Assessing inflammation in Chinese subjects with subtypes of heart failure: an observational study of the Chinese PLA Hospital Heart Failure Registry

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Abstract

Background Inflammation is an important element of the pathophysiological process of heart failure (HF) and is correlated with subtypes of HF. The association between multiple biomarkers of inflammation and HF subtypes in Chinese subjects remains unclear. This study aimed to compare the differences in inflammation biomarkers among Chinese patients with different subtypes of HF who have been identified to date.

Methods We included 413 consecutive patients with HF, including 262 with preserved ejection fraction (HFpEF), 55 with middle-ranged ejection fraction (HFmrEF) and 96 with reduced ejection fraction (HFrEF). Ten inflammation biomarkers were analyzed and compared according to the HF subtypes. One hundred contemporary non-HF subjects were also recruited as the control group. Moreover, the correlations between the inflammatory biomarkers and left ventricular ejection fraction of the HF subtypes were assessed.

Results The mean age of the HF patients was 65.0 ± 12.0 years, 65.8% were male. Distinct subtypes of HF demonstrated different inflammation biomarker panels. IL-6, PTX-3, ANGPTL-4 and TNF-α were correlated with HFrEF; IL-1β and PTX-3 were correlated with HFmrEF; and IL-1β and IL-6 were correlated with HFpEF. The multivariable logistic regression showed that IL-1β [relative ratio (RR) = 1.08, 95% CI: 1.02–1.15, P = 0.010], IL-6 (RR = 1.03, 95% CI: 1.01–1.06, P = 0.016), PTX-3 (RR = 1.31, 95% CI: 1.11–1.55, P = 0.001), and ANGPTL-4 (RR = 1.05, 95% CI: 1.02–1.07, P < 0.001) were independently associated with HFmrEF and HFrEF. IL-6 (RR = 1.03, 95% CI: 1.01–1.04, P = 0.019), PTX-3 (RR = 1.23, 95% CI: 1.06–1.43, P = 0.007), and ANGPTL-4 (RR = 1.03, 95% CI: 1.01–1.06, P = 0.005) were independently associated with the HF subtype.

Conclusions Diverse inflammation biomarkers have multifaceted presentations according to the subtype of HF, which may illustrate the diverse mechanisms of inflammation in Chinese HF patients. IL-6, PTX-3, and ANGPTL-4 were independent inflammation factors associated with HFrEF and HF.

Keywords: Biomarkers; Chinese patients; Correlation; Heart failure; Inflammation

1 Introduction

Heart failure (HF) is a clinical syndrome defined as cardiac output that is incapable of meeting the tissue metabolic demand due to structural or functional impairment in ventricular filling or ejection. Multiple risk factors, such as hypertension, coronary artery disease (CAD) and cardiomyopathy, contribute to the increasing prevalence of HF worldwide, conferring high rates of cardiovascular hospitalization and mortality. Inflammation is a major factor responsible for the pathophysiologic process of HF. Different inflammatory cytokines intervene with the development and deterioration of HF. Various inflammation biomarkers have been associated with different subtypes of HF, i.e., HF with preserved ejection fraction (HFpEF), HF with middle-ranged ejection fraction (HFmrEF) and HF with reduced ejection fraction (HFrEF). Indeed, elucidating the relationship between different inflammation biomarkers and the subtypes of HF is meaningful and may lead to novel approaches for diagnosis and prognosis evaluations in the management of HF. Recent studies have shown that a panel of inflammatory biomarkers could contribute to the clinical risk stratification of patients with HF. For example, the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study (n = 1497) explored 20 inflammatory biomarkers among patients with HFrEF and showed that an inflammatory biomarker-
based model could predict the future risk of adverse cardiovascular outcomes with a Harrell’s C statistic of 0.747.\(^{[10]}\)

However, patient-level evidence regarding the relationship between inflammation biomarkers and the subtypes of HF remains sparse, especially among Chinese subjects. In the present study, we aimed to investigate the differences and correlations of multi-inflammatory biomarkers among Chinese patients with different subtypes of HF.

2 Methods

We recruited 413 consecutive HF patients at Chinese PLA General Hospital from January 2014 to June 2016. The diagnostic criteria for HF were based on the latest European Society of Cardiology HF guidelines, including: (1) typical symptoms and/or signs; (2) evidence of cardiac structural and/or functional abnormality; and (3) elevated levels of natriuretic peptides.\(^{[17]}\) All HF patients were divided into three groups based on the left ventricular ejection fraction (LVEF) at admission as follows: HFP EF as LVEF ≥ 50%, HFrEF as LVEF of 40%–49% and HfReF as LVEF < 40%. LVEF was measured with a Siemens ACUSON SC2000 ultrasound system and a 4V1c transducer (Siemens Medical System, Mountainview, CA) by Simpson’s biplane methods. All echocardiography results were confirmed by two independent experienced senior ultrasound doctors. Both echocardiography doctors were blinded to the patient recruitment and biomarker analyses. One hundred contemporary non-HF subjects were selected and included in the control group. All HF and non-HF patients were confirmed based on detailed inclusion/exclusion criteria. The inclusion criteria were as follows: age ≥ 18 years, New York Heart Association (NYHA) Class II-IV in HF patients and NYHA Class I/II in non-HF patients. Participants with the following situations were excluded: (1) patients of ethnic minority in China; (2) patients in the acute onset phase of decompensated HF, patients with acute coronary syndrome (ACS), or patients who had been stable for less than 3 months according to two independent researchers (B.H. L and J.X. L); (3) patients with a history of corticosteroid intake within 6 months; (4) patients with a history of a mental disorder; (5) patients who were pregnant; (6) patients with current infectious disease; (7) patients with malignant tumor or cancer; (8) patients with a serum creatinine level > 2.0 mg/dL; and (9) patients who were unable or unwilling to provide informed consent. All baseline clinical data, including the demographic data, medical history, current medications and laboratory test results, were collected upon admission.

This study protocol was approved by the Ethics Committee of Chinese PLA General Hospital and registered in the Chinese Clinical Trial Registry (ChiCTR-RRC-17013396). All subjects provided informed consent, and the medical care of all patients was consistent with relevant clinical guidelines and protocols.

2.1 Plasma inflammatory biomarkers and biomedical analyses

We selected 10 inflammatory cytokines in this study, including the B cell activating factor of TNF family (BAFF), human cartilage glycoprotein 39/chiitinase-3-like protein 1 (YKL-40/CHI3L1), neurotensin (NT), angiopoietin-like protein 4 (ANGPTL-4), pentraxin 3 (PTX-3), soluble tumor necrosis factor receptors 1 (TNF-R 1), interleukin 1β (IL-1β), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin 6 (IL-6). Blood samples were collected on the morning of the first day of admission for the inflammatory biomarker analysis. All patients have rested for 5 minutes before blood sampling, and all samples were collected into lithium-heparin tubes, which were immediately stored at 0–4°C in case of plasma fractionation. All samples were stored at −75°C up to use within one hour after collection. Each sample underwent ≤ 3 “freeze and thaw” cycles prior to assessment to maintain the quality of the sample. All blood samples were analyzed by the central laboratory of Chinese PLA General Hospital (Beijing Key Laboratory of Chronic Heart Failure Precision Medicine, Beijing, China). Enzyme-linked immunosorbent assay (ELISA) kits (Abcam, Cambridge, MA, USA) for all biomarkers were used to assess the levels of the plasma inflammatory cytokines. The detection rates of the ELISA kits were 100%, and the inter- and intra-assay coefficients of variation were < 10%.

2.2 Data analysis

Statistical analyses were performed with SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean ± SD and categorical variables as frequency (%). Continuous and categorical variables were compared using Student’s t-test or chi-square test, respectively. The non-normally distributed variables were assessed using the Mann-Whitney U test. The correlation coefficient analyses were based on a nonparametric method (Spearman rank). A multivariable model was established to investigate whether the inflammation biomarkers were independently related to HF (Model 1) or HfReF (Model 2). Factors with a P < 0.1 in the univariable analysis were included in the multivariable model. A two-sided P < 0.05 was considered statistically significant.
3 Results

3.1 Baseline characteristics

The baseline characteristics of the non-HF and HF patients are summarized in Table 1. In the HF group (n = 413), the mean age was 65.0 ± 12.0 years, and 65.8% of the patients were male. The patients in the HF group were older than those in the non-HF group. The patients in the non-HF group all had coronary arterial disease. Hyperlipidemia was more common in the non-HF group, whereas the HF patients more frequently suffered from atrial fibrillation. The prevalence of diabetes, myocardial infarction and stroke (ischemic and hemorrhagic) were similar between the two groups. The non-HF group showed higher frequencies of diabetes, myocardial infarction and stroke (ischemic and hemorrhagic) were similar between the two groups. The non-HF patients more frequently suffered from atrial fibrillation. The HF patients received more diuretics, digoxin, aspirin, warfarin and statin than the non-HF patients but had an equal frequency of other oral medication intake.

3.2 Plasma levels of multi-inflammatory biomarkers in HF patients by subtype

Among the 10 investigated inflammatory biomarkers, the patients with HF showed higher levels of IL-1β, IL-6, PTX3 and ANGPTL4 than the non-HF patients (Table 2). However, the HF patients had lower concentrations of TNF-α than the non-HF patients.

Among the three subtypes of HF patients (Table 2), 262 patients had HFrEF, 55 patients had HFmrEF, and 96 patients had HFpEF. The HFmrEF patients showed higher levels of IL-1β, IL-6, PTX-3, and ANGPTL-4 and lower levels of TNF-α, NT and BAFF than the non-HF patients. The patients with HFmrEF had higher levels of IL-1β, IL-6, and IL-6, and a lower level of NT.

Table 1. Baseline characteristics in relation to the presence or absence of HF.

| Variable                      | No-HF (n = 100) | HF (n = 413) | P-value |
|-------------------------------|-----------------|-------------|---------|
| Age, yrs                      | 58.1 ± 9.4      | 65.0 ± 12.0 | < 0.001 |
| Male                          | 67 (67.0%)      | 217 (65.8%) | 0.794   |
| Clinical characteristics       |                 |             |         |
| Hypertension                  | 70 (70.0%)      | 280 (67.9%) | 0.694   |
| Coronary arterial disease     | 100 (100.0%)    | 317 (75.3%) | < 0.001 |
| Myocardial infarction         | 22 (22.0%)      | 113 (27.9%) | 0.478   |
| Diabetes                      | 28 (26.5%)      | 123 (30.0%) | 0.726   |
| Hyperlipidemia                | 40 (40.0%)      | 101 (24.9%) | 0.002   |
| Atrial fibrillation           | 0 (0.0)         | 71 (17.0%)  | < 0.001 |
| Ischemic stroke               | 12 (12.0%)      | 61 (16.2%)  | 0.456   |
| Hemorrhagic stroke            | 0 (0.0)         | 2 (0.5%)    | 0.486   |
| Current smoking               | 52 (52.0%)      | 163 (40.1%) | 0.025   |
| Current alcohol               | 42 (42.0%)      | 126 (31.0%) | 0.033   |

Table 2. Plasma levels of multi-inflammatory biomarkers in HF and subtypes.

| Characteristics | Non-HF (n = 100) | HF (n = 413) | P-value |
|-----------------|------------------|-------------|---------|
| IL-1β, ng/L     | 16.7 ± 0.5       | 18.0 ± 0.2  | 0.006   |
| IL-6, ng/L      | 57.4 ± 0.9       | 60.6 ± 0.5  | 0.013   |
| PTX-3, ng/L     | 6.8 ± 0.2        | 7.3 ± 0.1   | 0.002   |
| ANGPTL-4, ng/L  | 40.6 ± 1.2       | 45.7 ± 0.6  | < 0.001 |
| TNF-α, ng/L     | 307.4 ± 6.2      | 287.3 ± 3.2 | 0.008   |
| TNFR-1, ng/L    | 173.5 ± 4.2      | 182.0 ± 2.0 | 0.075   |
| NT, ng/L        | 119.8 ± 2.3      | 115.7 ± 1.2 | 0.085   |
| BAFF, ng/L      | 2902.7 ± 62.5    | 2747.4 ± 27.4 | 0.140   |
| CRP, ng/L       | 1851.8 ± 44.6    | 1870.3 ± 20.9 | 0.701   |
| YKL-40-CHI3L1, ng/L | 157.4 ± 2.8 | 157.1 ± 1.8 | 0.894   |

Table 2. Plasma levels of multi-inflammatory biomarkers in HF and subtypes.

Data are presented as means ± SD or n (%). ACEI: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; CCB: calcium channel blocker; HF: heart failure.

Data are presented as means ± SD. *Compared with non-HF. ANGPTL-4: angiopoietin-like protein 4; BAFF: B cell activating factor of TNF family; CRP: C-reactive protein; HF: heart failure; HFmrEF: heart failure with midrange ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; IL-1β: interleukin 1β; IL-6: interleukin 6; NT: neutrosin; PTX-3: pentraxin 3; TNF-α: tumor necrosis factor-α; TNFR-1: tumor necrosis factor receptors 1; YKL-40-CHI3L1: human cartilage glycoprotein 39/chitinase-3-like protein 1.
PTX-3 than the non-HF patients. However, only ANGPTL4 was higher in the HFpEF subgroup than in the non-HF group.

### 3.3 Interconnections between inflammation biomarkers and HF subtypes

The correlations between LVEF and elevated inflammatory biomarkers in patients with different subtypes of HF are displayed in Table 3. Upon evaluating all inflammation biomarkers, IL-6, PTX-3, ANGPTL-4, and TNF-α were clearly correlated with LVEF in the patients with HFrEF. Furthermore, in the HFmrEF subgroup, only IL-1β and PTX-3 were related to LVEF. Additionally, linearly dependent relationships between LVEF and IL-1β and IL-6 were observed in the patients with HFpEF.

After adjusting for other covariates (age, sex, comorbidities, alcohol and tobacco consumption, and statin intake) in the multivariable logistic regression model, four inflammation biomarkers were independently associated with HF, including IL-1β [relative ratio (RR) = 1.08, 95% CI: 1.02–1.15, \( P = 0.016 \)], PTX-3 (RR = 1.31, 95% CI: 1.11–1.55, \( P = 0.001 \)), and ANGPTL-4 (RR = 1.05, 95% CI: 1.02–1.07, \( P < 0.001 \)). Considering HFrEF as a dependent variable in Model 2, the multivariable logistic regression analysis showed that IL-6 (RR = 1.03, 95% CI: 1.01–1.04, \( P = 0.019 \)), PTX-3 (RR = 1.23, 95% CI: 1.06–1.43, \( P = 0.007 \)) and ANGPTL-4 (RR = 1.03, 95% CI: 1.01–1.06, \( P = 0.005 \)) were independently associated with HFrEF. Moreover, the male sex (RR = 2.34, 95% CI: 1.19–4.56, \( P = 0.014 \)), older age (RR = 0.97, 95% CI: 0.95–0.99, \( P = 0.009 \)) and statin intake (RR = 0.38, 95% CI: 0.20–0.71, \( P = 0.002 \)) were independently associated with HFrEF.

### 4 Discussion

In the present study, the HFrEF patients demonstrated higher levels of IL-1β, IL-6, PTX-3 and ANGPTL-4 than the non-HF patients. Furthermore, among the four inflammation biomarkers with higher levels, LVEF in the HFrEF patients was strongly correlated with IL-6, PTX-3, and ANGPTL-4. However, the HFrEF patients had a lower

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**Table 3. Correlation between inflammation biomarkers and LVEF (%) in patients with different subtypes of HF.**

| Characteristics | HFrEF (\( n = 96 \)) | HFmrEF (\( n = 55 \)) | HFpEF (\( n = 262 \)) |
|-----------------|----------------------|----------------------|----------------------|
|                 | Correlation | R square | \( P \)-value | Correlation | R square | \( P \)-value | Correlation | R square | \( P \)-value |
| IL-1β, ng/L     | 0.138       | 0.019      | 0.181       | 0.029       | 0.001     | 0.045       | 0.191       | 0.037       | 0.002 |
| IL-6, ng/L      | 0.387       | 0.150      | < 0.001     | 0.168       | 0.028     | 0.220       | 0.180       | 0.032       | 0.003 |
| PTX-3, ng/L     | 0.398       | 0.158      | < 0.001     | 0.430       | 0.185     | 0.001       | 0.101       | 0.010       | 0.103 |
| ANGPTL-4, ng/L  | 0.332       | 0.110      | 0.001       | 0.163       | 0.026     | 0.236       | 0.049       | 0.002       | 0.426 |
| TNF-α, ng/L     | 0.333       | 0.111      | 0.001       | 0.186       | 0.035     | 0.174       | 0.023       | 0.001       | 0.712 |

ANGPTL-4: angiopoietin-like protein 4; HF: heart failure; HFmrEF: heart failure with midrange ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; IL-1β: interleukin 1β; IL-6: interleukin 6; LVEF: left ventricular ejection fraction; PTX-3: pentraxin 3; TNF-α: tumor necrosis factor-α.

**Table 4. Logistic regression model of the independent factors associated with HF (Model 1) and HFrEF (Model 2).**

| Factors          | HF (Model 1) 1 | HFrEF (Model 2) 2 |
|------------------|----------------|-------------------|
|                  | RR 95% CI     | \( P \)-value    | RR 95% CI     | \( P \)-value |
| IL-1β            | 1.08 1.02–1.15 | 0.010 | 1.05 | 0.99–1.17 | 0.104 |
| IL-6             | 1.03 1.01–1.06 | 0.016 | 1.03 | 1.01–1.05 | 0.019 |
| PTX-3            | 1.31 1.11–1.55 | 0.001 | 1.23 | 1.06–1.43 | 0.007 |
| ANGPTL-4         | 1.05 1.02–1.07 | < 0.001 | 1.03 | 1.01–1.06 | 0.005 |
| Age              | 1.06 1.03–1.08 | < 0.001 | 0.97 | 0.95–0.99 | 0.009 |
| Male gender      | 1.97 0.97–4.03 | 0.062 | 2.34 | 1.19–4.56 | 0.014 |
| Diabetes mellitus| 1.52 0.84–2.74 | 0.165 | 1.19 | 0.67–2.13 | 0.029 |
| Hypertension     | 0.76 0.43–1.35 | 0.343 | 0.65 | 0.38–1.11 | 0.111 |
| Smoking          | 0.84 0.41–1.75 | 0.648 | 1.00 | 0.51–1.96 | 0.995 |
| Alcohol          | 0.74 0.37–1.48 | 0.389 | 0.76 | 0.39–1.48 | 0.414 |
| Statin           | 0.49 0.21–1.15 | 0.099 | 0.38 | 0.20–0.71 | 0.002 |

1 Heart failure as a dependent variable; 2 Heart failure with reduced ejection fraction as a dependent variable. ANGPTL-4: angiopoietin-like protein 4; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; IL-1β: interleukin 1β; IL-6: interleukin 6; LVEF: left ventricular ejection fraction; PTX-3: pentraxin 3; RR: relative ratio.
TNF-α level than the non-HF patients, and the TNF-α level was correlated with LV-EF. In the multivariable regression analysis, we found that IL-1β, IL-6, PTX-3 and ANGPTL-4 were independently associated with HF, while the latter three biomarkers were independently associated with HFrEF.

In the present study, the HfPEF patients had higher levels of ANGPTL4, whereas the HfMgEF patients had higher levels of IL-1β, IL-6, and PTX-3. The results of the correlation analysis revealed that IL-1β and PTX-3 were associated with LV-EF in the HfMgEF subgroup. In contrast, in the HfPEF subgroup, correlations between inflammation biomarkers and LV-EF were found only with IL-1β and IL-6.

Since inflammation is a pathophysiologic pathway responsible for HF onset and deterioration,[7–9,18] it is important to illuminate the relationship between different inflammatory cytokines and different subtypes of HF. A panel of biomarkers may help establish the diagnosis and prognosis of HF patients. However, controversial opinions still exist regarding the phenotypic differences among patients with different subtypes of HF.[19,20] With the implementation and advent of investigated and de novo inflammatory biomarkers, our study included 10 biomarkers in the first general analysis, followed by a subgroup analysis.

TNF-α and IL-6 are proinflammatory biomarkers that have been extensively investigated. IL-6 is a proinflammatory cytokine thought to be released in direct response to TNF-α to affect communication between myocytes and fibroblasts. IL-6 is also associated with cardiac dysfunction, modification of the cardiac extracellular matrix, and severity of left ventricular dysfunction.[21] Several cross-sectional studies have demonstrated that TNF-α and IL-6 were elevated in HfPEF patients.[22,23] TNF-α and IL-6 were associated with the development of HF in previous studies.[24,25] Additionally, increased levels of TNF-α and IL-6 were associated with a negative prognosis in patients with chronic HF.[26,27] In our study, we also found that both biomarkers were correlated with HF. Furthermore, these factors were both correlated with LV-EF in patients with HFrEF, and IL-6 was independently correlated with HFrEF.

Our study demonstrates that ANGPTL-4 is increased in patients with HfPEF. In previous studies, reduced ANGPTL-4 was associated with a beneficial effect on lipid metabolism disorder, CAD and overall cardiovascular risk.[28,29] ANGPTL-4 may be potentially correlated with HfPEF in patients due to lipid metabolism disorder and CAD, both of which are common cardiovascular risks in the clinic.

IL-1β mediates inflammatory leukocyte recruitment and activation both in vitro and in vivo,[30,31] while delaying myofibroblast activation.[31] The overactivation of the matrix-degrading process, which is mediated by IL-1β, leads to left ventricular dilation and systolic dysfunction, while the removal of IL-1β inhibits myofibroblast conversion.[32] Based on previous studies, HfPEF may be represented by interstitial fibrosis, myocardial inflammation, and myocyte hypertrophy associated with oxidative stress,[33] indicating that a correlation may exist between HfPEF and IL-1β. In our partial results, IL-1β indeed was correlated with the HfPEF and HfMgEF subtypes.

As a novel inflammatory biomarker in the cardiovascular field, evidence regarding the correlation between PTX-3 and HF is limited. In our small sample study, PTX-3 showed diagnostic value in HF patients.[34] Another study illuminated that baseline elevated PTX-3 was associated with various cardiac outcomes, including all-cause mortality, cardiovascular mortality and hospitalization for worsening HF.[35] We further investigated the correlations between different subtypes of HF and PTX-3 and found that elevated plasma PTX-3 was associated with HFrEF and HfMgEF.

Cardiomyocyte death is a main cause of HfFrEF in which markers of myocardial impairment or cardiac stretch are prominent.[15,19] However, in HfPEF, evidence suggests that myocardial remodeling caused by microvascular endothelial inflammation may be a major mechanism, and thus, the different biomarker profiles mainly reflect inflammatory markers.[15,19] In addition, HfMgEF has been identified as a novel subtype within HF classifications.[17] Evidence elucidating the pathophysiological mechanisms underlying HfMgEF and the relationship and differences between HfFrEF and HfPEF is limited. A previous study reported that the biomarker profiles of patients with acute HfMgEF exhibited an intermediate interaction between both cardiac stretch and inflammation biomarkers.[15] However, our understanding of the weight and correlations of different inflammatory biomarkers in de novo and traditional subtypes of HF is limited.

4.1 Strengths and limitation

This study is the first to investigate the relationship between inflammatory biomarkers and HF in Chinese subjects. Elevated inflammatory biomarkers were shown in specific subtypes of HF. Significant correlations were found between these biomarkers and LV-EF. However, some limitations exist in the present study. We present only a cross-sectional relationship between inflammatory biomarkers and HF without a dynamic evaluation of the inflammation status, such as the peak levels of inflammatory biomarkers, which may be more significant. Furthermore, baseline differences, such as the higher CAD prevalence in the non-HF group, may have had some effects on the results. Although we statistically evaluated data of 413 HF subjects, due to the very
small subgroup numbers, we could not include all parameters that we initially planned in the multivariate analyses. Increasing the sample size in future HF projects may help solve this issue.

4.2 Conclusions

Chinese HF patients showed elevated levels of inflammatory biomarkers, and the various subtypes exhibited different correlations with the cytokine profiles. In particular, a strong correlation was found between the inflammatory biomarkers and LVEF. Therefore, our findings clearly show the need for continued detailed investigations of inflammatory markers in HF patients in both research and clinical settings to provide the best individualized patient care.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (No.31701155), the National Key Research and Development Program of China (2017YFC0114001), Chinese PLA General Hospital Medical Big Data Research and Development Project (No.2017MBD-007). The authors had no conflicts of interest to disclose. We thank Mark Thomas for advice and data analysis for this study.

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