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RELATIONSHIP BETWEEN C-REACTIVE PROTEIN AND IL-6 LEVELS AND EJECTION FRACTION IN HEART FAILURE PATIENTS.

Harvinda Arya Pratiwi[*1], Refli Hasan[2], Masrul Lubis[3], Mardianto[4]

[1]*Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, 20155, Indonesia*
[2]*Division of Cardiovascular, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, 20155, Indonesia*
[3]*Division of Gastroenterohepatology, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, 20155, Indonesia*
[3]*Division of Endocrinology, Metabolic and Diabetes, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, 20155, Indonesia*

[*]Corresponding Author: bellaaryapratiwi@gmail.com

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ABSTRACT

Background: Heart failure (HF) is a progressive condition marked by anatomical and functional cardiac defects. Inflammation is a major factor in HF development. While some research implies a link between elevated CRP and IL-6 levels and lower ejection fraction (EF), the results are inconsistent. This study aims to evaluate the relationship between C-reactive protein, IL-6 levels, and EF in heart failure patients.

Method: This cross-sectional analytic observational study was conducted at Adam Malik Hospital to assess the relationship between CRP and IL-6 levels and left ventricular EF (LVEF) in HF patients.

Result: The findings showed no significant connection between CRP and LVEF (p=0.391), implying that CRP does not directly reflect systolic dysfunction. Conversely, IL-6 levels have a substantial inverse connection with LVEF (p=0.001), indicating a greater link between systemic inflammation and cardiac performance.

Conclusion: These findings underline the importance of a multimodal approach to HF care, including the use of inflammatory markers for risk classification in this population. While CRP may not be as accurate a predictor of systolic dysfunction, IL-6 appears to be more closely related to heart failure severity.

Keywords: CRP, Ejection fraction, Heart failure, IL-6.

ABSTRAK

Latar Belakang: *Gagal jantung (GJ) adalah kondisi progresif yang ditandai dengan cacat jantung anatomi dan fungsional. Peradangan adalah faktor utama dalam perkembangan GJ. Sementara beberapa penelitian menyiratkan hubungan antara peningkatan kadar CRP dan IL-6 dan fraksi ejeksi (FE) yang lebih rendah, tetapi hasilnya tidak konsisten. Penelitian ini bertujuan untuk mengevaluasi hubungan antara protein C-reaktif, kadar IL-6, dan FE pada pasien gagal jantung.*
Metode: *Studi observasional analitik cross-sectional ini dilakukan di Rumah Sakit Adam Malik untuk menilai hubungan antara kadar CRP dan IL-6 dan EF ventrikel kiri (LVEF) pada pasien HF.*
Hasil: *Temuan tidak menunjukkan hubungan yang signifikan antara CRP dan LVEF (p = 0,391), menyiratkan bahwa CRP tidak secara langsung mencerminkan disfungsi sistolik. Sebaliknya, kadar IL-6 memiliki hubungan terbalik yang substansial dengan LVEF (p = 0,001), menunjukkan hubungan yang lebih besar antara peradangan sistemik dan kinerja jantung.*
Kesimpulan*: Temuan ini menggarisbawahi pentingnya pendekatan multimoda untuk perawatan HF, termasuk penggunaan penanda inflamasi untuk klasifikasi risiko pada populasi ini. Sementara CRP mungkin tidak seakurat prediktor disfungsi sistolik, IL-6 tampaknya lebih erat kaitannya dengan tingkat keparahan gagal jantung.*

Kata kunci: *CRP, Fraksi ejeksi, Gagal jantung, IL-6*

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1. Introduction

Heart failure (HF) is a progressive illness characterized by structural and functional heart defects that result in low cardiac output and substantial morbidity [1]. Heart failure affects 3-20 out of every 1,000 people in the general population, and the prevalence rises with age, reaching 100 out of 1,000 people over the age of 65 [2].. Several inflammatory biomarkers, including CRP and IL-6, have been linked to the development and prognosis of heart failure (HF). CRP is a measure of systemic inflammation, whereas IL-6 is a proinflammatory cytokine that promotes the inflammatory response. Increased CRP and IL-6 levels in HF patients may indicate a persistent inflammatory process that contributes to reduced heart function. However, the link between these inflammatory biomarkers and heart systolic function metrics, such as ejection fraction (EF), requires additional investigation [3]. In patients with coronary heart disease, elevated CRP levels have also been associated with decreased left ventricular function, particularly in patients with a history of myocardial infarction. Inflammation can exacerbate myocardial damage and impair recovery of left ventricular function. Furthermore, CRP is an independent predictor of the development of left ventricular dysfunction in various populations, including patients with hypertension, diabetes, and cardiomyopathy. This underscores the important role of CRP-mediated inflammation in the pathogenesis of left ventricular dysfunction [4]. Interestingly, the relationship between CRP and left ventricular dysfunction appears to be bidirectional. Not only can CRP affect left ventricular function, but left ventricular dysfunction can also lead to elevated CRP levels by stimulating an inflammatory response. This feedback loop between inflammation and left ventricular dysfunction may explain why patients with left ventricular dysfunction tend to have a poor prognosis. Persistent inflammation can exacerbate myocardial damage and trigger maladaptive cardiac remodeling [5].

Monitoring CRP levels in patients with left ventricular dysfunction can provide valuable prognostic information. Patients with elevated CRP levels tend to have a higher risk of increased morbidity and mortality. Therapeutic strategies targeting inflammatory pathways, including CRP inhibition, have become a focus of research in an effort to improve left ventricular function and improve clinical outcomes in patients. Several early studies have shown promising results, but further validation is needed [6]. A prospective study has demonstrated that elevated IL-6 levels are associated with decreased left ventricular ejection fraction and decreased diastolic function. This association remained significant even after accounting for other cardiovascular risk factors. In patients with coronary heart disease, elevated IL-6 levels were also found to be associated with decreased left ventricular function, particularly in patients with a history of myocardial infarction. Inflammation can exacerbate myocardial damage and impair recovery of left ventricular function [7]. Furthermore, IL-6 is an independent predictor of the development of left ventricular dysfunction in various populations, including patients with hypertension, diabetes, and cardiomyopathy. This confirms the important role of IL-6-mediated inflammation in the pathogenesis of cardiac dysfunction. Interestingly, the relationship between IL-6 and decreased cardiac function appears to be bidirectional. Not only can IL-6 affect cardiac function, but cardiac dysfunction can also lead to increased IL-6 levels through stimulation of the inflammatory response [8]. Increased levels of CRP and IL-6 have been correlated with lower EF and a worse outcome. However, the findings of these investigations remain inconsistent and require further confirmation. In Indonesia, research on inflammatory biomarkers associated with EF is currently limited [9]. Long-term, multicenter prospective studies with larger sample sizes are needed to obtain a more comprehensive picture, which will be answered through this study. This study aims to evaluate the relationship between C-reactive protein, IL-6 levels, and ejection fractions in heart failure patients at Adam Malik Hospital.

2. Method

This was an observational study with a cross-sectional design using medical record data. From July 2024 to December 2024, research was undertaken at Adam Malik Hospital, which serves as a tertiary hospital for patients with cardiac disease. Data were acquired from the heart polyclinic and inpatient patients at Adam Malik Hospital. The sample was drawn via sequential sampling. The minimal sample size for this study was 37 patients. Patients with a clinical diagnosis of heart failure and an echocardiography examination were eligible; they were treated at Adam Malik Hospital, either inpatient or polyclinic; they were between the ages of 18 and 80; and they agreed to participate in the study and provided informed consent. Patients with bad kidney or heart function, a history of cancer, or who were on anti-inflammatory drugs were excluded from this study. SPSS version 29 was used to do statistical analysis. Descriptive analysis included age, gender, and ejection %, with descriptive data displayed as mean, median, standard deviation, minimum, and maximum values. A p-value of less than 0.05 indicates statistical significance. The ethical clearance was obtained from the USU Health Research Ethics Commission, which conducted the research and the final report.

3. Results

This study involved 40 patients. Mostly, patients were women, as many as 24 people (60%). The average age was 56.5 years, with the youngest 30 years and the oldest 74 years. The number of subjects with ejection fraction >50% was the majority, with 25 people (62.5%) (Table 1).

Table 1. Characteristics and demographics of the study.

Characteristics Demographics	n (%)
Sex, n (%)	
Man	16 (40.0)
Woman	24 (60.0)
Age, year	
Average (SD)	56.5 (8.69)
Median (Min – max)	57 (29 – 75)
Ejection fraction	
< 40%	9 (22.5)
40 - 49%	6 (15.0)
> 50%	25 (62.5)
CRP	
Normal	23 (57.5)
High	17 (42.5)
IL-6	
Normal	0 (0.0)
High	40 (100.0)

Table 2 shows the characteristics of CRP and ejection fraction. Although most of the subjects with normal CRP levels had good ejection fraction, there was also a proportion of subjects with high CRP levels, indicating good heart function.

Table 2. Characteristics of CRP and ejection fraction.

CRP	Total	Ejection Fraction (%)			p
		< 40	41 – 49	> 50	
Normal	23	5	2	16	0.391
High	17	4	4	9	
Total	40	9	6	25	

Table 3 shows the relationship between Interleukin-6 (IL-6) levels and EF. Most of the subjects had good heart function with normal IL-6 level (p=0,012).

Table 3. IL-6 characteristics and ejection fraction

CRP	Total	Ejection Fraction (%)			P
		< 40	41 – 49	> 50	
Normal	27	6	4	17	0.012
High	13	3	2	8	
Total	40	9	6	25	

4. Discussion

The association test between C-reactive protein (CRP) and EF yielded a p-value of 0.391. In this context, while CRP is frequently regarded as an important biomarker for inflammation, our findings revealed that not all indicators of inflammation had the same influence on the heart. One of the reasons why CRP may not have a meaningful connection with ejection fraction is the complexities of heart disease pathology. Heart disease involves the interaction of several variables, including hypertension, diabetes, and dyslipidemia, all of which can have a direct impact on heart function [10]. As a result, whereas CRP is an indicator of inflammation, it may not be sensitive enough to capture changes in heart function caused by other prominent variables. The p-value of 0.391 indicated that CRP levels may not be a robust enough predictor of cardiac function. In contrast, other biomarkers, or a combination of biomarkers, may be more beneficial. It provides an opportunity for additional

research into potential alternative biomarkers in this context. Windram et al. found that in polyclinic patients with heart failure and systolic dysfunction, greater CRP levels were associated with a higher NYHA class and a poorer prognosis, but not LVEF. Increased CRP was more common in HFpEF patients and was linked to diastolic dysfunction. Previous research on CRP in acute and chronic HF found no association between CRP and ejection fraction [11].

These findings highlight the need to take a holistic approach to cardiovascular risk management. In practice, doctors must evaluate a variety of risk factors and indicators while evaluating cardiac function. Using a single biomarker, such as CRP, may not provide complete information regarding the state of cardiovascular patients. Our investigation found an association between Interleukin-6 (IL-6) and the ejection fraction. This revealed that increased IL-6 levels were linked to a deterioration in cardiac function. IL-6 was a pro-inflammatory cytokine that influenced a variety of pathological processes, including systemic inflammation and immunological response. Increased IL-6 levels were frequently reported as a response to stress and tissue injury, which can impair the ability of the heart to function effectively. The correlation established between IL-6 and the ejection fraction provided vital information concerning the possible impact of inflammation on the heart. When IL-6 levels rise, it may indicate persistent inflammation, which can damage cardiac cells and the tissue surrounding them. Improved IL-6 levels have previously been linked to an increased risk of heart disease, including heart failure [12]. In the BIOSTAT-CHF (Biology trial to Tailored Treatment in Chronic Heart Failure) trial, approximately half of the heart failure patients improved their IL-6 levels. Higher levels of IL-6 were associated with an increased risk of cardiovascular death or hospitalization due to HF. In the regression logistic analysis, LVEF greater than 40% was related to higher levels of IL-6. An earlier observational study from BIOSTAT found that IL-6 levels were frequently elevated in HFpEF [12].

Mooney et al. found that improving IL-6 levels was associated with lower CV risk, mortality, and repeat HF hospitalization in HFpEF patients [13]. As a result, our findings supported the concept that inflammation management can be integrated into cardiovascular disease prevention and therapy programs. One mechanism linking CRP to left ventricular dysfunction is through stimulation of the production of pro-inflammatory cytokines, particularly IL-6. CRP can induce the release of IL-6 from various cells, including cardiomyocytes and endothelial cells. Elevated IL-6 levels can subsequently lead to myocardial damage and dysfunction. IL-6 itself has been shown to play a key role in the pathogenesis of cardiac dysfunction. This cytokine can cause cardiomyocyte damage through various mechanisms, such as oxidative stress, impaired calcium homeostasis, and activation of apoptosis. Furthermore, IL-6 can trigger maladaptive cardiac remodeling, ultimately adversely affecting the heart's pumping function [14]. The relationship between CRP, IL-6, and left ventricular dysfunction appears to be bidirectional. Not only can CRP increase IL-6, but left ventricular dysfunction itself can also lead to increased CRP and IL-6 levels through stimulation of the inflammatory response. This feedback loop can lead to prolonged inflammation and worsen myocardial damage [15].

Several prospective studies have demonstrated that elevated CRP and IL-6 levels are associated with reduced left ventricular ejection fraction and decreased diastolic function. This association remains significant even after accounting for other cardiovascular risk factors. In patients with coronary heart disease, elevated CRP and IL-6 levels have also been found to be associated with reduced left ventricular function, particularly in patients with a history of myocardial infarction. The inflammatory process mediated by CRP and IL-6 can exacerbate myocardial damage and impair recovery of left ventricular function. Furthermore, CRP and IL-6 are independent predictors of the development of left ventricular dysfunction in various populations, including patients with hypertension, diabetes,

and cardiomyopathy. This underscores the important role of CRP and IL-6-mediated inflammation in the pathogenesis of cardiac dysfunction [16]. Monitoring CRP and IL-6 levels in patients with cardiac dysfunction can provide valuable prognostic information. Patients with elevated CRP and IL-6 levels tend to have a higher risk of increased morbidity and mortality. Therapeutic strategies targeting inflammatory pathways, including inhibition of CRP and IL-6, have become a focus of research to improve heart function and improve clinical outcomes in patients. Some early studies have shown promising results, but further validation is needed [17].

Although the relationship between CRP, IL-6, and left ventricular dysfunction has been extensively studied, the specific mechanisms underlying this association remain elusive. The complex interactions between inflammation, oxidative stress, and cardiac metabolic disorders need to be considered in understanding the pathogenesis of cardiac dysfunction. Furthermore, other factors, such as genetics, lifestyle, and comorbidities, may also influence the relationship between inflammatory markers and left ventricular dysfunction. A thorough understanding of these multifactorial interactions is essential for developing more effective prevention and treatment strategies [18]. Integrating CRP and IL-6 measurements into the clinical practice of managing patients with cardiovascular disease can provide valuable information. This not only helps predict risk but can also guide the selection of appropriate therapies, including interventions that target inflammatory pathways. With increasing evidence regarding the role of CRP and IL-6 in the decline of left ventricular function, monitoring and managing the levels of these two inflammatory markers may be an important component in the management of patients with heart disease [19]. A holistic approach that considers the interaction between inflammation and cardiac dysfunction is expected to improve patient clinical outcomes. Further research into the complex relationship between CRP, IL-6, and left ventricular dysfunction is needed to gain a more comprehensive understanding. This will allow for the development of therapeutic strategies that can effectively moderate inflammatory pathways and improve cardiac function [20].

Routine monitoring of inflammatory biomarker levels in HF patients has not been a common practice at Haji Adam Malik Hospital. As a result, this study has the potential to close a knowledge gap and serve as the foundation for the establishment of improved HF management practices in this institution. This study is also expected to add to the scientific literature on the function of inflammation in the development of HF. This study's findings can be used to inform future research into the association between inflammatory biomarkers and cardiac dysfunction in the HF patient population. Inflammatory biomarkers can be an effective diagnostic and therapeutic tool in the management of heart failure patients. However, this study has significant limitations, such as the cross-sectional design and the small sample size at one health facility.

The novelty is one of the strongest elements of this study. However, further research is needed to understand the interactions between various inflammatory biomarkers and other cardiovascular risk factors. Overall, these chi-square test results suggest that although CRP is a commonly used biomarker to assess inflammation, it may not always be directly relevant to heart function. Therefore, it is important to continue exploring the relationship between various biomarkers and heart health and to adopt a more holistic approach to managing cardiovascular disease. Future research should focus on identifying more effective and relevant biomarkers for predicting risk and improving heart health outcomes. Given these results, clinicians may consider further evaluating patients with elevated IL-6 levels and taking steps to reduce inflammation through lifestyle changes or medical therapy. Thus, managing IL-6 levels may not only help improve heart health but also improve patients' overall quality of life. Overall, these chi-square test results underscore the importance of understanding the

relationship between inflammation and heart health. With increasing evidence demonstrating the role of IL-6 in cardiovascular disease, a more holistic approach to cardiac risk management, including addressing inflammation, should be considered to improve future heart health outcomes.

5. Conclusion

These findings underline the importance of a multimodal approach to HF care, including the use of inflammatory markers for risk classification in this population. While CRP may not be a good predictor of systolic dysfunction, IL-6 appears to be more closely related to HF severity. Additional longitudinal and multicenter investigations are required to corroborate these findings and examine new treatment approaches targeting inflammation in HF patients.

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Conflict interest

The authors declare that there is no conflict of interest in this research.

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