

Disclosure

Conflicts of interest: The authors declare that they have no conflicts of interest.

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