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The Effect of TNF-α and FIB-4 Score on Diastolic Dysfunction in Child Pugh C Liver Cirrhosis

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Liver cirrhosis is a major global health concern, often complicated by cardiac dysfunction such as diastolic heart failure. Tumor necrosis factor-alpha (TNF-α) and FIB-4 score are widely used biomarkers in cirrhotic patients, but their predictive value for cardiac complications remains unclear. To determine the effect of TNF-α and FIB-4 scores on the severity of diastolic dysfunction in patients with Child-Pugh C liver cirrhosis. This analytical cross-sectional study included 40 Child-Pugh C cirrhotic patients. Serum TNF-α levels were measured using ELISA. Diastolic function was evaluated using echocardiography. Ordinal logistic regression was used to analyze the association between TNF-α, FIB-4, and diastolic dysfunction grades. The majority of participants had moderate (65.0%) or severe (35.0%) chronic inflammation based on TNF-α levels, with a median TNF-α of 45.52 pg/mL. Significant liver fibrosis (FIB-4 >3.25) was observed in 82.5% of participants. Grade I diastolic dysfunction was the most prevalent (52.5%). TNF-α levels were significantly associated with the degree of diastolic dysfunction (p=0.042), whereas FIB-4 scores showed no significant correlation (p=0.533). Elevated TNF-α is strongly associated with worsening diastolic dysfunction in Child-Pugh C cirrhosis, suggesting its role in systemic inflammation and myocardial injury. In contrast, the FIB-4 index may not reflect cardiac involvement in advanced cirrhosis. TNF-α may serve as a potential biomarker for cardiovascular risk stratification in cirrhotic patients, supporting early intervention and integrated care approaches.

Keywords: Tumor Necrosis Factor-alpha, FIB-4 Score, Diastolic Dysfunction, Child-Pugh C Cirrhosis, Inflammation

INTRODUCTION

Liver cirrhosis is a global health burden, contributing significantly to morbidity and mortality. In addition to hepatic complications, cardiac involvement such as left ventricular diastolic dysfunction is increasingly recognized as a component of cirrhotic cardiomyopathy (Peng et al., 2016; Sharma & John, 2022). Early identification of this complication remains a challenge, especially in decompensated stages of cirrhosis classified as Child-Pugh C (Bodys-Pełka et al., 2021).

The pathophysiology of cirrhotic cardiomyopathy involves chronic systemic inflammation, oxidative stress, and neurohormonal disturbances. Tumor necrosis factor-alpha (TNF-α), a key pro-inflammatory cytokine, plays a significant role in these processes by promoting nitric oxide production and calcium regulation abnormalities, which contribute to impairedmyocardial contractility (Jang et al., 2021; Silva et al., 2019). TNF-α also affects other organs and may be associated with the severity of cardiovascular dysfunction in cirrhotic patients (Mocan et al., 2019).

The FIB-4 score is a widely used noninvasive tool for estimating liver fibrosis based on laboratory parameters. While it has established value in hepatic disease assessment, its potential role in reflecting extrahepatic complications such as cardiac dysfunction remains unclear. Some studies suggest its limited association with diastolic dysfunction, and its utility in predicting cardiac outcomes is still under debate (So-Armah et al., 2020; Xu et al., 2022; Yang et al., 2024).

This study aims to determine the relationship between TNF-α levels and FIB-4 scores with the severity

of left ventricular diastolic dysfunction in patients with Child-Pugh C liver cirrhosis. The findings are expected to contribute to the identification of clinical biomarkers that can aid in risk stratification and early detection of cirrhotic cardiomyopathy.

METHODS

Study Design and Setting

This study employed an analytical observational approach with a cross-sectional design. The study was conducted at Dr. Moewardi Surakarta Regional General Hospital, a tertiary level teaching hospital and regional referral centre. The aim was to evaluate the relationship between tumor necrosis factor-alpha (TNF-α) levels and Fibrosis-4 (FIB-4) score with diastolic dysfunction in decompensated liver cirrhosis patients of Child-Pugh C classification.

Study Population and Sampling

The target population included adult patients with Child-Pugh C liver cirrhosis who received inpatient or outpatient care at the Department of Internal Medicine, particularly the Gastroenterohepatology Division. Subjects were selected using a consecutive sampling method, including all patients meeting the inclusion criteria during the study period until the required sample size was achieved.

Inclusion and Exclusion Criteria

Research subjects were included if they fulfilled the inclusion criteria, namely:

1. Age ≥18 years,
2. Diagnosis of liver cirrhosis with child-pugh c classification based on clinical and laboratory data, and
3. Willing to participate in the study and sign informed consent.
4. The exclusion criteria included:
5. History of primary heart disease such as ischaemic heart disease, valvular disorders, or congestive heart failure,
6. Presence of acute infection or sepsis during the examination,
7. Presence of malignancy or autoimmune heart disease, and
8. Incomplete echocardiographic examination data.

Variable Measurement

The independent variables in this study were TNF-α levels and the FIB-4 score, while the dependent variable was the degree of left ventricular diastolic dysfunction. TNF-α levels were measured using peripheral venous blood samples analyzed via enzyme-linked immunosorbent assay (ELISA), and expressed in picograms per milliliter (pg/mL). Measurement of TNF-α concentration was performed using a microplate reader (iMark™, Bio-Rad Laboratories, USA), as per manufacturer's protocol.

Meanwhile, the FIB-4 score was calculated based on the formula:

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

The FIB-4 score was categorised as non-significant if ≤3.25 and significant if >3.25.

Left ventricular diastolic dysfunction was assessed through transthoracic echocardiographic examination performed by a certified cardiologist. Parameters analysed included septal e' wave velocity, E/e' ratio, left atrial volume index (LAVI), and tricuspid regurgitation (TR) velocity. The assessment of diastolic dysfunction was classified into normal function, Grade I, Grade II, and Grade III based on the American Society of Echocardiography guidelines.

Echocardiographic Assessment

All patients underwent transthoracic echocardiography performed by a single cardiologist using standard protocol. Diastolic dysfunction was graded based on mitral inflow pattern (E/A ratio), deceleration time (DT), and tissue Doppler imaging (e'), following the American Society of Echocardiography classification: Grade I (mild), Grade II (moderate), and Grade III (severe).

Study Procedures

After obtaining ethical approval and informed consent, patients who fulfilled the criteria were enrolled into the study. Laboratory examinations were performed to assess AST, ALT, platelet values, as well as TNF-α levels. Demographic and clinical data were recorded in the study data form. Echocardiographic examinations were performed under haemodynamically stable conditions, with no signs of acute infection or other emergencies that could affect cardiac interpretation.

Ethical Considerations

This study has received approval from the Health Research Ethics Committee of Dr Moewardi Hospital/Faculty of Medicine, Sebelas Maret University with number: 1.427/V/HREC/2024. All participants have given written consent before participating in the study according to the principles of the Declaration of Helsinki.

Statistical Analysis

Data analysis was conducted using SPSS version 25.00 software. Descriptive data were presented as median, minimum-maximum values, and percentages. The correlation between TNF-α levels and FIB-4 score with the degree of diastolic dysfunction was analysed using the Spearman correlation test. To determine the simultaneous and independent effects of the two independent variables on diastolic dysfunction, ordinal logistic regression analysis was performed. A *p* value of <0.05 was considered statistically significant.

interval. The selection of these statistical tests aimed to ensure that the results obtained were able to show the effects of the intervention in a valid manner and could be interpreted clinically.

RESULT AND DISCUSSION

TNF-α Value

The value of TNF-α in this study was presented in the following table 1.

Based on Table 1, the majority of cirrhotic patients in this study exhibited moderate chronic inflammation, accounting for 65.0% of the sample. Meanwhile, 35.0% of patients showed severe chronic inflammation, indicating a

predominance of moderate systemic inflammatory response among the study population

Table 1.
Distribution of Serum TNF-α Levels among Cirrhotic Patients by Inflammation Severity Classification

TNF-α	*f*	%
Category		
Moderate chronic inflammation	26	65.0%
Severe chronic inflammation	14	35.0%
TNF-α (pg/mL)**		

FIB-4 Score

The FIB-4 Score in this study was presented in the following table 2.

Table 2.
FIB-4 Scores among Study Participants Based on Fibrosis Severity Classification

Nilai FIB-4	*f*	%
Category		
Not significant	7	17.5%
Significant	33	82.5%
FIB-4**		

Table 2 shows that the majority of participants with Child-Pugh class C liver cirrhosis exhibited significant fibrosis, as indicated by FIB-4 scores in 82.5% of cases. A smaller proportion of participants (17.5%) showed non-significant fibrosis, suggesting a predominance of advanced hepatic fibrosis among the study subjects.

Diastolic Dysfunction

The diastolic dysfunction from the subjects in this study was shown in the following table 3.

Table 3.
Classification of Left Ventricular Diastolic Dysfunction among Study Participants

Diastolic dysfunction	*f*	%
Normal	12	30.0%
Grade I	21	52.5%
Grade II	6	15.0%
Grade III	1	2.5%

Table 3 indicates that diastolic function among patients with Child-Pugh class C liver cirrhosis was predominantly categorized as Grade I (52.5%), followed by normal diastolic function (30.0%), Grade II (15.0%), and Grade III (2.5%).

Correlation of TNF-α and FIB-4 with Diastolic Dysfunction

Correlation between these two variables was presented in the following figure 1.

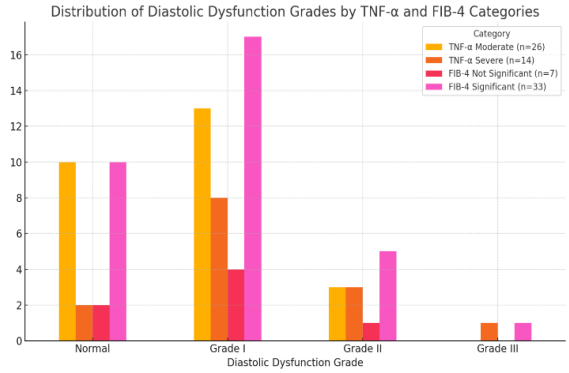

Figure 1. Distribution of Diastolic Dysfunction Grades by TNF-α and FIB-4 Categories

Figure 1 shows that among patients with moderate chronic inflammation based on TNF-α levels, the majority exhibited Grade I diastolic dysfunction (32.5%). Similarly, among those with severe chronic inflammation, most also presented with Grade I diastolic dysfunction (20.0%). Correlation analysis revealed an association between TNF-α levels and the degree of diastolic dysfunction in patients with Child-Pugh class C liver cirrhosis, with a p-value of 0.042, indicating statistical significance. The results indicate that among patients with significant fibrosis based on FIB-4 scores, the majority exhibited Grade I diastolic dysfunction (42.5%). Similarly, among those with non-significant fibrosis, most also presented with Grade I diastolic dysfunction (10.0%). Correlation analysis showed no association between FIB-4 values and the degree of diastolic dysfunction in patients with Child-Pugh class C liver cirrhosis, as indicated by a p-value of 0.533, which was not statistically significant.

Effect of TNF-α and FIB-4 Score on Diastolic Dysfunction

Multivariate analysis was conducted using Ordinal Logistic Regression with a significance level set at 0.05. The evaluation results regarding the influence of TNF-α and FIB-4 on the Degree of Diastolic Dysfunction in patients with Child-Pugh C liver cirrhosis are presented in the figure 2.

The figure 2. shows the p-values from the ordinal logistic regression analysis evaluating the influence of TNF-α and FIB-4 on the severity of diastolic dysfunction in patients with Child-Pugh class C liver cirrhosis. TNF-α demonstrates a statistically significant association ($p = 0.047$), indicating its potential role in predicting diastolic dysfunction severity. In contrast, FIB-4 does not show a significant association ($p = 0.658$), suggesting its limited predictive value for cardiac involvement in this population.

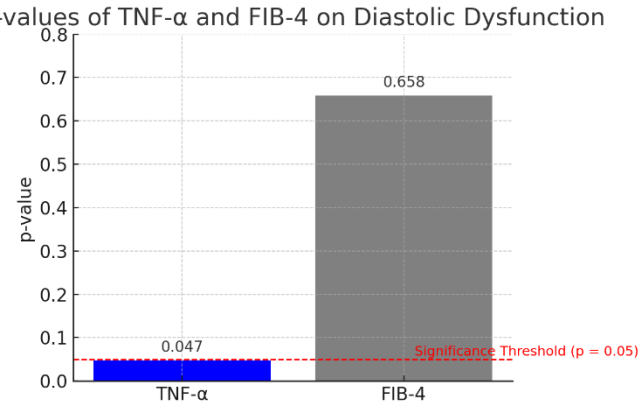

Figure 2. P-values of TNF-α and FIB-4 on Diastolic Dysfunction

Correlation Analysis

Liver cirrhosis is associated with heightened insulin resistance and systemic inflammation (Koncoro et al., 2017). Tumor Necrosis Factor-alpha (TNF-α), a cytokine with tumor-suppressing properties, interacts with two distinct receptors to initiate signal transduction pathways and cellular responses. However, persistent or excessive TNF-α activity contributes to chronic inflammation and various disease-related complications (Jang et al., 2021). As a multifunctional pro-inflammatory cytokine, TNF-α is primarily secreted by monocytes and macrophages. It belongs to the cytokine family, a group of immune molecules responsible for intercellular signaling and for coordinating both innate and adaptive immune responses. Cytokines exert their effects through various mechanisms based on their target location: they act in an autocrine fashion when affecting the cell that produced them, in a paracrine manner when influencing nearby cells, and in an endocrine manner when their effects are exerted on distant cells or tissues (Damanik et al., 2024).

TNF-α classification is based on its concentration levels in pg/mL, divided into the following ordinal categories:

1. Healthy: <5–10 pg/mL
2. Mild chronic inflammation: 10–20 pg/mL
3. Moderate chronic inflammation: 20–50 pg/mL
4. Severe chronic inflammation: >50 pg/mL

TNF-α levels in subjects with liver cirrhosis can also affect multiple organs that are associated with its concentration. High circulating TNF-α levels may lead to neurohormonal activation, cardiomyocyte hypertrophy, extracellular matrix protein production, as well as cardiomyocyte apoptosis and necrosis, which can subsequently result in left ventricular diastolic dysfunction (Mocan et al., 2019). Research findings indicate that TNF-α levels were above the normal range. This observation aligns with previous studies, which have reported elevated TNF-α concentrations in patients with chronic Hepatitis B (Bekçibaşı & Arslan, 2021). Damanik (2024) classified TNF-α levels using a cut-off value, distinguishing between normal (<81.9 ng/L) and elevated (>82 ng/L) levels. The mean TNF-α concentration in the case group was higher compared to the control group (187.661 ng/L vs. 78.315 ng/L).

Interpretation of Findings

Diastolic dysfunction of the left ventricle is recognized as a significant precursor to numerous cardiovascular conditions. Research over the last decade has increasingly highlighted the role of chronic, low-grade inflammation as a contributing factor in the development of heart failure. One of the key inflammatory mediators involved is tumor necrosis factor-alpha (TNF-α) (Mocan et al., 2019). TNF-α contributes to diastolic dysfunction by suppressing the expression of the SERCA2a gene through the IKK/IκB/NF-κB pathway, where NF-κB directly interacts with the SERCA2a promoter. Interestingly, this suppressive effect can be mitigated by simvastatin, suggesting that statins may have therapeutic value in treating inflammation-driven diastolic dysfunction (Tsai et al., 2015).

Individuals with left ventricular diastolic dysfunction often exhibit elevated serum levels of tumor necrosis factor-alpha (TNF-α), which show a positive association with the left atrial volume index (LAVI). Notably, patients diagnosed with Grade 2 diastolic dysfunction present with significantly higher TNF-α concentrations compared to those with Grade 1. Furthermore, TNF-α levels tend to rise in conjunction with the severity of heart failure symptoms (Missiri et al., 2020).

The findings of this study highlight the prognostic value of TNF-α in assessing the cardiovascular status of patients with liver cirrhosis. The observed increase in diastolic dysfunction in patients with elevated TNF-α levels suggests a significant correlation between hepatic and cardiac dysfunction, with important implications for clinical management. Simultaneous monitoring of both parameters is therefore necessary to improve care planning for patients with cirrhosis, particularly those classified as Child-Pugh C.

This study confirms that elevated TNF-α levels in Child-Pugh C cirrhotic patients are associated with more severe diastolic dysfunction. These findings reinforce the role of systemic inflammation marked by increased TNF-α in exacerbating organ dysfunction, particularly of the heart. As a pro-inflammatory cytokine, TNF-α not only reflects hepatic inflammation but also contributes to myocardial injury through mechanisms such as neurohormonal activation, oxidative stress, and apoptosis. Thus, TNF-α levels may serve as a biomarker to identify cirrhotic patients at high risk for cardiovascular complications.

The results of this study demonstrate that the FIB-4 score does not have a statistically significant association with diastolic dysfunction in patients with Child-Pugh C liver cirrhosis, as indicated by a p-value exceeding 0.05. These findings align with prior research, which reported no significant link between the NAFLD fibrosis score (NFS) or the FIB-4 index and the risk of left ventricular diastolic dysfunction (LVDD). For instance, although adjusted hazard ratios (aHR) for LVDD in individuals with APRI <

0.5 and APRI ≥ 0.5 were 1.20 (95% CI: 1.01–1.42) and 1.36 (95% CI: 0.90–2.06), respectively (P = 0.036), other fibrosis indices, including FIB-4, did not yield significant associations (Kim et al., 2024). Furthermore, no correlation between the FIB-4 index and LVDD was found based on LVEF measurements (Nakashima et al., 2022). Sato et al., (2017) observed no significant variation in echocardiographic LVEF parameters among different FIB-4 score categories.

The findings of this study indicate that, although most patients with Child-Pugh C liver cirrhosis presented with FIB-4 scores within a range suggestive of significant fibrosis, there was no statistically significant association between FIB-4 scores and the severity of left ventricular diastolic dysfunction (p = 0.533). This outcome suggests that the extent of liver fibrosis, as measured by the FIB-4 index, does not correlate directly with the degree of cardiac diastolic impairment in patients with advanced liver disease. As such, the FIB-4 index remains more appropriate for evaluating hepatic fibrosis than for assessing cardiovascular complications, particularly diastolic dysfunction.

Nevertheless, the FIB-4 index continues to hold clinical value as a noninvasive marker for estimating hepatic fibrosis and predicting prognosis in patients with chronic liver disease. Its utility in risk stratification supports informed decision-making regarding patient monitoring and therapeutic strategies. However, considering its limitations in detecting extrahepatic manifestations such as cardiac involvement its use should be complemented by more targeted diagnostic approaches. Incorporating additional tools specifically designed to evaluate systemic organ involvement may enhance diagnostic precision and improve the overall quality of patient care in the context of liver cirrhosis.

Comparison with Prior Studies

These findings align with previous research suggesting that TNF-α plays a crucial role in mediating myocardial dysfunction, particularly through mechanisms of inflammation, neurohormonal activation, and cellular remodeling. Studies have reported elevated TNF-α levels in patients with chronic viral hepatitis and cirrhosis, indicating its systemic involvement beyond hepatic injury (Bekçibaşı & Arslan, 2021; Mocan et al., 2019). Moreover, research by Tsai et al., (2015) and Missiri et al. (2020) also confirmed the correlation between increased TNF-α and worsening grades of diastolic dysfunction, supporting its potential as a prognostic biomarker for cardiac involvement.

In contrast, the lack of a statistically significant relationship between FIB-4 and diastolic dysfunction is consistent with findings by Kim et al., (2024), Nakashima et al., (2022), and Sato et al., (2017), who reported that fibrosis indices including FIB-4 did not correlate with echocardiographic parameters of cardiac dysfunction. This suggests that FIB-4, while useful for assessing hepatic fibrosis, may lack sensitivity for detecting subclinical cardiovascular complications.

Biological Mechanism Linking TNF-α to Diastolic Dysfunction

Tumor Necrosis Factor-alpha (TNF-α), a cytokine with tumor-suppressing properties, interacts with two distinct receptors to initiate signal transduction pathways and cellular responses. However, persistent or excessive TNF-α activity contributes to chronic inflammation and various disease-related complications (Jang et al., 2021). As a multifunctional pro-inflammatory cytokine, TNF-α is primarily secreted by monocytes and macrophages. It belongs to the cytokine family, a group of immune molecules responsible for intercellular signaling and for coordinating both innate and adaptive immune responses. Cytokines exert their effects through various mechanisms based on their target location: they act in an autocrine fashion when affecting the cell that produced them, in a paracrine manner when influencing nearby cells, and in an endocrine manner when their effects are exerted on distant cells or tissues (Damanik et al., 2024).

TNF-α levels in subjects with liver cirrhosis can also affect multiple organs that are associated with its concentration. High circulating TNF-α levels may lead to neurohormonal activation, cardiomyocyte hypertrophy, extracellular matrix protein production, as well as cardiomyocyte apoptosis and necrosis, which can subsequently result in left ventricular diastolic dysfunction (Mocan et al., 2019). Diastolic dysfunction of the left ventricle is recognized as a significant precursor to numerous cardiovascular conditions. Research over the last decade has increasingly highlighted the role of chronic, low-grade inflammation as a contributing factor in the development of heart failure. One of the key inflammatory mediators involved is tumor necrosis factor-alpha (TNF-α) (Mocan et al., 2019).

TNF-α contributes to diastolic dysfunction by suppressing the expression of the SERCA2a gene through the IKK/IκB/NF-κB pathway, where NF-κB directly interacts with the SERCA2a promoter. Interestingly, this suppressive effect can be mitigated by simvastatin, suggesting that statins may have therapeutic value in treating inflammation-driven diastolic dysfunction (Tsai et al., 2015).

Individuals with left ventricular diastolic dysfunction often exhibit elevated serum levels of tumor necrosis factor-alpha (TNF-α), which show a positive association with the left atrial volume index (LAVI). Notably, patients diagnosed with Grade 2 diastolic dysfunction present with significantly higher TNF-α concentrations compared to those with Grade 1. Furthermore, TNF-α levels tend to rise in conjunction with the severity of heart failure symptoms (Missiri et al., 2020).

Study Limitations

This study has several limitations. The cross-sectional design does not allow causal interpretation between TNF-α, FIB-4, and diastolic dysfunction. The relatively small sample size and single-center setting may limit the generalizability of the findings. Furthermore, other inflammatory markers and advanced imaging modalities were not evaluated, which could have provided

a more comprehensive cardiac assessment. Future longitudinal studies with larger populations are needed to validate these results and explore additional mechanisms.

CONCLUSION

In patients with Child-Pugh C liver cirrhosis, elevated TNF-α levels are significantly associated with more severe diastolic dysfunction, suggesting its role as a potential biomarker for cardiovascular risk. In contrast, the FIB-4 index does not show a significant correlation with cardiac involvement in this population. Regular monitoring of TNF-α levels may help identify cirrhotic patients at higher risk of cardiac complications. Future longitudinal studies are needed to assess its predictive value and potential role in guiding therapeutic interventions.

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