RESEARCH PAPER

Estimation Of Interleukin 6 Levels And Its Correlation With Severity Of Chronic Heart Failure

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Received: 27-11-2024; Revised: 6-12-2024; Accepted: 18-12-2024; Available Online: 27-12-2024

ABSTRACT

Background: Chronic heart failure is associated with persistent systemic inflammation, which contributes to ventricular dysfunction and disease progression. Interleukin-6 (IL-6) is a pro-inflammatory cytokine that may reflect the severity of myocardial impairment. Evaluating its relationship with clinical and echocardiographic parameters may help clarify its potential role as a biomarker in chronic heart failure.

Aim and Objectives: To estimate serum IL-6 levels in patients with chronic heart failure and determine their correlation with disease severity, assessed using New York Heart Association (NYHA) functional class and left ventricular ejection fraction (LVEF).

Results: The study included 45 patients with chronic heart failure. NYHA Classes II, III and IV comprised 21 (46.67%), 17 (37.78%) and 7 (15.56%) patients, respectively. The overall mean LVEF was 41 ± 9%. Mean LVEF declined significantly from 49 ± 7% in NYHA Class II to 35 ± 4% in Class III and 33 ± 4% in Class IV ($p=0.001$). NYHA class demonstrated a strong negative correlation with LVEF ($r=-0.669$; $p=0.001$). The overall mean serum IL-6 level was 16.68 ± 4.49. Mean IL-6 levels were 15.83 ± 4.04, 17.50 ± 4.62 and 17.27 ± 5.63 in NYHA Classes II, III and IV, respectively, without a statistically significant difference ($p=0.254$). IL-6 showed a weak, non-significant positive correlation with NYHA class ($r=0.153$; $p=0.316$). However, IL-6 demonstrated a statistically significant moderate negative correlation with LVEF ($r=-0.480$; $p=0.001$).

Conclusion: Serum IL-6 was significantly associated with reduced LVEF but not with NYHA functional class. These findings suggest that IL-6 may reflect objective echocardiographic impairment more closely than symptom-based functional severity. Serum IL-6 may therefore serve as a supplementary marker of myocardial dysfunction in chronic heart failure...

Keywords: Chronic heart failure; interleukin-6; inflammatory cytokine; ejection fraction; NYHA functional class; ventricular dysfunction; cardiac inflammation; disease severity; biomarker; systolic function.

How to cite this article*:* Bhat BV, Ashokavardhana S, Yashwanth NS, Ashok ML., Estimation Of Interleukin 6 Levels And Its Correlation With Severity Of Chronic Heart Failure. Int J Drug Deliv Technol. 2026;16(75s): 564-570. DOI: 10.25258/ijddt.16.75s.66

Source of support: Nil.

Conflict of interest: Nil.

INTRODUCTION

Chronic heart failure is a complex clinical syndrome resulting from structural or functional cardiac abnormalities that impair ventricular filling or the ejection of blood. It is characterized by symptoms such as breathlessness, fatigue and reduced exercise tolerance, accompanied by clinical signs including peripheral oedema, pulmonary congestion and elevated jugular venous pressure (1). Despite substantial progress in diagnostic and therapeutic strategies, chronic heart failure remains a major cause of morbidity, repeated hospitalization, impaired quality of life and mortality worldwide. Its prevalence increases considerably with advancing age and the growing burden of hypertension, coronary artery disease, diabetes mellitus, obesity and other cardiovascular risk factors (2).

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Heart failure is commonly classified according to left ventricular ejection fraction. Based on echocardiographic findings, patients may be categorized as having heart failure with reduced ejection fraction, heart failure with mid-range ejection fraction and heart failure with preserved ejection fraction. These phenotypes differ in their underlying mechanisms, clinical characteristics and response to treatment (3). The severity of functional limitation is frequently assessed using the New York Heart Association functional classification, ranging from Class I, in which ordinary physical activity does not cause symptoms, to Class IV, in which symptoms occur even at rest. However, conventional clinical and echocardiographic assessments may not fully represent the complex biological processes responsible for disease progression (4).

Chronic heart failure is increasingly recognized as a systemic inflammatory state rather than solely a disorder of cardiac pumping function. Persistent haemodynamic stress, myocardial injury, neurohormonal activation, tissue hypoxia and oxidative stress can stimulate the release of several inflammatory mediators (5). These mediators contribute to endothelial dysfunction, cardiomyocyte injury, adverse ventricular remodelling, skeletal muscle wasting and progressive deterioration of cardiac performance. Therefore, inflammatory biomarkers may provide additional information regarding the underlying disease activity and severity of heart failure (6).

Interleukin-6 is a multifunctional pro-inflammatory cytokine produced by activated immune cells, vascular endothelial cells, cardiac fibroblasts and cardiomyocytes. Its synthesis may be stimulated by myocardial stress, tissue injury and systemic congestion. Interleukin-6 exerts its biological effects through classical and trans-signalling pathways and contributes to hepatic acute-phase responses, immune activation, vascular dysfunction and myocardial remodelling (7,8). Increased circulating interleukin-6 levels have been reported in patients with heart failure and may reflect greater inflammatory activation. Higher concentrations may also be associated with worsening functional status, impaired ventricular function, increased symptom burden and adverse clinical outcomes (9).

Measurement of interleukin-6 may therefore help identify patients with a greater degree of inflammatory activation and more severe chronic heart failure. Establishing its relationship with clinical functional class and echocardiographic categories could improve understanding of the inflammatory mechanisms involved in heart failure progression (9,10). It may also support future evaluation of interleukin-6 as a biomarker for risk stratification and as a potential target for inflammation-modulating therapies (11).

The present cross-sectional study was undertaken among adult patients with echocardiographically confirmed heart failure attending hospitals attached to Bangalore Medical College and Research Institute (12). It aimed to estimate serum interleukin-6 levels and correlate them with the severity of chronic heart failure, assessed using New York Heart Association functional grading and echocardiographic classification based on left ventricular ejection fraction (13).

AIMS AND OBJECTIVES

Aim

To estimate serum interleukin-6 (IL-6) levels and evaluate their correlation with the severity of chronic heart failure.

Objective

To correlate serum IL-6 levels with chronic heart failure severity assessed using NYHA functional classification and echocardiographic left ventricular ejection fraction.

MATERIALS AND METHODS

This cross-sectional study was conducted from February 2021 to August 2022 among patients attending the outpatient and inpatient departments of hospitals attached to Bangalore Medical College and Research Institute, Bengaluru. Following approval from the Institutional Ethics Committee, 45 patients fulfilling the eligibility criteria were enrolled after obtaining valid written informed consent. Adults aged more than 18 years with echocardiographically confirmed heart failure were included. Heart failure was classified according to left ventricular ejection fraction as heart failure with preserved ejection fraction (HFpEF; EF ≥50%), heart failure with mid-range ejection fraction (HFmrEF; EF 41%–49%) and heart failure with reduced ejection fraction (HFrEF; EF ≤40%). Patients who declined consent, were younger than 18 years, had malignancy, infection, autoimmune disease, liver cirrhosis or chronic kidney disease, or demonstrated clinical features of active infection were excluded.

Demographic and clinical information, duration of disease, treatment history and complications were recorded using a structured case-record form. The severity of heart failure was assessed using the New York Heart Association functional classification and echocardiographic parameters. Relevant investigations were performed to exclude conditions likely to influence inflammatory markers. Serum interleukin-6 levels were measured in all enrolled patients and correlated with NYHA functional class and echocardiographic classification of heart failure. The sample size was calculated using a previously reported mean IL-6 level of 14.3 ± 6.58 and an absolute precision of 2 at a 95% confidence level. The minimum calculated sample size was 41, which was rounded to 45 patients.

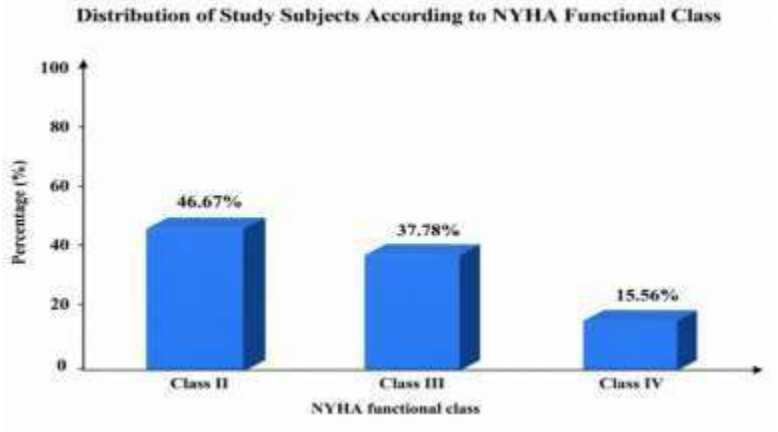
Data were entered into Microsoft Excel and analysed using IBM SPSS version 26. Normality was assessed using the Kolmogorov–Smirnov test. Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as mean ± standard deviation or median with interquartile range, depending on their distribution. The chi-square test or Fisher's exact test was used for categorical variables. The independent Student's t-test and Mann–Whitney U test were applied to normally and non-normally distributed continuous variables, respectively. Pearson's correlation coefficient was used to assess correlations between continuous variables. A p-value <0.05 was considered statistically significant.

RESULTS

Table 1. Distribution of patients according to NYHA functional class

NYHA functional class	Number (n)	Percentage (%)
Class II	21	46.67
Class III	17	37.78
Class IV	7	15.56
Total	**45**	**100.00**

Graph 1. Distribution of patients according to NYHA functional class

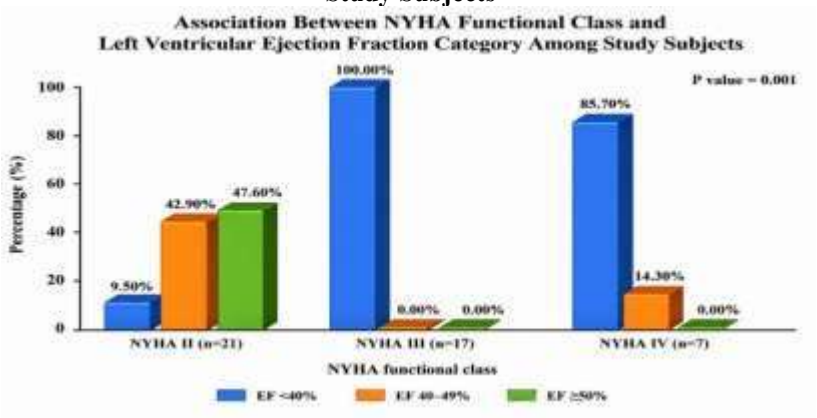


In the present study, 21 (46.67%) patients belonged to NYHA Class II, 17 (37.78%) to Class III and 7 (15.56%) to Class IV. NYHA Class II was the most frequent functional category, followed by Classes III and IV.

Table 2. Association Between NYHA Functional Class and Left Ventricular Ejection Fraction Category Among Study Subjects

Ejection-fraction category	NYHA II, n (%)	NYHA III, n (%)	NYHA IV, n (%)	Total, n (%)	P value
EF <40%	2 (9.50)	17 (100.00)	6 (85.70)	25 (55.60)	
EF 40–49%	9 (42.90)	0 (0.00)	1 (14.30)	10 (22.20)	
EF ≥50%	10 (47.60)	0 (0.00)	0 (0.00)	10 (22.20)	
Total	**21 (100.00)**	**17 (100.00)**	**7 (100.00)**	**45 (100.00)**	**0.001**

Graph 2. Association Between NYHA Functional Class and Left Ventricular Ejection Fraction Category Among Study Subjects

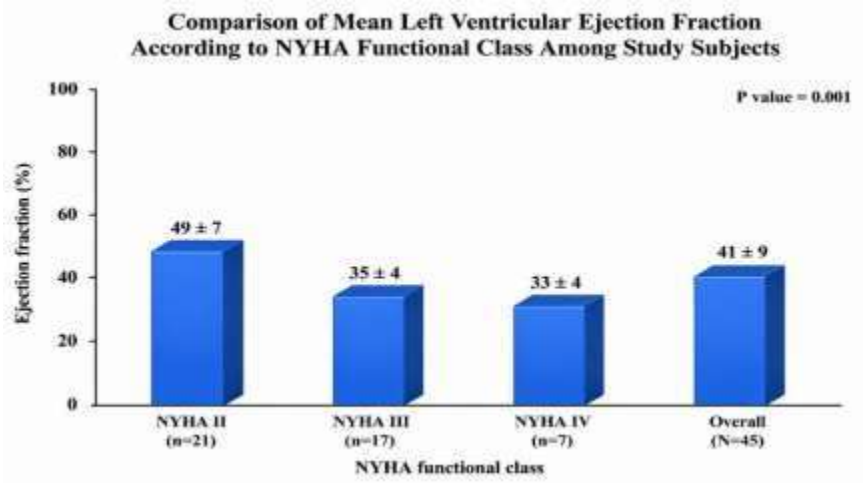


In the present study, among the 21 patients in NYHA Class II, 2 (9.50%) had EF <40%, 9 (42.90%) had EF 40–49%, and 10 (47.60%) had EF ≥50%. Among the 17 patients in NYHA Class III, 17 (100.00%) had EF <40%, while none (0.00%) had EF 40–49% or EF ≥50%. Among the 7 patients in NYHA Class IV, 6 (85.70%) had EF <40%, 1 (14.30%) had EF 40–49%, and none (0.00%) had EF ≥50%. Overall, 25 patients (55.60%) had EF <40%, 10 patients (22.20%) had EF 40–49%, and 10 patients (22.20%) had EF ≥50%, with a total of 45 (100.00%) study subjects. The association between NYHA functional class and left ventricular ejection fraction category was statistically significant (P = 0.001).

Table 3. Comparison of Mean Left Ventricular Ejection Fraction According to NYHA Functional Class Among Study Subjects

Parameter	NYHA II (n=21), Mean ± SD	NYHA III (n=17), Mean ± SD	NYHA IV (n=7), Mean ± SD	Overall (N=45), Mean ± SD	P value
Ejection fraction (%)	49 ± 7	35 ± 4	33 ± 4	41 ± 9	0.001

Graph 3. Comparison of Mean Left Ventricular Ejection Fraction According to NYHA Functional Class Among Study Subjects

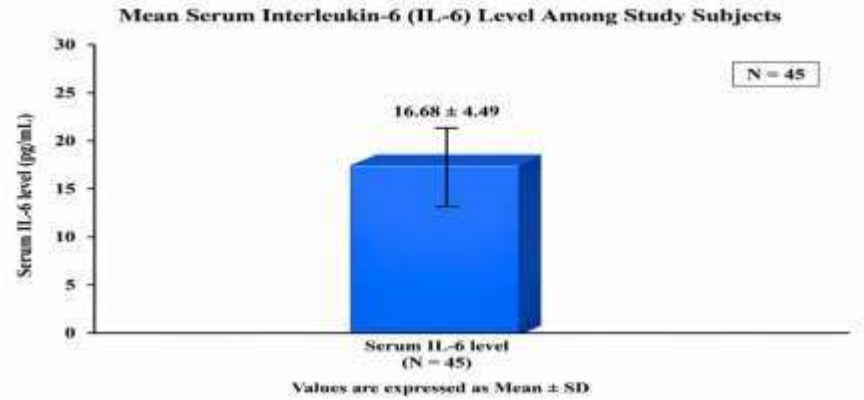


In the present study, the mean left ventricular ejection fraction was 49 ± 7% among patients in NYHA Class II (n=21), 35 ± 4% among patients in NYHA Class III (n=17), and 33 ± 4% among patients in NYHA Class IV (n=7). The overall mean left ventricular ejection fraction among the 45 study subjects was 41 ± 9%. The difference in mean left ventricular ejection fraction across the NYHA functional classes was statistically significant (P = 0.001).

Table 4. Mean Serum Interleukin-6 (IL-6) Level Among Study Subjects

Parameter	Number (N)	Mean	SD
Serum IL-6 level	45	16.68	4.49

Graph 4. Mean Serum Interleukin-6 (IL-6) Level Among Study Subjects

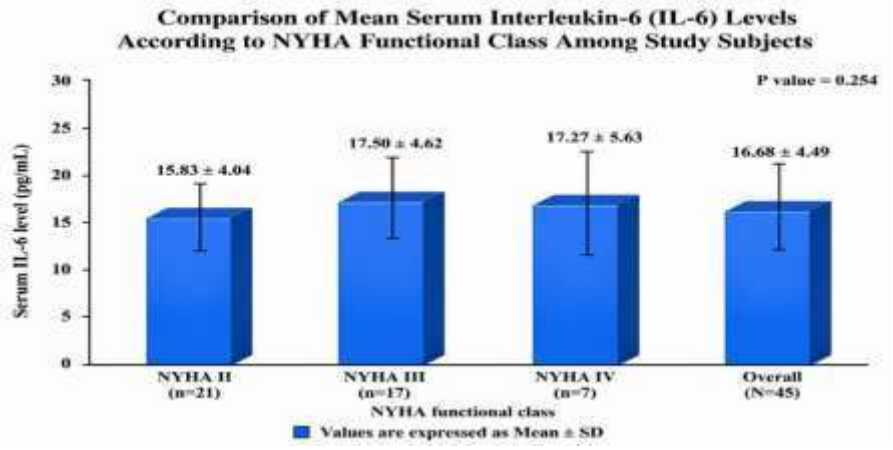


In the present study, the mean serum interleukin-6 (IL-6) level among the 45 study subjects was 16.68, with a standard deviation of 4.49

Table 5. Comparison of Mean Serum Interleukin-6 (IL-6) Levels According to NYHA Functional Class Among Study Subjects

Parameter	NYHA II (n=21), Mean ± SD	NYHA III (n=17), Mean ± SD	NYHA IV (n=7), Mean ± SD	Overall (N=45), Mean ± SD	P value
Serum IL-6 level	15.83 ± 4.04	17.50 ± 4.62	17.27 ± 5.63	16.68 ± 4.49	0.254

Graph 5. Comparison of Mean Serum Interleukin-6 (IL-6) Levels According to NYHA Functional Class Among Study Subjects

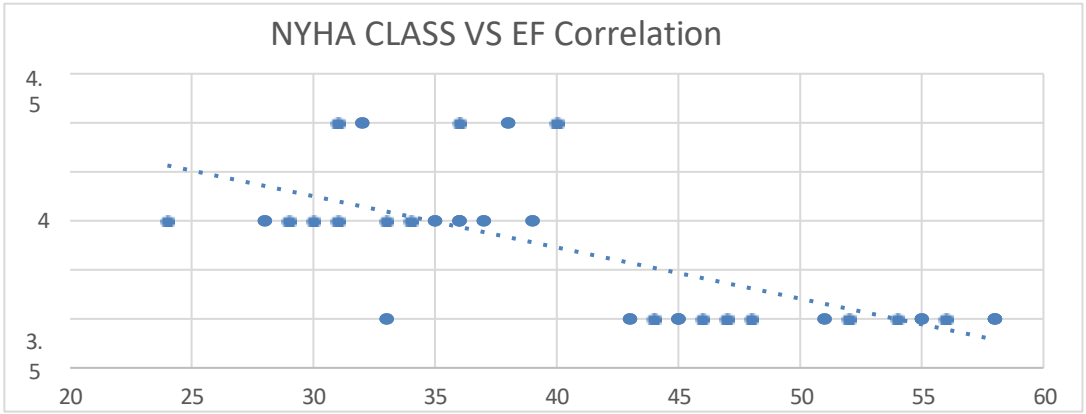


In the present study, the mean serum interleukin-6 (IL-6) level was 15.83 ± 4.04 among patients in NYHA Class II (n=21), 17.50 ± 4.62 among patients in NYHA Class III (n=17), and 17.27 ± 5.63 among patients in NYHA Class IV (n=7). The overall mean serum interleukin-6 (IL-6) level among the 45 study subjects was 16.68 ± 4.49. The difference in mean serum interleukin-6 (IL-6) levels across the NYHA functional classes was not statistically significant (P = 0.254).

Table 6. Correlation of Left Ventricular Ejection Fraction and Serum Interleukin-6 (IL-6) Levels with NYHA Functional Class Among Study Subjects

Variable correlated with NYHA class	Correlation coefficient (r)	P value	N	Interpretation
Ejection fraction	−0.669	0.001	45	Strong negative, statistically significant
Serum IL-6	0.153	0.316	45	Weak positive, not statistically significant

Graph 6. Correlation of Left Ventricular Ejection Fraction and Serum Interleukin-6 (IL-6) Levels with NYHA Functional Class Among Study Subjects

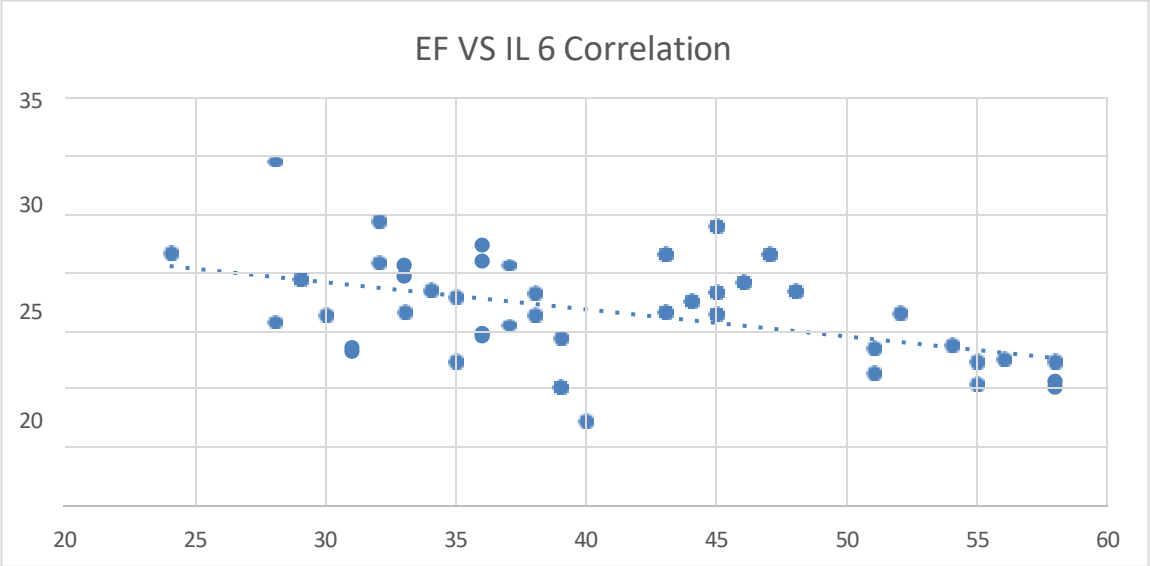


In the present study, left ventricular ejection fraction showed a strong negative correlation with NYHA functional class (r = −0.669) among 45 study subjects, and this correlation was statistically significant (P = 0.001). Serum interleukin-6 (IL-6) levels showed a weak positive correlation with NYHA functional class (r = 0.153) among 45 study subjects, and this correlation was not statistically significant (P = 0.316).

Table 7. Correlation Between Serum Interleukin-6 (IL-6) Levels and Left Ventricular Ejection Fraction Among Study Subjects

Variables	Correlation coefficient (r)	P value	N	Interpretation
Serum IL-6 and ejection fraction	−0.480	0.001	45	Moderate negative, statistically significant

Graph 7. Correlation Between Serum Interleukin-6 (IL-6) Levels and Left Ventricular Ejection Fraction Among Study Subjects



In the present study, serum interleukin-6 (IL-6) levels showed a moderate negative correlation with left ventricular ejection fraction (r = −0.480) among 45 study subjects, and this correlation was statistically significant (P = 0.001).

DISCUSSION

The present study evaluated serum interleukin-6 (IL-6) levels and their relationship with the clinical and echocardiographic severity of chronic heart failure in 45 patients. NYHA Class II was the most common functional category, comprising 46.67% of patients, followed by Class III in 37.78% and Class IV in 15.56%. The mean age was 54 ± 14 years, and neither age nor sex differed significantly among the NYHA classes. Similarly, diabetes mellitus and hypertension were not significantly associated with NYHA functional class. These findings indicate that the differences in functional severity observed in this cohort could not be attributed to significant variations in these baseline characteristics.

Diabetes mellitus and hypertension were present in 75.60% and 57.80% of patients, respectively. Although neither condition differed significantly across the NYHA classes, their high prevalence reflects the considerable cardiometabolic burden among patients with chronic heart failure. Lin et al. (2016) identified diabetes mellitus as an important risk factor for heart failure with preserved ejection fraction (14). These observations support the clinical importance of identifying and controlling associated cardiometabolic disorders in patients with heart failure.

Echocardiographic severity demonstrated a clear relationship with functional limitation. The mean ejection fraction decreased from 49 ± 7% in NYHA Class II to 35 ± 4% in Class III and 33 ± 4% in Class IV. This difference was statistically significant (p=0.001). NYHA class also demonstrated a strong negative correlation with ejection fraction (r=−0.669; p=0.001), indicating that worsening functional class was associated with declining ventricular systolic function. Shi et al. (2016), de Oliveira et al. (2013), Jia et al. (2014) and Zheng et al. (2017) likewise reported an association between lower ejection fraction and higher NYHA functional class.

The overall mean serum IL-6 level was 16.68 ± 4.49. Mean IL-6 levels were 15.83 ± 4.04, 17.50 ± 4.62 and 17.27 ±

5.63 in NYHA Classes II, III and IV, respectively. Although IL-6 was numerically higher in Classes III and IV than in Class II, the difference was not statistically significant (p=0.254). Correspondingly, IL-6 showed only a weak positive and statistically non-significant correlation with NYHA class (r=0.153; p=0.316). Thus, IL-6 was not associated with clinically assessed functional severity in the present cohort. In contrast, Iacoviello et al. (2011) reported a positive relationship between IL-6 and NYHA functional class. Differences in sample size, patient characteristics and heart-failure phenotypes may explain this variation.
Importantly, serum IL-6 demonstrated a moderate negative correlation with ejection fraction (r=−0.480; p=0.001). Therefore, increasing IL-6 levels were significantly associated with worsening echocardiographic cardiac function. This finding agrees with Sattar et al. (2014), Luzak et al. (2006) and Iacoviello et al. (2011), who reported inverse relationships between IL-6 and left ventricular ejection fraction. Kanda and Takahashi (2004) also linked increased IL-6 with deterioration of cardiac function and heart-failure progression. Overall, IL-6 was associated with objective echocardiographic severity but not with NYHA functional class, suggesting that it may reflect myocardial dysfunction more closely than symptom-based functional limitation.

CONCLUSION

The present study evaluated serum interleukin-6 levels and their relationship with the severity of chronic heart failure among 45 patients. NYHA Class II was the most common functional category, followed by Classes III and IV. The overall mean serum IL-6 level was 16.68 ± 4.49. Although serum IL-6 levels were numerically higher in NYHA Classes III and IV than in Class II, the difference and correlation with NYHA class were not statistically significant. Conversely, serum IL-6 demonstrated a statistically significant moderate negative correlation with left ventricular ejection fraction, indicating that higher IL-6 levels were associated with poorer ventricular systolic function. Ejection fraction also decreased significantly with increasing NYHA functional class. These findings suggest that serum IL-6 is more closely associated with objective echocardiographic severity than with symptom-based functional classification. Therefore, IL-6 may serve as a supplementary marker of myocardial dysfunction in chronic heart failure, although larger prospective studies are required to establish its clinical and prognostic utility..

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