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Correlation Between TNF-α Levels and APRI Score with Ejection in Hepatic Cirrhosis

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Cirrhotic cardiomyopathy is a condition of heart dysfunction characterized by impaired myocardial contractility, left ventricular hypertrophy, diastolic dysfunction, chronotropic dysfunction, and electrophysiological disturbances of the heart. One of the complications in patients with hepatic cirrhosis is influenced by several factors, particularly TNF-α levels and the APRI score. This study aimed to analyze the effect of TNF-α and APRI score on ejection fraction in Child-Pugh C hepatic cirrhosis. Methods: This study employed an analytical observational design with a cross-sectional approach. The sample consisted of 40 inpatients with Child-Pugh C hepatic cirrhosis at the dr. Moewardi Surakarta Regional General Hospital. Samples were selected using consecutive sampling. Data analysis was performed using Spearman's correlation test and linear regression. Results: The correlation between TNF-α levels and ejection fraction in Child-Pugh C hepatic cirrhosis is r = -0.559, p<0.001 (moderate correlation). The correlation between APRI score and ejection fraction in Child-Pugh C hepatic cirrhosis is r = -0.445, p<0.001 (moderate correlation). There is a significant correlation between TNF-α levels and APRI score with ejection fraction in Child-Pugh C hepatic cirrhosis. The implication is that clinicians may incorporate TNF-α levels and the APRI score into clinical algorithms to monitor cirrhotic patients who are at high risk of developing cardiovascular complications.

Keywords: Tumor Necrosis Factor-alpha, APRI Score, ejection Fraction, Hepatic Cirrhosis

INTRODUCTION

The liver is a central component of the immune system, containing Kupffer cells, that play a crucial role in maintaining immune homeostasis (Nusse & Kubes, 2025). Kupffer cells play a key role in clearing foreign antigens and presenting these antigens to lymphocytes as part of the hepatic immune response (Zheng et al., 2023). The liver also contains numerous monocytes/macrophages, which originate from the bone marrow and migrate, especially during liver injury or infection (Li et al., 2022).

Cirrhosis is a chronic liver disease characterized by the loss of normal lobular architecture due to fibrosis, accompanied by the destruction of parenchymal cells and subsequent regeneration that forms nodules. In hepatic cirrhosis, the inflammatory mediator TNF-α plays a role (Guillot & Tacke, 2024). It regulates macrophage activity and immune responses in tissues by inducing the production of growth factors and other cytokines. In addition, the interaction between T and B lymphocytes with other immune cells in the liver indicates that the liver plays a crucial role as an immunological barrier and serves as a site for regulating immune tolerance (Hassan et al., 2023)

The APRI (Aspartate Aminotransferase to Platelet Ratio Index) score is a non-invasive predictor used to assess the degree of liver fibrosis. APRI is used to evaluate patients with liver disease caused by chronic hepatitis B, chronic hepatitis C, or other etiologies (Najafi et al., 2024). Recent studies also demonstrate that APRI is accurate for detecting cirrhosis in patients with chronic hepatitis B and C, although its sensitivity as a standalone predictor of fibrosis remains limited (Gür-Altunay & Yürük-Atasoy, 2023). In patients with NAFLD, APRI showed an AUC of 0.76, with a sensitivity of 80.8% and specificity of 63.2%

(Alam et al., 2025). Meanwhile, a systematic review reported that APRI performs better than FIB-4 in detecting advanced fibrosis (Yan et al., 2025).

TNF-α levels and APRI score can reflect the degree of inflammation and fibrosis in hepatic cirrhosis. Advanced-stage cirrhosis can influence the development of cardiomyopathy (Hu et al., 2024). Cirrhotic cardiomyopathy (CCM) was first described in 2005 during the World Congress of Gastroenterology in Montreal, defined as characteristic changes including systolic and diastolic dysfunction, along with electrophysiological abnormalities, in patients with liver cirrhosis. Previous research by Liu found that higher liver fibrosis scores including the APRI score, the AST/ALT ratio, and the GPR (gamma-glutamyl transferase to platelet ratio) were associated with an increased risk of heart-transplant mortality in patients with non-ischemic dilated cardiomyopathy (NIDCM) (Liu et al., 2023).

However, few studies have investigated the relationship between TNF-α, APRI score, and cardiac ejection fraction in patients with advanced hepatic cirrhosis. Therefore, this study aims to analyze the effects of TNF-α levels and the APRI score (Aspartate Aminotransferase to Platelet Ratio Index) on left ventricular ejection fraction in patients with Child–Pugh C hepatic cirrhosis.

METHODS

Research Type

This study employed an analytical observational cross-sectional design. A cross-sectional study is an observational research method that collects data at a single point in time from a sample selected based on specific inclusion and exclusion criteria.

Population and Study Subjects

Study participants included inpatients at RSUD Dr. Moewardi Surakarta and outpatients with Child-Pugh C liver cirrhosis at the Gastroenterohepatology Clinic. The study period was from April 2024 to April 2025. Patients selected as samples in this study were chosen based on meeting the inclusion criteria and the absence of any applicable exclusion criteria.
The exclusion criteria consisted of patients with diabetes mellitus with HbA1c ≥ 8.1% within the past 3 months, chronic obstructive pulmonary disease, chronic kidney disease stage IV to V according to the Kidney Disease Outcomes Quality Initiative (KDOQI) 2002 criteria, essential hypertension based on the JNC VII guidelines, coronary artery disease (CAD) or a history of CAD, severe valvular heart disease, cardiac tumors or pericardiac tumors causing cardiac compression, constrictive pericarditis or significant pericardial effusion, hemoglobin level ≤ 8 g/dL within the last 2 weeks, or active bleeding within the past week. The inclusion criteria were patients aged 18 years or older who were willing to participate in the study, as indicated by their signature on the informed consent form.

The minimum required sample size to ensure representativeness and allow generalization was calculated using the formula for a single-sample correlation coefficient.

$$n = \left[\frac{(Z\alpha + Z\beta)}{0{,}5\mathrm{Ln}\ (1+r)/(1-r)}\right]^2 + 3$$

Parameters: Zβ = 0.842 (β = 0.10), Zα = 1.96 (95% CI, α = 0.05), r = correlation coefficient = 0.5, Ln = natural logarithm).

The calculation produced a sample size of n = 29.02, which was rounded to 29. With an anticipated dropout rate of 10%, the adjusted sample size became 32. Based on this formula, the minimum required sample size was 32 participants. Statistical regression analysis requires careful consideration of sample size. A larger sample increases statistical power, making any difference, whether clinically relevant or not, more likely to appear statistically significant. Therefore, this study ultimately included 40 participants.

Research Variables

The independent variables in this study are TNF-α level and APRI score in patients with Child-Pugh C hepatic cirrhosis. TNF-α levels were measured using the DEMEDITEC TNF-α kit based on the ELISA method. The results were reported in pg/mL (Normal range: 4.6–12.4 pg/mL). The APRI score is calculated as the ratio of the AST level to the upper limit of normal AST (31 U/L), divided by the platelet count.

The dependent variable is ejection fraction in patients with Child-Pugh C hepatic cirrhosis. Ejection fraction is a measurement of systolic and diastolic chamber dimensions, calculated automatically by echocardiography using the Simpson's method (N ≥ 50%).

Statistical Analysis

The data obtained were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25.00. Data normality was assessed using the Shapiro–Wilk test. Bivariate analysis was performed using Spearman's rank correlation test for data that were not normally distributed, and Pearson's product-moment correlation test if the data were normally distributed. Data analysis was conducted using linear regression. The decision criterion for determining the significance of relationships between variables was based on the probability value (p-value), where $p < 0.05$ indicates a statistically significant relationship, and $p > 0.05$ indicates no statistically significant relationship.

Ethics

This Study was approved by the Medical Ethics Comitee of Dr. Moewardi Hospital (1426/V/HREC/2024). All patients voluntaryli singned the informed consent.

RESULTS AND DISCUSSION

Characteristics of Study Subjects

This study included 40 patients with Child-Pugh C hepatic cirrhosis who met the inclusion and exclusion criteria. The study was conducted at the Gastroenterology Outpatient Clinic and inpatient wards of RSUD Dr. Moewardi Surakarta. The study was conducted from April 2024 to April 2025. In this study, data were obtained from 60 patients with Child–Pugh C hepatic cirrhosis at Dr.

Moewardi General Hospital, Surakarta. Screening was then conducted based on the inclusion and exclusion criteria, resulting in a final sample of 40 patients with Child–Pugh C hepatic cirrhosis.

For the TNF-α variable, the average was 49.34 ± 14.21, ranging from 27.64 pg/mL to 95.18 pg/mL. For the APRI score, the average was 4.64 ± 7.44, with a range of 0.10 to 35.64. For Simpson's EF (ejection fraction), the average was 58.38 ± 6.85, ranging from 42 to 71.

Table 1.
Characteristics Subject Study

	Mean	SD	Med	Min	Max
Age	57.05	±10.72	56.50	37.00	82.00
Gender					
Woman	11	27.5%			
Man	29	72.5%			
TNF a	49.34	±14.21	45.53	27.64	95.18
APRI	4.64	±7.44	1.75	0.10	35.64
EF	58.38	±6.85	58.50	42.00	71.00

Effect of TNF-α Levels on Left Ventricular Ejection Fraction in Patients with Child-Pugh C Hepatic Cirrhosis

Table 2.
Analysis Bivariate the Effect of Tnf-A Levels on Left Ventricular Ejection Fraction (Simpson EF) in Patients with Child Pugh C Hepatic Cirrhosis

Variables	EF SIMPSON			Note
	N	r	p-value	
TNF α	40	-0.559	<0.001*	Sig

As shown in Table 2, the correlation between TNF-α levels and Simpson's EF in patients with Child-Pugh C hepatic cirrhosis yielded an r value of -0.559 (p<0.001), indicating a negative correlation of moderate strength (r = 0.400–0.599). Therefore, TNF-α levels significantly affect left ventricular ejection fraction (Simpson's EF) in patients with Child-Pugh C hepatic cirrhosis. The higher TNF-α levels were associated with reduced EF.

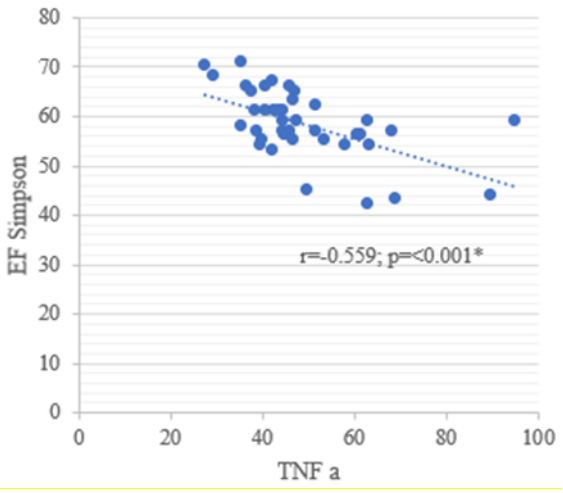

Figure 1. Scatterplot TNF a levels with EF Simpson
Description: Y= EF Simpson; x= TNF a; r k = Spearman rank ; * Significant p<0.05

As shown in Figure 1, the scatterplot data distribution reveals a correlation between TNF-α levels and Simpson's EF, forming a linear pattern that slopes from the upper left to the lower right. This data distribution indicates that as TNF-α levels increase, Simpson's EF values tend to decrease. This demonstrates a negative influence of TNF-α levels on Simpson's EF.

Effect of APRI Score on Left Ventricular Ejection Fraction in Patients with Child-Pugh C Hepatic Cirrhosis

Table 3.
Analysis Bivariate the Influence of Apri Score with Left Ventricular Ejection Fraction (Simpson EF) in Patients with Child Pugh C Hepatic Cirrhosis

Variables	EF SIMPSON			Note
	N	r	p-value	
APRI SCORE	40	-0.445	0.004*	Sig

Description: r= Correlation test Spearman rank : /* significant at p<0.05

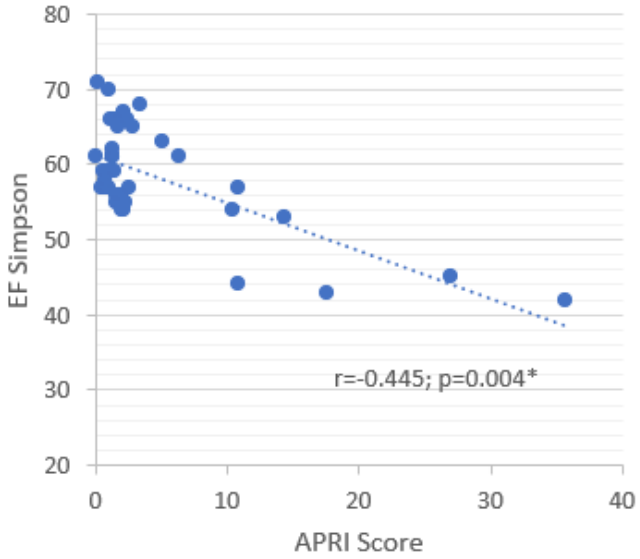

Figure 2 . Scatterplot APRI Score level with EF Simpson
Description: Y= EF Simpson; x= APRI Score; r k = Spearman rank ; * Significant p<0.05

As shown in Figure 2, the scatterplot shows that the data points form a linear pattern sloping from the upper left to the lower right, indicating that as the APRI score increases, Simpson's EF decreases. This demonstrates a negative influence of the APRI score on Simpson's EF.

The correlation between APRI score and Simpson's EF in patients with Child-Pugh C hepatic cirrhosis is r = -0.445, indicating a moderate negative correlation (r = 0.400–0.599). The p-value is 0.004 (p < 0.05), meaning this

correlation is statistically significant. Therefore, APRI score significantly affects left ventricular ejection fraction (Simpson's EF) in patients with Child-Pugh C hepatic cirrhosis.

Correlation of TNF-α Levels and APRI Score on Left Ventricular Ejection Fraction in Patients with Child-Pugh C Hepatic Cirrhosis

Multivariate analysis was performed using linear regression at a significance level (α) of 0.05. The statistical test results showed that both TNF-α (adjusted $p < 0.001$) and APRI score (adjusted $p < 0.001$) had p-values less than 0.05, indicating that TNF-α and APRI score are significantly associated with Simpson's EF.

DISCUSSION

TNF-α plays a multifaceted role in normal physiology that is highly relevant to human health and disease. In the central nervous system (CNS), this cytokine regulates homeostatic functions, including neurogenesis, myelination, blood–brain barrier permeability, and synaptic plasticity. However, it can also potentiate neuronal excitotoxicity and CNS inflammation. Similar mechanisms involving TNF-α are also observed in hepatic cirrhosis (Gonzalez Caldito, 2023).

Elevated TNF-α concentrations in patients with hepatic cirrhosis can affect multiple organs, as indicated by the association with circulating TNF-α levels. High levels of TNF-α in circulation may trigger neurohormonal activation, cardiomyocyte hypertrophy, production of extracellular matrix proteins, and cardiomyocyte apoptosis and necrosis, all of which can lead to diastolic dysfunction in liver disease (Vachliotis & Polyzos, 2023).

The study results show that TNF-α levels were above normal. This is consistent with previous research indicating that TNF-α levels are elevated in patients with chronic hepatitis B (Bekçibaşı & Arslan, 2021). Similarly, the increase in APRI (AST to Platelet Ratio Index) in patients with Child-Pugh C hepatic cirrhosis is a direct consequence of the combination of severe hepatocellular damage and progressive portal hypertension. APRI is calculated as the ratio of AST to the upper limit of normal AST, divided by platelet count × 100, thus reflecting two key aspects: hepatocellular necroinflammation (elevated AST) and the degree of portal hypertension (reduced platelets) (Archer et al., 2022).

An elevated APRI (Aspartate Aminotransferase-to-Platelet Ratio Index) in cirrhotic patients reflects the pathophysiological interplay between hepatocellular necroinflammation and hypersplenism due to portal hypertension. Rising AST levels indicate acute to chronic hepatocellular injury, while falling platelet counts reflect splenic sequestration and reduced thrombopoietin production. As a result, APRI is often markedly elevated in advanced and decompensated cirrhosis (Moosavy et al., 2023; Oikonomou et al., 2023).

Recent meta-analytic and systematic review evidence positions APRI as a low-cost, practical screening tool in resource-limited settings. However, its diagnostic accuracy is only moderate and generally inferior to liver stiffness measurement (transient elastography). Therefore, APRI should be used as a triage tool, not as a replacement for elastography (Chen et al., 2023; Liguori et al., 2025).

Besides its diagnostic role, several recent cohort studies have reported the prognostic value of APRI in decompensated patients. Higher APRI values are associated with increased risk of mortality and recurrent decompensation. However, this prognostic performance tends to be stronger when APRI is combined with indicators of liver synthetic function (such as ALBI) or used together with MELD/MELD-Na scores (Santol et al., 2025; Starlinger et al., 2021).

The pathophysiology of contractility impairment in hepatic cirrhosis is multifactorial and may involve several mechanisms: (1) the release of vasodilatory and inflammatory mediators (NO, CO, and cytokines such as TNF-α) as a consequence of bacterial translocation and splanchnic congestion, which suppresses inotropy through cGMP-mediated pathways and endocannabinoid signaling; (2) adrenergic dysfunction (down-regulation/desensitization of β-adrenergic receptors), which reduces contractile reserve; (3) structural myocardial alterations (diffuse fibrosis and myofilament/titin changes) that contribute to diastolic abnormalities and may influence strain parameters; and (4) metabolic/hemodynamic consequences of liver failure (e.g., toxin accumulation, anemia, volume alterations). These interconnected mechanisms explain why cardiac dysfunction in cirrhosis often remains subclinical at rest but contributes to increased mortality and perioperative cardiovascular events when stress is imposed (Liu et al., 2022).

Recent studies have shown that some cirrhosis patients exhibit reduced cardiac ejection fraction. Other patients have normal EF at rest but show impaired contractility under pharmacological or physical stress. This indicates subclinical systolic dysfunction. This is consistent with reports that Child-Pugh C cirrhosis patients are more prone to reduced EF compared to Child-Pugh A or B patients, especially during the decompensated phase. This is due to diffuse myocardial fibrosis, impaired beta-adrenergic signaling, and systemic inflammation that contribute to cardiac remodeling (Izzy & VanWagner, 2021).

The study results indicate that TNF-α and APRI score have an impact on ejection fraction in patients with Child Pugh C hepatic cirrhosis. Statistical analysis revealed that both TNF-α (adjusted $p < 0.001$) and APRI score (adjusted $p < 0.001$) had p-values less than 0.05, indicating that TNF-α and APRI score are significantly associated with Simpson's EF. The correlation between TNF-α levels and ejection fraction in Child-Pugh C hepatic cirrhosis is $r = -0.559$ (moderate correlation). The correlation between APRI score and ejection fraction in Child-Pugh C hepatic cirrhosis is $r = -0.445$ (moderate correlation).

This finding is consistent with the study by Ryu et al., which showed that TNF antagonism in cirrhosis models improved contractility. Cardiac tissue from cirrhotic animals showed increased TNF-α, inflammation, and

fibrosis, all of which correlated with reduced cardiac function. Conclusion: strong preclinical evidence shows that TNF-α plays a direct role in impairing myocardial function (Ryu et al., 2024).

This study is consistent with previous research conducted in mice, in which administration of Galectin-3 (a fibroblast stimulant) led to a significant increase in TNF-α levels compared with controls ($p < 0.01$). A significant reduction in LVEF was also observed following Galectin-3 administration, with a 20–30% decrease in ejection fraction ($p < 0.01$). Galectin-3 upregulates TNF-α expression in cardiac tissue, and TNF-α subsequently induces myocardial contractile dysfunction. Importantly, these mediator effects are reversible when TNF-α is inhibited. These findings further support the concept of TNF-α–mediated myocardial depression (Yoon et al., 2022).

This is also supported by the study conducted by Yumusak, which confirms that pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) are elevated in the hearts of cirrhotic rats and human biopsies. Inhibiting these cytokines in animal models has been shown to reduce cardiac remodeling and improve contractility. Recommendation: Measure inflammatory mediators if you want to link them to structural or functional changes in the heart (Yumusak & Doulberis, 2024).

The limitations of echocardiography in assessing diastolic dysfunction underscore the need for additional imaging modalities, such as CMR, to achieve a more comprehensive evaluation. Further research is needed to determine the best diagnostic method for evaluating diastolic dysfunction in patients with liver cirrhosis and to better understand the relationship between liver and heart function. The use of a cross-sectional study design presents inherent limitations. This design does not allow determination of the causal direction between serum biomarker levels and the reduction in left ventricular ejection fraction. Then, this study was conducted in a single-center setting with a small sample size, meaning it was carried out at only one location. Although hepatic cirrhosis has well-defined diagnostic criteria, other confounding variables, such as ethnicity and patient lifestyle factors, may influence study outcomes.

The implications of these findings include the potential use of APRI scores and TNF-α levels as contemporary predictors, emphasizing the need for periodic monitoring to prevent the development of cirrhotic cardiomyopathy in patients with hepatic cirrhosis. Second, there are implications for the development of innovative biomarkers for cirrhotic cardiomyopathy. The significant association between TNF-α and ejection fraction highlights the opportunity to explore additional inflammatory biomarkers as early predictive tools for cirrhotic cardiomyopathy.

CONCLUSION

The correlation between TNF-α levels and ejection fraction in Child-Pugh C hepatic cirrhosis is $r = -0.445$, $p<0.001$ (moderate correlation). The correlation between APRI score and ejection fraction in Child-Pugh C hepatic cirrhosis is $r = -0.445$, $p<0.001$ (moderate correlation). Similarly, multivariate analysis reveals a significant association between TNF-α, APRI scores and Simpson's EF.

RECOMMENDATIONS

It is recommended that further prospective studies be conducted using more accurate imaging modalities, such as speckle-tracking echocardiography or cardiac MRI, to evaluate the relationship between liver function and ejection fraction comprehensively. This may also help identify other factors that play a more significant role in causing reduced ejection fraction in patient with cirrhosis. It is expected that future diagnostic and management approaches will become more comprehensive and holistic, particularly in addressing both gastrointestinal and cardiovascular conditions in patients. Multidisciplinary collaboration among physicians is crucial for enhancing the quality of life for patients with hepatic cirrhosis.

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