Therapeutic Stratification in Chronic Heart Failure: A 52-Weeks Prospective Study

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ABSTRACT

Background: Chronic heart failure (CHF) is a complex syndrome in which systemic inflammation may play a role in its progression and complications. Interleukin-6 (IL-6) is a potential biomarker of inflammation. The aim of this study was to assess the predictive value of baseline IL-6 in CHF.

Materials and methods: This was randomized, double-blind study at the Practical Medical Center of Cardiology, Uzbekistan, between January 2024 and January 2025. We included 165 adult patients with CHF and randomized them to receive standard therapy plus IV iron (n=83) or standard therapy (n=82). Participants had a medical history, NYHA class, transthoracic echocardiography, NT-proBNP, ferritin, transferrin saturation, and serum IL-6 (ELISA) at baseline. The primary outcome was the composite of death and/or hospitalization.

Results: Baseline demographic, clinical, echocardiographic, and laboratory characteristics were comparable between groups. Patients with IL-6≥7 pg/mL had significantly worse event-free survival than those with IL-6<7 pg/mL. By 42 weeks, event-free survival declined to 53% in the high IL-6 group, compared with 77% in the low IL-6 group. Elevated IL-6 was associated with a markedly increased risk of death and/or hospitalization (HR 3.12; 95% CI 1.84-5.29; p<0.0001). Among patients with elevated IL-6, intravenous iron therapy showed a favorable trend toward improved event-free survival (HR=0.54; p≈0.08). NYHA IV status further worsened prognosis in the high IL-6 subgroup.

Conclusions: Baseline IL-6≥7 pg/mL identifies a high-risk inflammatory phenotype in chronic heart failure and may improve prognostic stratification and individualized therapeutic decision-making.

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Introduction

Heart failure (HF) is one of the primary health issues worldwide that presents significant clinical and socioeconomic demands despite the great improvements in evidence-based treatment in the last few decades [1,2]. HF is a multifactorial and heterogeneous syndrome, which occurs not only due to structural defects of the cardiac system, but also due to processes taking place in the rest of the body, including the activation of neurohormones, the dysregulation of metabolism, kidney dysfunction, and chronic inflammation of low grade [3,4]. There is a high degree of variability in the progression of the disease: patients with similar clinical presentations can have significantly different outcomes, and it is this fact that highlights the weakness of traditional risk indicators in completely reflecting the underlying pathophysiology [5,6].

Gaining momentum, chronic inflammation has been recognized as a primary pathogenesis in HF, and interleukin -6 (IL-6) has been found to be a key mediator [7,8]. IL-6 is a pleiotropic cytokine that is implicated in immune signalling, Acute-phase hepatic response, endothelial control and metabolic regulation [9,10]. In the cardiovascular system, IL-6 induces cardiomyocyte hypertrophy, fibroblast activation, endothelial dysfunction, and disruption of myocardial energy metabolism, and thus leads to adverse remodelling and progression of HF [11]. The levels of circulating IL 6 are always high in patients with HF than in healthy persons, especially during late stages of the disease [12,13]. However, it is still debatable whether IL-6 is mostly a marker of disease severity or has a direct pathogenic effect in disease deterioration [14]. The fact that unexpected decompensation can occur to clinically stable patients is an indicator that inflammatory activation indicated by IL-6 levels can be a prior occurrence prior to clinical worsening [6,13].

Observational studies of IL-6 as a prognostic variable in HF have also been conducted, the majority of which show the relationship of high levels of IL-6 with higher mortality or risk of hospitalization [11,14]. Nevertheless, these correlations are not uniform across the studies, in others, the predictive power of IL-6 is decreased when comorbidities or kidney impairment or other biomarkers are included [8,11]. Additionally, numerous studies that have been conducted before were either cross-sectional or used more traditional regression models that might not be sufficient to dealing with time-varying outcomes of HF [12]. Survival analysis delivers a more stringent methodological framework, which allows the right treatment of censored data and dynamic risk

assessment during follow-up [7,15]. Nevertheless, there are comparatively few studies that have used detailed survival-based designs to assess IL-6 and even less that have examined whether or not IL-6 stratification characterizes clinically significant survival patterns [13,14].

It is unclear how IL -6 measurement has therapeutic implications. The ideal biomarker must not only be predictive but also informative in terms of the magnitude of treatment as well as in patient selection [14,15]. Despite the proven efficacy of IL 6-targeted anti-inflammatory interventions in other chronic inflammatory diseases, they are not properly defined in the context of HF, and they might need proper risk stratification [8].

Purpose of the study: The aim of this study was to assess the predictive value of baseline IL-6 in CHF. In particular, our objectives included finding out whether IL-6 alone predicts adverse outcomes after a prolonged period, whether IL-6-related stratification results in specific survival patterns/curves, and whether IL-6 can be valuable in risk stratification in treatment in the clinical sub-population and therapeutic sub-population.

Materials and Methods

Study design and population

This was randomized double blind prospective single-centered study carried out in the Samarkand Regional Branch of the Republican Specialized Scientific and Practical Medical center of Cardiology, Samarkand, Uzbekistan. Recruitment of patients was done between January 2024 and January 2025. A total of 165 adult patients with CHF were randomized in an 1:1 allocation ratio into two treatment groups: standard guideline-based heart failure therapy combined with intravenous iron therapy (n=83) and standard heart failure therapy alone (n=82). Random sequence generation, allocation concealment, and maintenance of blinding were performed throughout the study to minimize bias. Eligible participants were aged 18 years or older and had a documented clinical history of CHF for at least three months before inclusion. CHF patients were included regardless of left ventricular ejection fraction status, allowing enrollment of both heart failure with reduced or preserved ejection fraction.

Clinical assessment and follow-up

Upon baseline, a detailed clinical assessment of the participants was conducted that involved medical history, physical examinations, and functional status assessment based on the NYHA classification. The assessment of left-ventricular functioning was conducted with standard transthoracic echocardiography. Routine laboratory tests included general blood analysis, biochemical, urine test, and NT-proBNP. Follow-up visits were to be made at a frequency of 3 months. The outcomes were collected at the clinic visits and by reviewing the medical record. The main outcome was a composite of all causes of mortality and/or heart failure hospitalization. Time-to-event was determined as the interval between the date of the IL-6 baseline to the first event or to the last follow-up.

Measurement of IL-6

Measurement of the venous blood samples was done at baseline under resting conditions and ADC ELISA-200 was used to measure serum IL-6 levels. The processing of samples in the same laboratory was done to reduce inter-assay variability, however some pre-analytical variability could not be completely eliminated. According to the exploratory analyses and previous literature, a cut-off value of 7pg/mL was used to stratify the patients into two groups.

Therapeutic stratification

All the participants were provided with guideline-based medical treatment of heart failure. Intervention group recived intravenous iron therapy (ferric carboxymaltose) was conducted as per the local practice as well as clinical indications. To investigate the variations in the extent of event-free survival, patients with higher IL-6 levels (≥ 7pg/mL) were further stratified by the treatment strategy (standard HF therapy alone or HF therapy with intravenous iron) to explore the possible difference.

Distribution dependent on the expression of continuous variables in mean standard deviation or median interquartile range, whereas categorical variables were expressed in frequencies and percentages. The Kaplan Meier method was used to do the survival analyses and log rank test was used to determine the difference between groups. To determine the association between IL-6 concentrations and outcomes, a cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% CIs. Subgroup analysis was done based on therapy group and NYHA classification in the high-IL-6 group. The statistical significance was taken to be two-sided $p<0.05$. R studio 4.5.1 were used to conduct statistical analyses.

Results

Baseline Characteristics

Baseline characteristics of the 165 enrolled patients randomized into two groups are presented in Table 1. The two groups were generally well balanced, with no statistically significant differences observed across major demographic, clinical, or laboratory parameters. The mean age was 65.1±11.6 years in the IV iron group and 67.3±10.9 years in controls (p=0.26), and approximately half of the patients were male (55.4% vs. 51.2%, p=0.75).

Most participants had HFrEF (75.9% vs. 71.9%, p=0.88), while HFpEF accounted for about one quarter in both groups. NYHA functional class distribution was comparable, with similar proportions across classes I-IV. Left ventricular systolic function was moderately reduced in both groups (mean LVEF 36.4±6.2% vs. 37.8±5.7%, p=0.21). Ferritin and TSAT levels were also comparable between groups, with about half of patients exhibiting TSAT <20%. Median IL-6 levels were inconsiderably higher in the control group (7.6 [5.4-11.2] pg/mL) compared with the IV iron group (6.8 [4.9-9.6] pg/mL) (p=0.09).

According to survival analysis, individuals with IL-6 ≥7 pg/mL demonstrated a significantly reduced probability of event-free survival throughout follow-up. By approximately 40 weeks, survival probability declined to nearly 50% in the high IL-6 group, while remaining above 75% in patients with

IL-6<7 pg/mL. Elevated IL-6 was associated with a more than threefold increase in risk of death and/or hospitalization (HR 3.12; 95% CI 1.84-5.29; p<0.0001), confirming its strong prognostic relevance.

Table 1. Baseline characteristics of study population

Characteristic	IV Iron Group N=83	Control Group N=82	p-value
Mean Age (years)	65.1±11.6	67.3±10.9	0.26
Male n(%)	46 (55.4%)	42 (51.2%)	0.75
HFrEF (%)	63 (75.9%)	59 (71.9%)	0.88
HFpEF (%)	20 (24.1%)	23 (28.1%)	0.41
NYHA 1	16 (19.3%)	14 (17.1%)	0.94
NYHA 1I	25 (30.1%)	28 (34.1%)	
NYHA III	26 (31.3%)	24 (29.3%)	
NYHA 1V	16 (19.3%)	16 (19.5%)	
Mean LVEF (%)	36.4±6.2	37.8±5.7	0.21
Median LVEF (%)	35.6 (IQR: 29.7-38.9)	36.1 (IQR: 30.2-39.1)	0.56
Serum Ferritin (µg/L)	57.9±16.2	54.7±12.6	0.71
Serum Ferritin (µg/L)	51 (IQR: 29-71)	49 (IQR: 31-67)	0.67
Median IL-6 (pg/mL)	6.8 (IQR: 4.9-9.6)	7.6 (IQR: 5.4-11.2)	0.09
TSAT (%)	15 (IQR: 12.4-18.2)	15 (IQR: 12.5-18.2)	0.84
TSAT <20%	45 (54.2%)	43 (51.2%)	0.43

Note: *HFrEF-Heart Failure with Reduced Ejection Fraction, TSAT-Transferrin Saturation, HFpEF-Heart Failure with Preserved Ejection Fraction, LVEF-Left Ventricular Ejection Fraction.*

Among patients with elevated IL-6, intravenous iron therapy was associated with improved survival compared with standard HF treatment. Although the difference did not reach conventional statistical significance (HR 0.54; p≈0.08), the consistent separation of survival curves suggests a clinically meaningful protective effect.

Functional class profoundly affected the prognosis of the IL-6 high patients. Patients with NYHA IV had a substantially greater drop in event-free survival than NYHA III. The survival probability in NYHA IV patients at 40 weeks was 30-35% compared to 65-70% for NYHA III patients (p=0.0052).

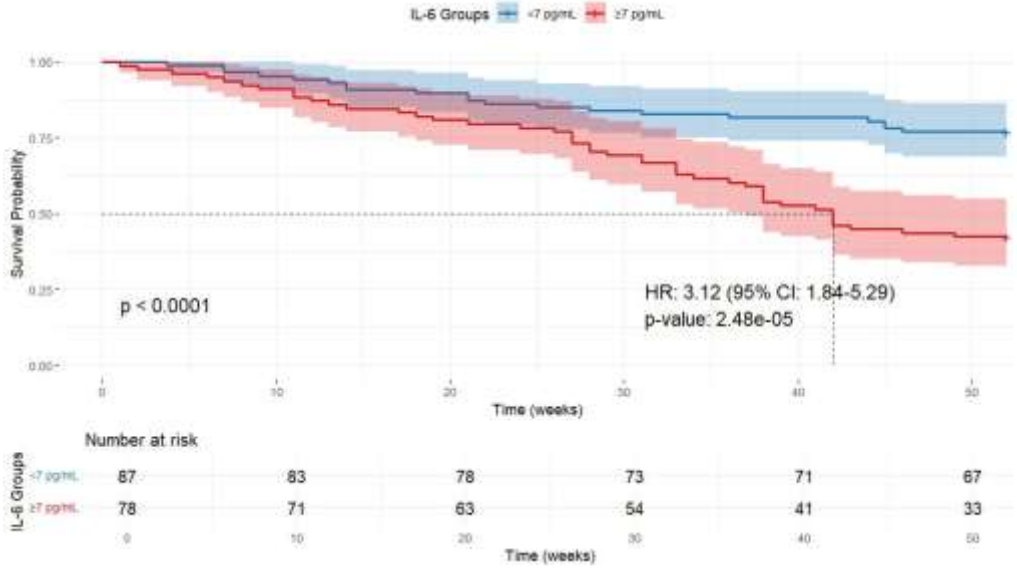


Figure 1. Prognostic Impact of Elevated IL-6 (≥7 pg/mL) on Survival in Patients with Heart Failure

Discussion

Our survival analysis reveals a strong association of high IL-6 with poor prognosis in CHF. In our study, patients with IL-6 ≥7 pg/mL had significantly worse event-free survival than patients with IL-6 <7 pg/mL (53% vs 77% by 42 weeks), and elevated IL-6 was associated with a more than three-fold increase in the risk of death and/or hospitalisation (HR 3.12; 95% CI 1.84-5.29; p<0.0001). This is in line with

other studies that demonstrated association between IL-6 and other inflammatory cytokines with heart failure severity, hospitalisation and death [6,11-13]. Biologically, this is plausible because IL-6 plays a role in systemic inflammation, endothelial dysfunction, myocardial remodeling, cardiomyocyte hypertrophy and metabolic dysfunction [3-5,9].

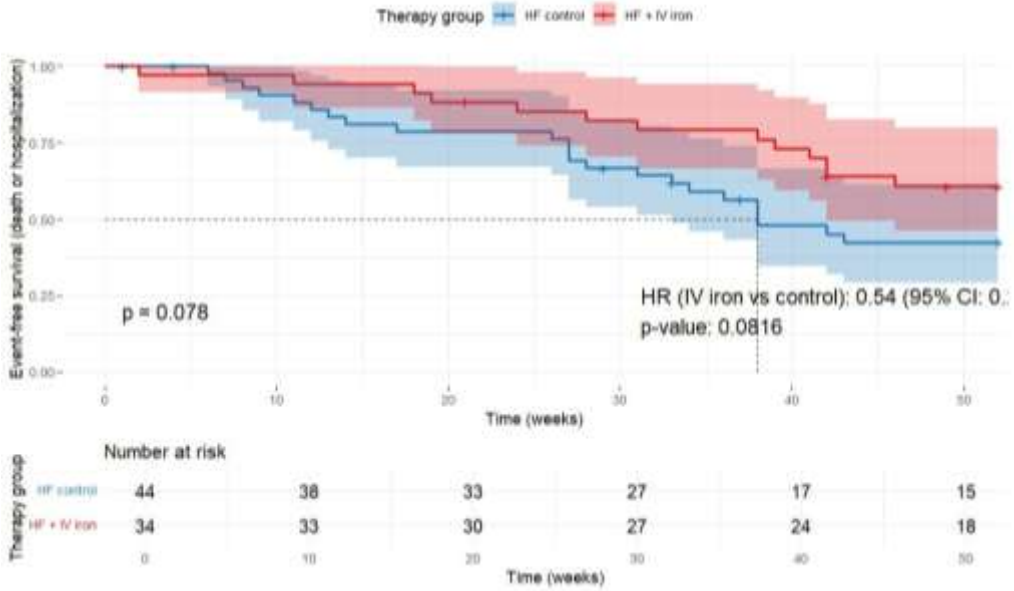


Figure 2. Impact of Intravenous Iron on Event-Free Survival in Patients with Elevated IL-6 (≥7 pg/mL)

In our study, intravenous iron treatment for patients with high IL-6 levels had a promising trend in event-free survival (HR=0.54; p≈0.08), which suggests that restoring the iron homeostasis in the inflammatory state may be beneficial, although this finding should be interpreted with caution. Moreover, NYHA IV status was associated with poor outcome in the high IL-6 group, suggesting that using both inflammatory biomarkers and clinical classification may provide better risk stratification, consistent with the general notion that biomarkers can be used to enhance the prognostic evaluation in heart failure [15,16]. In summary, our results support that IL-6 defines a high-risk inflammatory subpopulation in chronic heart failure and could be used for individual monitoring and decision on therapy.

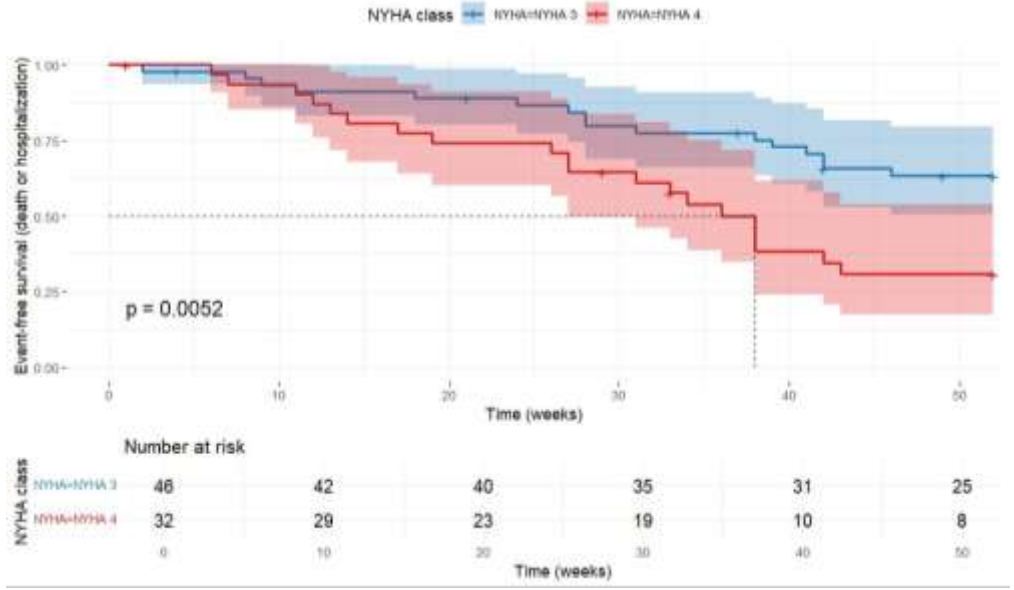


Figure 3. Event-Free Survival in Patients with Elevated IL-6 (≥7 pg/mL) Stratified by NYHA Functional Class

Conclusions

High IL-6 levels are a strong independent marker for poor prognosis in patients with heart failure. IL-6 confirms the presence of a high-risk inflammatory HF phenotype with a high mortality risk. Intravenous iron administration may improve the risk of CHF patients with high IL-6 and NYHA class exacerbates IL-6 risk. Clinical implication of IL-6 levels may improve risk stratification and personalised therapy in HF.

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