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ORIGINAL RESEARCH

Prognostic Value of Inflammatory Cytokines in Predicting Hospital Readmissions in Heart Failure with Preserved Ejection Fraction

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Purpose: The aim of this study was to explore the relationship between inflammatory cytokines and the risk of heart failure (HF) readmission in patients with heart failure with preserved ejection fraction (HFpEF).

Patients and Methods: We enrolled 429 patients with HFpEF admitted to the cardiology department in our hospital from January 2020 to July 2022. The patients were divided into the readmission or non-readmission groups according to whether they were readmitted for heart failure within 1 year of discharge. The clinical features and laboratory date of the subjects were collected and analyzed. Multivariate cox regression analysis was used to identify predictors of HF readmission. In addition, receiver operating characteristic (ROC) curves were used to determine the prognostic value of each factor.

Results: The levels of IL-1β, IL-6, IL-10, IL-17, TNF-α, NT-proBNP, heart rate, total cholesterol and NYHA class were significantly higher in the readmission group than in the non-readmission group ($p < 0.05$). IL-1β, IL-6, IL-17, TNF-α, NT-proBNP, heart rate and NYHA class were identified as independent predictors of HF readmission.

Conclusion: Inflammatory markers, including IL-1β, IL-6, IL-17 and TNF-α were related to the HF readmission in patients with HFpEF.

Keywords: heart failure with preserved ejection fraction, inflammation, cytokine, readmission, risk assessment

Introduction

Heart failure (HF) is an advanced and terminal stage of various heart diseases.[1] It has a serious impact on patients' quality of life, increases hospitalization and mortality rates, and places a heavy economic burden on families and society.[2] The incidence of heart failure with preserved ejection fraction (HFpEF) has increased in recent year.[3] Management of HFpEF and prevention of heart failure progression is critical, as treatment options for HFpEF remain limited.[4]

Previous studies showed that there was close relationship between repeated readmissions and the decline in physical status in patients with HF.[5] Also, it affected the patient's treatment compliance and lead to the decline of cardiac function.[6] Therefore, accurate assessment of patients' risk of readmission within 1 year is essential for early detection and intervention of disease and improve the prognosis of patients.

Chronic Inflammation plays a vital role in the progression of HFpEF.[7] This chronic inflammatory state can lead to adverse cardiac remodeling and eventually heart failure.[8] It has been demonstrated that there was a strong association

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between various cytokines and HF.[9] However, only a few studies have investigated the association between cytokines and the risk of readmission in patients with heart failure with preserved ejection fraction within 1 year.

The purpose of this study was to determine whether the expression of 12 cytokines [IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, interferon (IFN)-α, interferon (IFN)-γ, and tumor necrosis factor(TNF)-α] was differential in readmission group and non-readmission group in patients with HFpEF and whether they can be adopted to facilitate the early detection and intervention of disease in patients with HFpEF and improve the prognosis of patients.

Materials and Methods

Study Population

This retrospective study was based on the database of the Department of Cardiovascular Medicine, The Affiliated Municipal Hospital of Xuzhou Medical University from January 2020 to July 2022. The flow chart of our study was shown in Figure 1. Patients with HFpEF who survived to discharge at 1 year were included in our study. The main exclusion criteria were as follows: (1) patients lost to follow-up; (2) patients with recent infection; (3) severe valvular heart diseases; (4) hepatic or renal dysfunction; (5) hematological system diseases or autoimmune diseases; (6) a history of tumor.

Clinical Data Collection

The demographic and clinical characteristics of each patient were recorded at the beginning of first hospitalization, including age, gender, height, weight, body mass index (BMI), NYHA class, comorbidities, discharge medication usage, heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were collected from the electronic medical record system of the hospital by trained physicians who were blinded to the aim of the study. Laboratory data were obtained including white blood cells (WBC), high sensitivity-C reactive protein (hs-CRP), potassium, sodium, fasting blood glucose (FBG), creatinine, albumin, triglycerides, total cholesterol, low density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), glycosylated hemoglobin (HbA1c), serum creatinine, estimated glomerular filtration rate (eGFR), N-terminal-pro brain natriuretic peptide (NT-proBNP), left atrial diameter (LAD), left ventricular diameter (LVD), left ventricular ejection fraction (LVEF). Also, serum cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, IFN-α, IFN-γ, and TNF-α) were included. Inflammatory cytokines were assessed using flow cytometry and the Pylon 3D automated immunoassay system (ET Healthcare) in our hospital. HFpEF is defined as symptoms and signs of HF with left ventricular ejection fraction (LVEF) ≥50%, usually accompanied by structural or

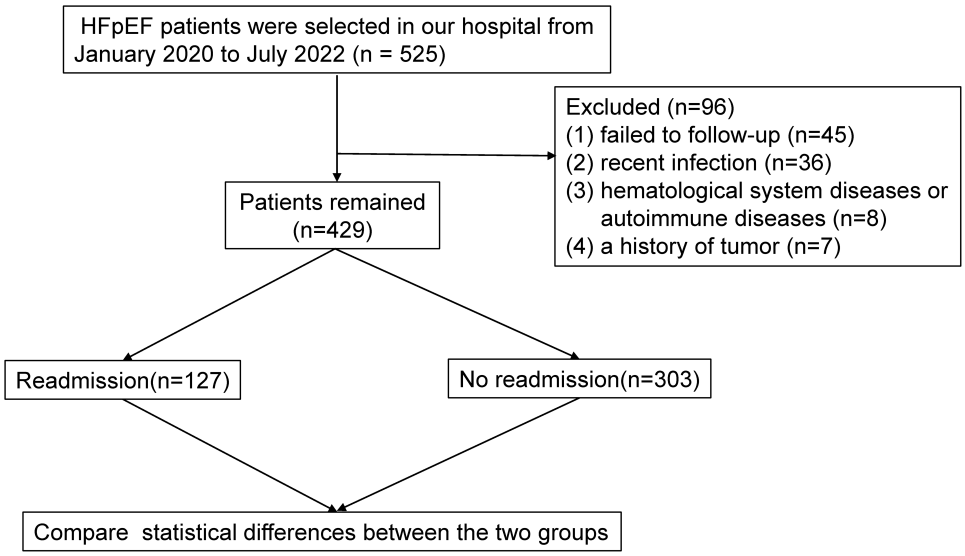

Figure 1 Flow chart of our study.
Abbreviation: HFpEF, heart failure with preserved ejection fraction.

functional heart abnormalities such as left ventricular hypertrophy, left atrial enlargement, diastolic dysfunction or elevated natriuretic peptides.[10] The endpoint of the study was defined as HF readmission within 1 year after hospital discharge.

Follow Up

All enrolled patients were followed-up regularly in the outpatient clinic or by remote telephone conversations with patients or family members. The follow-up continued for one year. Patients were divided into readmission and non-readmission groups based on whether they were readmitted because of HF within 1 year.

Statistical Analysis

All analyses were performed using SPSS version 25.0 (SPSS, Chicago, IL, USA), Stata version 13.0 and R version 4.0.3. Categorical variables were shown as rates (%) and continuous variables were expressed as mean standard deviation or median and interquartile range. The *t*-test was used to compare two groups, and one-way analysis of variance was used to compare three or more groups among numerical data with normal distribution. The Mann–Whitney *U*-test was used for quantitative data with non-normally distributed variables to compare between two groups and the Kruskal–Wallis test was used to compare between three or more groups. Cox regression analysis model was performed to assess the risk factors involved in the HF readmission in patients with HFpEF. The area under the curve (AUC) was used to evaluate the predictive value of each factor. Meanwhile, the AUC was calculated and compared by De-Long's test to evaluate whether introducing the cytokines into the model of established risk factors could improve the predictive value. Additionally, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were also calculated to further evaluate the incremental predictive value of the cytokines. *P*-value <0.05 was considered statistically significant.

Results

The Baseline Data of Patients

In this study, a total of 429 patients with HFpEF were included in our hospital from January 2020 to July 2022. The demographic and clinical characteristics of the study population are shown in Table 1.

A mean age of the participants was 79 (68, 84) years and 222 (51.7%) patients were male. Among these patients, 142 patients (33.1%) smoked, 100 patients (23.3%) drank, 155 patients (36.1%) developed hypertension, and 148 patients (34.5%) suffered from diabetes mellitus. There were significant differences between the readmission group and non-readmission group in terms of NT-proBNP, heart rate, total cholesterol, and NYHA class ($p < 0.05$).

Serum Cytokines Levels Under Different Groups

As is shown in Figure 2, The levels of IL-1β, IL-6, IL-10, IL-17 and TNF-α were significantly higher in the readmission group than in the non-readmission group ($p < 0.05$). Based on the NYHA class, patients were divided into three groups: NYHA II (n = 70), NYHA III (n = 271), and NYHA IV (n = 88). There was a significant difference in IL-1β, IL-6, IL-10, IL-17, TNF-α levels based on the NYHA class (Figure 3). IL-1β, IL-6, IL-17 and TNF-α levels in the NYHA IV group were significantly higher than in the NYHA II group ($p<0.05$), Compared to the NYHA III group, IL-1β, IL-6, IL-10, IL-17, and TNF-α levels were significantly higher in the NYHA IV group ($p<0.05$).

Cox Regression Analysis of Readmission in Patients with HFpEF

Cox regression analysis was used to further assess the independent predictors of readmission in HFpEF. As shown in Table 2, the results of the univariate cox regression analysis suggested that NYHA class, heart rate, total cholesterol, NT-proBNP, IL-1β, IL-6, IL-10, IL-17 and TNF-α were associated with HF readmission. In multivariable cox regression models, NT-proBNP, heart rate, the levels of IL-1β, IL-6, IL-17 and TNF-α were analyzed as the independent factors of HF readmission.

Table 1 Clinical Characteristics of Patients

Variables	Total (n = 429)	Non-Readmission (n = 303)	Readmission (n = 126)	*P*-value
Age (years)	79 (68, 84)	76 (69, 84)	75 (66, 85)	0.123
Gender, n (%)				0.458
Male	222 (51.7)	153 (50.5)	69 (54.8)	
Female	207 (48.3)	150 (49.5)	57 (45.2)	
Height (m)	1.65 (1.60, 1.70)	1.64 (1.60, 1.70)	1.65 (1.60, 1.70)	0.523
Weight (kg)	62 (55, 72)	62 (55, 72)	62 (55, 70)	0.488
BMI (kg/m^2)	23.2 (20, 26.6)	23.4 (20, 26.6)	22.6 (20.1, 26.2)	0.208
Heart rate (b.p.m.)	75 (66, 87)	75 (65, 85)	80 (70, 94)	0.001
SBP (mmHg)	130 (114, 148)	130 (114.5, 148)	126.5 (111, 142)	0.208
DBP (mmHg)	74 (68, 80)	74 (68, 80.5)	74 (68, 80)	0.945
NYHA class, n (%)				0.003
II	70 (16.3)	58 (19.1)	12 (9.5)	
III	271 (63.2)	194 (64.0)	77 (61.1)	
IV	88 (20.5)	51 (16.8)	37 (29.4)	
Comorbidity				
CAD, n (%)	245 (57.1)	168 (55.4)	77 (61.1)	0.331
Atrial fibrillation, n (%)	154 (35.9)	107 (35.3)	47 (37.3)	0.696
Diabetes, n (%)	148 (34.5)	107 (35.3)	41 (32.5)	0.661
Hypertension, n (%)	155 (36.1)	107 (35.3)	48 (38.1)	0.663
Stroke, n (%)	64 (14.9)	49 (16.2)	15 (11.9)	0.327
COPD, n (%)	43 (10.0)	33 (10.9)	10 (7.9)	0.452
Smoking, n (%)	142 (33.1)	103 (34.0)	39 (31.0)	0.619
Drinking, n (%)	100 (23.3)	72 (23.8)	28 (22.2)	0.827
ACEI/ARB, n (%)	274 (63.9)	194 (64)	80 (63.5)	0.916
β-blocker, n (%)	271 (63.2)	186 (61.4)	85 (67.5)	0.281
CCB, n (%)	85 (19.8)	55 (18.2)	30 (23.8)	0.228
Statin, n (%)	288 (67.1)	206 (68)	82 (65.1)	0.638
Digitalis, n (%)	86 (20.0)	62 (20.5)	24 (19.0)	0.841
Diuretic, n (%)	304 (70.9)	220 (72.6)	84 (66.7)	0.264
Imaging index				
LAD (mm)	41 (37, 48)	41 (36, 49)	41 (39, 47)	0.261
LVD (mm)	50 (44, 58)	50 (44, 57)	50 (44, 58)	0.790
LVEF, n (%)	58 (55, 60)	58 (55, 60)	57 (54, 60)	0.104

(*Continued*)

Table 1 (Continued).

Variables	Total (n = 429)	Non-Readmission (n = 303)	Readmission (n = 126)	*P*-value
Laboratory index				
WBC ($\times 10^9$/L)	5.8 (4.4, 7.2)	5.8 (4.3, 7)	5.8 (4.5, 7.4)	0.617
hs-CRP (mg/L)	2.6 (1.3, 10.2)	2.6 (1.2, 10.2)	2.6 (1.4, 10.6)	0.665
Hb1Ac (%)	6.2 (5.9, 6.8)	6.2 (5.9, 6.8)	6.4 (5.9, 7)	0.238
NT-proBNP (pg/mL)	800 (248, 1347)	547 (224.5, 1241)	959 (378, 2006)	< 0.001
Albumin (g/L)	37.8 (33.8, 40.3)	37.8 (33.8, 39.8)	38.3 (33.5, 40.9)	0.285
Serum creatinine (μmol/L)	77 (61, 96)	77 (61, 95)	77 (61, 103.2)	0.598
Blood glucose (mmol/L)	6.3 (5.2, 7.4)	6.4 (5.3, 7.4)	6.3 (5.2, 7.7)	0.885
Serum sodium (mmol/L)	138 (135, 141)	138 (134, 141)	139 (136, 141)	0.063
Serum kalium (mmol/L)	4 (3.7, 4.2)	4 (3.6, 4.2)	4 (3.7, 4.3)	0.375
eGFR (mL/min*1.73m^{-2})	84.1 (65.3, 103.8)	85.8 (68.4, 104)	81.7 (58.5, 102.1)	0.115
Total cholesterol (mmol/L)	3.6 (2.9, 4.4)	3.6 (2.7, 4.3)	3.7 (2.9, 4.6)	0.008
Triglyceride (mmol/L)	1 (0.7, 1.4)	1 (0.7, 1.3)	1 (0.6, 1.6)	0.282
HDL-C (mmol/L)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)	1.2 (0.9, 1.5)	0.111
LDL-C (mmol/L)	1.9 (1.4, 2.6)	1.9 (1.4, 2.6)	2 (1.5, 2.6)	0.285
Inflammatory Cytokines				
IL-1β (pg/mL)	6.6 (6.4, 9.4)	6.5 (6.2, 7.8)	8.0 (6.6, 14.4)	< 0.001
IL-2 (pg/mL)	1.1 (0.4, 1.6)	1.1 (0.4, 1.5)	1.1 (0.7, 1.7)	0.082
IL-4 (pg/mL)	0.9 (0.5, 1.4)	0.8 (0.5, 1.5)	0.9 (0.5, 1.2)	0.222
IL-5 (pg/mL)	1.8 (1.2, 3.4)	1.9 (1.2, 3.2)	1.8 (1.2, 4.0)	0.358
IL-6 (pg/mL)	3.5 (1.9, 6.3)	2.8 (1.8, 5.8)	5.0 (2.6, 13.3)	< 0.001
IL-8 (pg/mL)	2.8 (1.9, 5.2)	2.6 (1.9, 4.3)	2.8 (2.1, 7.8)	0.135
IL-10 (pg/mL)	1.1 (0.9, 1.8)	1.1 (0.9, 1.6)	1.3 (0.9, 2.4)	0.008
IL-12p70 (pg/mL)	1 (0.9, 1.4)	1 (0.9, 1.2)	1.1 (0.9, 1.6)	0.103
IL-17 (pg/mL)	1.4 (0.9, 2.4)	1.2 (0.8, 2)	2.0 (1.1, 6.4)	< 0.001
IFN-α (pg/mL)	1.2 (0.6, 2.3)	1.2 (0.6, 2.2)	1.4 (0.8, 2.4)	0.059
IFN-γ (pg/mL)	5.4 (3.1, 8.5)	5.2 (3.2, 7.6)	5.9 (3, 11.1)	0.059
TNF-α (pg/mL)	2.1 (1.9, 3.1)	2.1 (1.7, 2.6)	2.7 (2, 4.3)	< 0.001

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor inhibitor; WBC, white blood cell count; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NT-proBNP: N-terminal-pro brain natriuretic peptide; HbA1c, glycosylated hemoglobin; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LVD, left ventricular diameter; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitors; IL-1β, interleukin-1βeta; IL-2, interleukin-2; IL-4, interleukin-4; IL-5, interleukin-5; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL-12p70, interleukin-12p70; IL-17, interleukin-17; IFN-α, interferon-alpha; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-alpha.

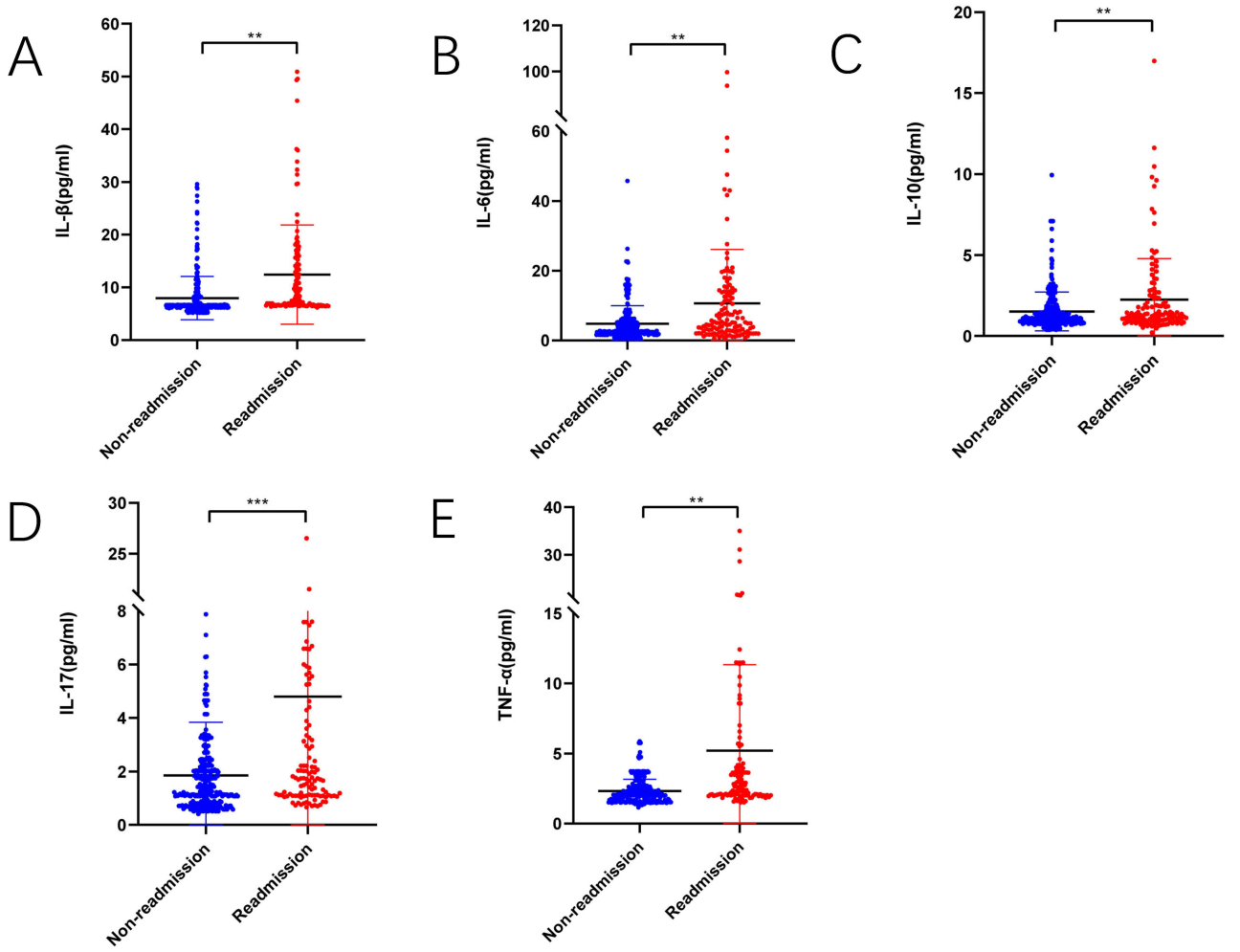

Figure 2 Prognosis of inflammatory cytokines in HF patients. Levels of IL-1β(**A**), IL-6(**B**), IL-10(**C**), IL-17(**D**) and TNF-α(**E**) in readmission and non-readmission patients of HF patients. **p< 0.01, ***p < 0.001.

Abbreviations: HF, heart failure; IL-1β, interleukin-1βeta; IL-6, interleukin-6; IL-10, interleukin-10; IL-17, interleukin-17; TNF-α, tumor necrosis factor-alpha.

Receiver Operating Characteristic Curve Analysis of Cytokines in Predicting HF Readmission in Patients with HFpEF

As shown in Figure 4, the Area Under Curve (AUC) for IL-1β, IL-6, IL-17 and TNF-α to predict HF readmission were 0.740 (95% CI: 0.691–0.788, p<0.001), 0.646 (95% CI: 0.588–0.705, p<0.001), 0.693 (95% CI: 0.637–0.748, p<0.001) and 0.730 (95% CI: 0.650–0.759, p<0.001), and cut-off were 6.6, 6.3, 5.3, and 6.7 respectively. It is demonstrated that IL-1β showed the best predictive value among cytokines. Meanwhile, the AUC obtained from the model of established risk factors, which consisted of heart rate, NYHA class, and NT-proBNP, was 0.743 (95% CI: 0.690−0.797, p < 0.001). Furthermore, adding the IL-1β to the model of established risk factors could lead to an increase in AUC (0.790 [95% CI: 0.741–0.839] vs 0.743 [95% CI: 0.690–0.797], p = 0.001), NRI (0.540 [0.349–0.731], p < *0.001*), and IDI (0.072[0.040 −0.104], p < 0.001) (Figure 4).

Discussion

This study mainly assessed the relationships between serum levels of 12 cytokines and HF readmission in patients with HFpEF. The results show that the cytokines IL-1β, IL-6, IL-17 and TNF-α were higher readmission groups than non-readmission groups in patients with HFpEF. Also, Serum cytokines levels included IL-1β, IL-6, IL-17 and TNF-α was different under three NYHA class groups.

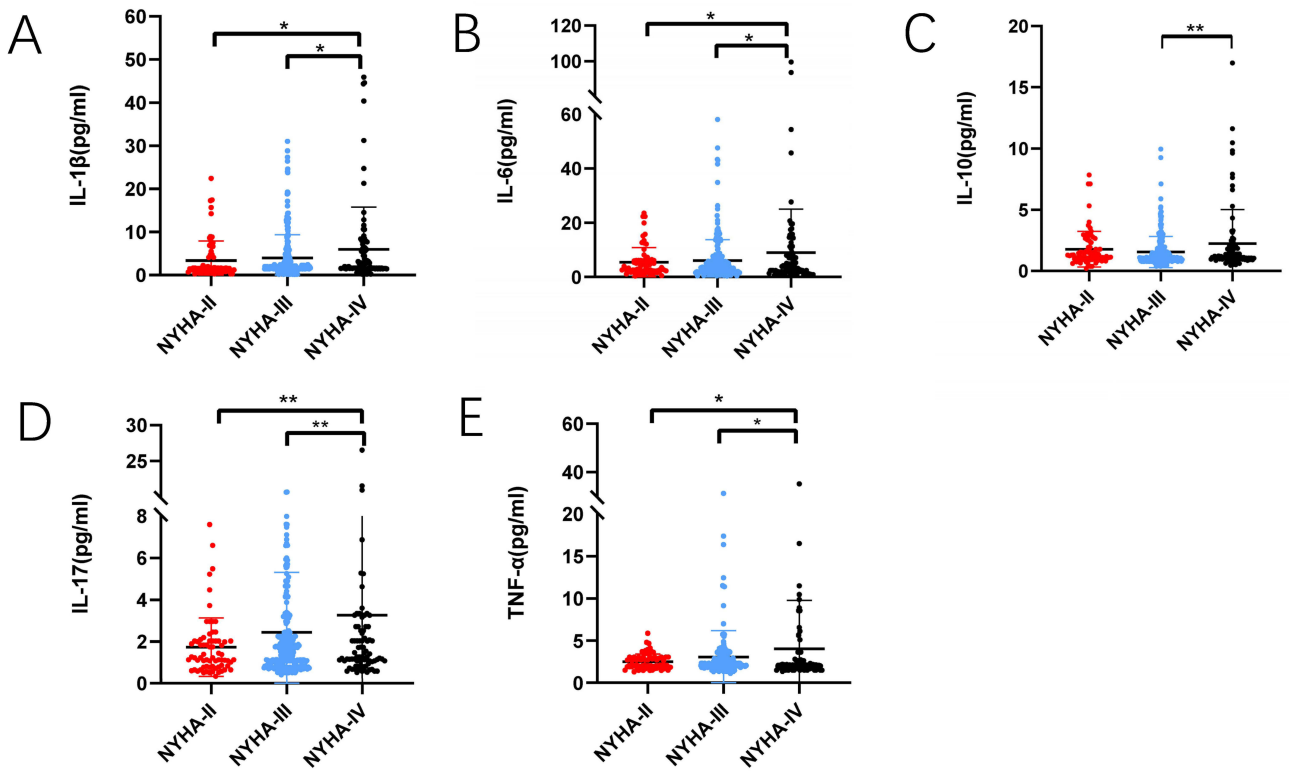

Figure 3 Levels of IL-1β(**A**), IL-6(**B**), IL-10(**C**), IL-17(**D**) and TNF-α(**E**) in HFpEF patients based on the NYHA class. *$p < 0.05$, **$p < 0.01$.
Abbreviations: HFpEF, heart failure with preserved ejection fraction; IL-1β, interleukin-1βeta; IL-6, interleukin-6; IL-10, interleukin-10; IL-17, interleukin-17; TNF-α, tumor necrosis factor-alpha.

With the increasing age of the population and the rise in cardiovascular disease and its risk factors, the incidence of heart failure in the elderly is expected to continue to rise in the future.[11] Approximately half of patients with heart failure develop heart failure with preserved ejection fraction (HFpEF).[12] HFpEF causes huge economic burden to society and family because of repeated hospitalization.[13] Despite extensive research in recent decades, HFpEF treatment options are few and it remains a global health problem.

Table 2 Cox Regression Analysis of Readmission Within 1 Year Among HF Patients

Variables	Univariate Analysis HR (95% CI)	*P* value	Multivariate Analysis HR (95% CI)	*P* value
Heart rate	1.015(1.006–1.023)	0.001	1.016 (1.007–1.025)	0.001
NYHA class	1.795(1.338–2.408)	0.001	1.519(1.107–2.085)	0.010
Total cholesterol	1.186(1.002–1.403)	0.047	1.088(0.906–1.307)	0.366
NT-proBNP	1.022(1.017–1.027)	0.001	1.021(1.015–1.027)	0.001
IL-1β	1.079(1.060–1.099)	<0.001	1.055(1.022–1.090)	0.001
IL-6	1.039(1.028–1.050)	<0.001	1.019(1.005–1.032)	0.008
IL-10	1.183(1.104–1.267)	0.001	0.908(0.799–1.032)	0.139
IL-17	1.174(1.138–1.211)	<0.001	1.066(1.020–1.113)	0.004
TNF-α	1.110(1.084–1.137)	<0.001	1.047 (1.010–1.085)	0.013

Abbreviations: NT-proBNP, N-terminal-pro brain natriuretic peptide; IL-1β, interleukin-1βeta; IL-6, interleukin-6; IL-10, interleukin-10; IL-17, interleukin-17; TNF-α, tumor necrosis factor-alpha.

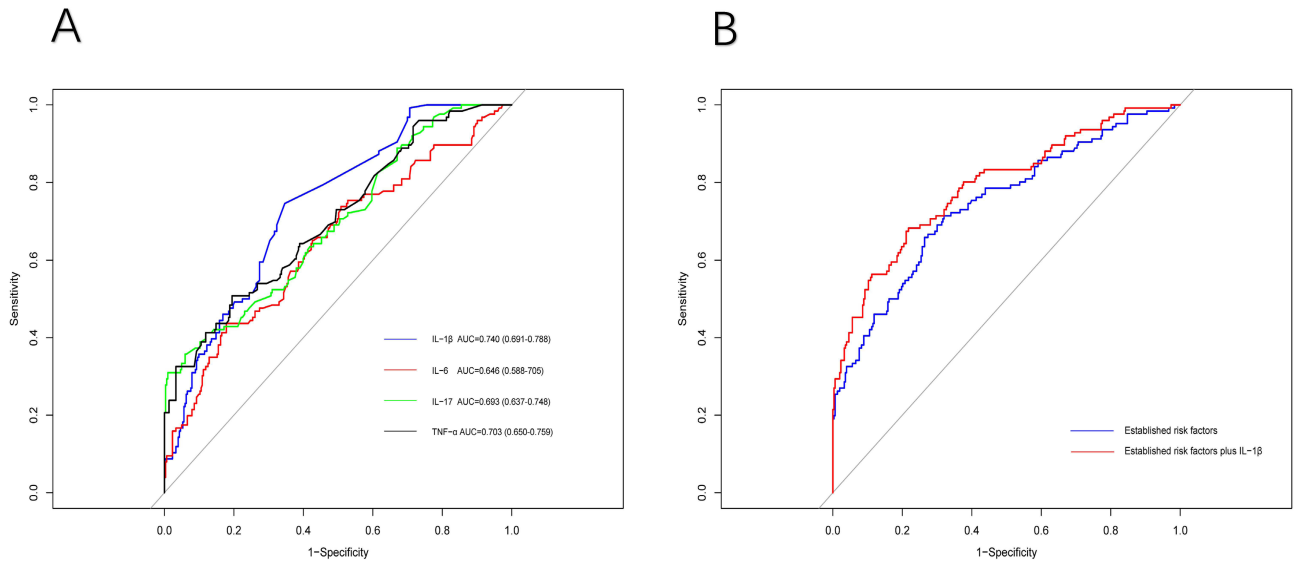

Figure 4 ROC curves of IL-1β, IL-6, IL-17 and TNF-α showing different abilities to predict HF readmission (**A**) and comparison of the AUC between the models (**B**).
Abbreviations: ROC, Receiver operating characteristic; HF, heart failure, IL-1β, interleukin-1βeta; IL-6, interleukin-6; IL-17, interleukin-17; TNF-α, tumor necrosis factor-alpha.

The relationship between inflammation and heart failure has become a hot research topic in recent years.[14] This chronic inflammatory state can lead to adverse cardiac remodeling, such as left ventricular hypertrophy, ultimately leading to HFpEF.[15] Inflammation also appears to be more common in HFpEF compared with HFrEF in studies, which may suggest a different pathophysiology.[16,17] This study may provide new inspiration for the clinical treatment of HFpEF.

The level of serum cytokines is often used to reflect the body's inflammatory state and inflammatory response bias.[18,19] It has been shown that cardiovascular disease was closely related to cytokines. Several studies have uncovered an association between CAD and cytokines.[20] In addition, the synthesis of cytokine-induced growth factors may have a chronic fibrogenic effect that contributes to the pathogenesis of heart failure with preserved ejection fraction (HFpEF).[21,22]

In our study, serum IL-1β, IL-6, IL-17, and TNF-α levels increased in readmission groups. Interestingly, the level of IL-1β, IL-6, IL-17, and TNF-α increase as grades of NYHA class. The interleukin-1 family of cytokines is a group of classical inflammatory factors. They are involved in the onset and development of many fibrotic diseases.[23] Also, Interleukin-1 is involved in pathogenic pathways and is a therapeutic target for inflammation in heart disease.[24] Interleukin-1β (IL-1β) is a pro-inflammatory cytokine that has been suggested to be involved in cardiac remodelling after ischaemia and impairment in ventricular contractility and relaxation.[25,26] IL-6 initiates the leucocyte infiltration. Persistent inflammation can lead to a destructive tissue reaction that causes tissue fibrosis. Individuals with elevated IL-6 levels have a higher risk of heart failure compared to those without a history of cardiovascular disease.[27] IL-17 enhanced the release of pro-inflammatory cytokines including IL-1 and IL-6.[28,29] Patients with higher levels of IL-17 were more likely to have atrial fibrillation (AF), kidney dysfunction and heart failure with preserved ejection fraction (HFpEF).[30,31] TNF-α has been shown to play a specific role in patients with HFpEF compared with HFrEF and controls, correlating with myocardial fibrosis and stiffening.[32,33] Consistent with previous studies, HFpEF patients with higher level of NT-proBNP, heart rate and NYHA class has a higher incidence of HF admission.[34,35]

Limitations

This was a single-centre trial, so there may have been a selection bias in the patients enrolled; We did not monitor dynamic changes in cytokines during the study period. Further prospective studies based on multicentre and large sample sizes are needed to verify our conclusions.

Conclusion

In summary, this study showed the inflammatory markers, IL-1β, IL-6, IL-17, and TNF-α, could be adopted to predict the HF readmission in patients with HFpEF, which may become potential therapeutic targets for clinical use in the future.

Ethics Statement

This study was designed in accordance with the Declaration of Helsinki and approved by the ethics committee of the Affiliated Xuzhou Municipal Hospital of Xuzhou Medical University. Due to the study being a retrospective analysis, the review committee waived the requirement for written informed consent. Confidential patient information was removed from the entire data set prior to analysis.

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All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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