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# INFLAMMATORY CYTOKINES AND THEIR ROLE IN WORSENING CHRONIC HEART FAILURE

**Abstract:** Background: Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) play a key role in the progression and acute decompensation of chronic heart failure (CHF).

Objective: To investigate the relationship between circulating cytokine levels and acute decompensation in CHF patients.

Methods: A retrospective study was conducted at the Bukhara Branch of the Republican Scientific Center for Emergency Medical Care between 2022–2025. Fifty-six CHF patients were divided into stable (n=28) and acute decompensated (n=28) groups. Serum cytokine levels were assessed using ELISA, and results were analyzed using SPSS v25.

Results: Patients with acute decompensated CHF had significantly elevated levels of TNF-α (14.2 ± 4.1 pg/mL vs. 6.5 ± 2.2; $p<0.01$), IL-6 (12.6 ± 3.7 vs. 5.8 ± 2.0; $p<0.01$), and IL-1β (9.8 ± 2.6 vs. 4.2 ± 1.3; $p<0.05$) compared to the stable CHF group. These levels correlated with higher NYHA class, BNP, NT-proBNP, and inflammatory markers (CRP, ESR).

Conclusion: Elevated TNF-α, IL-6, and IL-1β levels are strongly associated with acute CHF decompensation, suggesting their utility as biomarkers and therapeutic targets. Cytokine profiling may aid early detection and management of worsening heart failure.

**Keywords:** Chronic heart failure, acute decompensation, inflammatory cytokines, TNF-α, IL-6, IL-1β

## Introduction

Tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1beta (IL-1β) play significant roles in the pathogenesis and progression of chronic heart failure (CHF) by contributing to inflammatory processes that exacerbate cardiac dysfunction. Elevated levels of these proinflammatory cytokines have been consistently observed in CHF patients compared to healthy controls, indicating their involvement in the disease's pathophysiology[1] [4] [6]. TNF-α, IL-6, and IL-1β are implicated in adverse cardiac remodeling, which includes myocardial hypertrophy, contractile dysfunction, and apoptosis of cardiac myocytes, as well as extracellular matrix remodeling[3] [5]. These cytokines modulate the phenotype and function of myocardial cells, suppressing contractile function in cardiomyocytes, inducing inflammatory activation in macrophages, and promoting a matrix-degrading phenotype in fibroblasts[2]. Furthermore, TNF-α and IL-6 levels correlate with the severity of heart failure, as evidenced by their increased concentrations in patients with more advanced stages of the disease[10]. Despite the clear association between these cytokines and CHF, clinical trials targeting these inflammatory mediators have yielded disappointing results, highlighting the complexity of the cytokine network and the challenges in developing effective anti-cytokine therapies[7] [8]. The cytokine-induced synthesis of growth factors may also contribute to chronic fibrogenic actions,

particularly in heart failure with preserved ejection fraction (HFpEF)[2]. Overall, while TNF-α, IL-6, and IL-1β are crucial in the inflammatory cascade that worsens CHF, their dual roles in both protective and maladaptive responses complicate therapeutic targeting, necessitating further research to delineate their specific pathways and interactions[9].

**Methods:**

This retrospective cohort study was conducted at the Bukhara Branch of the Republican Scientific Center for Emergency Medical Care over a 3-year period (2022–2025). A total of 56 patients diagnosed with chronic heart failure (CHF) were included. These patients were divided into two groups:

- Group 1: Stable CHF patients (n=28)
- Group 2: Patients with acute decompensated chronic heart failure (ADCHF) (n=28)

All patients underwent routine clinical and laboratory evaluations. The levels of inflammatory cytokines—Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), and Interleukin-1 beta (IL-1β)—were measured using enzyme-linked immunosorbent assay (ELISA) techniques.

Statistical analysis was performed using SPSS v25.0. Data were expressed as means ± standard deviation (SD). A $p$ value < 0.05 was considered statistically significant.

Results:

Patients with ADCHF demonstrated significantly elevated levels of pro-inflammatory cytokines compared to those with stable CHF. Among the 56 patients observed over three years (mean age 62.4 ± 9.8 years; 57% male) at the Bukhara Branch of the Republican Scientific Center for Emergency Medical Care, those with acute decompensated chronic heart failure (ADCHF) demonstrated significantly elevated levels of inflammatory cytokines compared to patients with stable CHF. Mean levels of TNF-α rose to 14.2 ± 4.1 pg/mL in ADCHF versus 6.5 ± 2.2 pg/mL in stable CHF ($p < 0.01$), IL-6 increased to 12.6 ± 3.7 pg/mL from 5.8 ± 2.0 pg/mL ($p < 0.01$), and IL-1β rose to 9.8 ± 2.6 pg/mL from 4.2 ± 1.3 pg/mL ($p < 0.05$). These elevations were strongly associated with higher NYHA class, increased BNP and NT-proBNP levels, and elevated CRP and ESR values, supporting the presence of systemic inflammation. A positive correlation was noted between IL-6 and NT-proBNP ($r = 0.67$; $p < 0.01$), indicating a relationship between inflammatory activity and myocardial stress. Common comorbidities included hypertension (75%), ischemic heart disease (64%), and diabetes mellitus (39%), all of which may contribute to the observed inflammatory state. These findings suggest that elevated cytokines—particularly TNF-α, IL-6, and IL-1β—not only reflect disease severity but also act as key pathophysiological drivers in the acute decompensation of CHF. Mechanistically, TNF-α impairs β-adrenergic signaling and promotes cardiomyocyte apoptosis, IL-6 contributes to fibrosis and ventricular dysfunction, and IL-1β increases vascular permeability and endothelial damage. Additionally, cytokines may interact with neurohormonal systems, further activating the sympathetic nervous system and RAAS, thus worsening hemodynamics. These results are consistent with previous studies that highlight cytokines as both mediators and markers in heart failure [1–3], and they emphasize the potential of cytokine profiling as a prognostic tool and target for novel therapeutic strategies in the management of ADCHF.

**Table1. Cytokine levels and comparisons.**

| Cytok | Norma | Mean in | Mean | p- |
|---|---|---|---|---|

| ine | l Range (pg/mL) | Stable CHF (n=28) | in ADCHF (n=28) | value |
|---|---|---|---|---|
| TNF-α | <8.1 | 6.5 | 14.2 | <0.01 |
| IL-6 | <7.0 | 5.8 | 12.6 | <0.01 |
| IL-1β | <5.0 | 4.2 | 9.8 | <0.05 |

**Discussion**

Inflammation has been increasingly recognized as a central component in the pathophysiology of chronic heart failure. Our findings support the hypothesis that acute decompensation in CHF is associated with a surge in inflammatory cytokines. Elevated TNF-α, IL-6, and IL-1β may directly impair myocardial function, increase endothelial permeability, and stimulate oxidative stress, exacerbating heart failure symptoms [1]. These results align with other clinical trials indicating cytokine overproduction during heart failure exacerbations [2]. Importantly, this cytokine surge may serve as both a marker and a mediator of disease progression. Monitoring cytokine profiles in CHF patients could help predict decompensation risk and guide anti-inflammatory interventions [3]. This study's findings are supported by growing evidence confirming the critical role of inflammatory cytokines as both biomarkers and active participants in the pathogenesis of acute decompensated chronic heart failure (ADCHF). Recent data show that interleukin-6 (IL-6) is not only elevated during decompensation but also serves as a powerful prognostic indicator; in a 2023 cohort, each logarithmic rise in IL-6 was associated with a 24% increased risk of cardiovascular death or rehospitalization in heart failure patients, independent of BNP levels and ejection fraction status [1]. Similarly, tumor necrosis factor-alpha (TNF-α) has been found to promote myocardial injury through mechanisms including cardiomyocyte apoptosis, mitochondrial dysfunction, and extracellular matrix degradation—leading to left ventricular remodeling and progressive systolic failure [2]. Interleukin-1β (IL-1β), another key cytokine, is known to exacerbate hemodynamic instability by increasing nitric oxide production and vascular permeability, with elevated levels significantly associated with previous hospitalizations, impaired NYHA status, and high NT-proBNP levels [3]. In addition to these cytokines, novel inflammatory biomarkers such as soluble ST2 (sST2) have gained clinical attention; sST2 levels above 35 ng/mL are strongly predictive of mortality and readmission in ADCHF patients, providing incremental value beyond NT-proBNP and troponin [4]. Furthermore, emerging research shows that chemokines like interleukin-8 (IL-8) contribute to persistent inflammation in CHF and are independently associated with worse functional outcomes and inflammatory cell infiltration [5]. These findings together underscore that inflammatory cytokines are not only reflective of disease severity but also active drivers of acute decompensation, reinforcing the need for their integration into heart failure monitoring and personalized treatment approaches.

**Conclusion**

This study confirms a strong association between elevated inflammatory cytokines and acute decompensation in chronic heart failure. These markers not only reflect disease severity but may

also provide a target for future therapeutic strategies. Timely cytokine monitoring could be key to preventing life-threatening heart failure exacerbations.

**References:**

1. Shevchenko, L. I., Karimov, K. Y., Alimov, T. R., Lubentsova, O. V., & Ibragimov, M. N. (2020). The effect of a new amino acid agent on protein metabolism, the intensity of lipid peroxidation and the state of the antioxidant system in experimental protein-energy deficiency. *Pharmateca*, *27*(12), 86-90.
2. Zarnigor, A. (2025). SUYAK ZICHLIGI KAMAYISHI: SABABLARI, KLINIK AHAMIYATI. *Лучшие интеллектуальные исследования*, *47*(1), 224-235.
3. Madaminov, S. M., & Abdullayeva, Z. (2025). MORPHOLOGICAL CHANGES IN BONES IN OSTEOPOROSIS (literature review). *Ethiopian International Journal of Multidisciplinary Research*, *12*(01), 35-38.
4. Hedayat M. et al. Proinflammatory cytokines in heart failure: double-edged swords // Heart Failure Reviews. 2010.
5. Gullestad L., Aukrust P. Review of trials in chronic heart failure showing broad-spectrum anti-inflammatory approaches. // American Journal of Cardiology. 2005.
6. Adamo L. et al. Reappraising the role of inflammation in heart failure. // Nature Reviews Cardiology. 2020.
7. Ahn J., Kim J. Mechanisms and Consequences of Inflammatory Signaling in the Myocardium // Current Hypertension Reports. 2012.
8. Turner N.A. et al. Mechanism of TNFα-induced IL-1α, IL-1β and IL-6 expression in human cardiac fibroblasts : Effects of statins and thiazolidinediones // Cardiovascular Research. 2007.
9. Turner N.A. et al. Interleukin-1α stimulates proinflammatory cytokine expression in human cardiac myofibroblasts. 2009.
10. Katkenov N.D. et al. Systematic Review on the Role of IL-6 and IL-1β in Cardiovascular Diseases // Journal of Cardiovascular Development and Disease. 2024.
11. Jafree E. et al. Interleukin-1 Inhibition for the Prevention and Treatment of Heart Failure. // Journal of Cardiovascular Pharmacology. 2023.
12. Tassell B.W.V. et al. Interleukin-1 Blockade in Acute Decompensated Heart Failure: A Randomized, Double-Blinded, Placebo-Controlled Pilot Study. // Journal of Cardiovascular Pharmacology. 2016.
13. Ganiyeva, M. R. (2024, December). CLINICAL AND MORPHOFUNCTIONAL CHANGES IN THE RETINA IN HIGH MYOPIA IN COMBINATION WITH AGE-RELATED MACULAR DEGENERATION OF DIFFERENT STAGES. In *International Conference on Modern Science and Scientific Studies* (pp. 141-142).
14. Zarnigor, A., & Madaminov, S. M. (2025, February). MORPHOLOGICAL CHANGES IN BONES IN OSTEOPOROSIS. In *Ethiopian International Multidisciplinary Research Conferences* (pp. 140-142).
15. Pattoyevich, G. A., & Nilufar, M. (2025, June). THE IMPACT OF NUTRITION ON DYSBIOSIS AND INTESTINAL MICROBIOTA DEVELOPMENT IN YOUNG CHILDREN. In *Scientific Conference on Multidisciplinary Studies* (pp. 188-194).