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Review

Potential Prognostic Role of Fibrosis-5 Index (FIB-5) in Heart Failure; a Narrative Review

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Abstract: The Fibrosis-5 (FIB-5) index, a non-invasive marker of liver fibrosis, has emerged as a significant prognostic tool in heart failure (HF). Studies indicate that lower FIB-5 values are associated with worse outcomes, including major adverse cardiac and cerebral events (MACCEs), poor response to therapies like cardiac resynchronization therapy (CRT), and increased mortality. The index's ability to integrate hepatic and systemic dysfunction offers insights into the interplay between liver and heart health, particularly in advanced HF and acute decompensated HF. Combining FIB-5 with inflammatory markers like C-reactive protein improves risk stratification accuracy, suggesting a synergistic value in prognosis. Its predictive capacity for CRT response underscores its clinical relevance beyond hepatic assessment. However, questions remain about the incremental benefit of FIB-5 over established markers and its potential prognostic implications. Future research should focus on validating its utility in diverse HF populations and exploring its role in guiding strategies.

Keywords: cardiac dysfunction; liver biomarkers; systemic inflammation; organ crosstalk; risk stratification; Prognosis

Background

Heart failure (HF) is a complex clinical syndrome characterized by the inability of the heart to pump blood efficiently to meet the body's metabolic demands. It represents a significant global health burden, affecting millions of people worldwide and contributing to substantial morbidity, mortality, and healthcare costs. As the population ages and survival rates for cardiovascular diseases improve, the prevalence of heart failure continues to rise, making it a critical area of focus for medical research and clinical practice[1,2].

The prognosis of heart failure patients remains poor, with high rates of hospitalization and mortality despite advances in treatment strategies. Accurate prognostication is crucial for optimizing patient care, guiding therapeutic decisions, and allocating healthcare resources effectively. Traditional prognostic markers, such as New York Heart Association (NYHA) functional class and left ventricular ejection fraction (LVEF), while valuable, have limitations in their ability to predict outcomes accurately across the diverse spectrum of heart failure patients [1,3,4].

In recent years, there has been growing interest in the use of biomarkers to enhance prognostic assessment in heart failure[5]. Biomarkers are measurable indicators of biological processes, pathogenic mechanisms, or responses to therapeutic interventions. They offer the potential for more objective, precise, and individualized risk stratification. Various biomarkers have been investigated in the context of heart failure, including natriuretic peptides, cardiac troponins, and markers of inflammation and fibrosis [5–7].

While much attention has been focused on cardiac-specific biomarkers, there is increasing recognition of the importance of non-cardiac organs in heart failure pathophysiology and prognosis[8,9]. The liver, in particular, plays a crucial role in the complex interplay between heart failure and systemic manifestations. Liver dysfunction is common in heart failure patients and can result from both passive congestion due to elevated right-sided pressures and reduced perfusion from low cardiac output[10,11].

Liver-related biomarkers have emerged as promising prognostic tools in heart failure[12]. These biomarkers reflect various aspects of liver function and injury, including hepatocellular damage, cholestasis, and synthetic capacity[13]. Examples include transaminases (AST, ALT), alkaline

phosphatase (ALP), gamma-glutamyl transferase (GGT), bilirubin, and albumin. Additionally, novel liver-specific biomarkers such as Fibroblast Growth Factor 21 (FGF21) and microRNA-122 have shown potential in cardiac diseases prognostication [14–17].

However, the use of liver-related biomarkers in heart failure prognosis is not without challenges. The interpretation of these markers can be complex, as they may be influenced by factors unrelated to heart failure, such as medications, comorbidities, or pre-existing liver disease. Moreover, the optimal combination of biomarkers and their integration with clinical variables and imaging parameters remains to be determined.

This narrative review aims to explore the current state of knowledge regarding the role of Fibrosis-5 Index (FIB-5) in heart failure prognosis. By reviewing the available evidence, this review seeks to provide clinicians and researchers with a comprehensive understanding of the potential of FIB-5 to enhance prognostic assessment and guide management strategies in heart failure.

Liver fibrosis biomarkers and Heart Failure

Liver fibrosis, as highlighted in the study by Gelow et al., [18] emerges as a prevalent and impactful complication in patients with advanced HF, reflecting the intricate interplay between cardiac dysfunction and liver health. The study underscores that Liver fibrosis is not merely a coincidental finding but correlates strongly with significant clinical features, such as renal dysfunction, tricuspid regurgitation, and liver function abnormalities. These associations point to the hemodynamic burden placed on the liver by HF, emphasizing the organ's vulnerability to chronic congestion and reduced perfusion. Strikingly, the degree of fibrosis appears to influence therapeutic trajectories and outcomes, with patients exhibiting less severe fibrosis being more likely to qualify for advanced interventions such as ventricular assist devices or heart transplantation[18].

This relationship raises provocative questions about the utility of Liver fibrosis indices in refining HF prognosis and guiding management. Could integrating liver biomarkers and biopsy findings into routine HF assessment improve risk stratification? While the study affirms the predictive significance of Liver fibrosis, it also challenges clinicians to consider the broader implications of these findings. How should the presence of Liver fibrosis modify HF treatment strategies, and might earlier detection through non-invasive fibrosis indices alter disease progression or outcomes? These questions highlight the need for further research to elucidate the bidirectional influence of HF and Liver fibrosis, fostering a more integrated approach to managing this multifaceted condition[18].

Liver involvement in HF has been recognized for a long time and can occur through two primary mechanisms: retrograde and anterograde. Retrograde liver involvement arises when elevated right atrial pressure is passively transmitted to the hepatic veins, leading to hepatic congestion. In contrast, anterograde liver involvement results from a reduced arterial blood supply, typically occurring when the cardiac index falls below 2 L/min/m². Both mechanisms contribute to increased liver stiffness, though the underlying causes differ. In retrograde involvement, stiffness is predominantly due to congestion, while in anterograde involvement, it stems from hepatic cell necrosis and fibrosis[19].

Clinically, anterograde liver involvement—caused by diminished blood flow—leads to cell damage, resulting in marked elevations in aminotransferases and total bilirubin levels. This condition is frequently observed in scenarios such as cardiogenic shock or low cardiac output states, including the use of extracorporeal membrane oxygenation or mechanical circulatory support devices. Conversely, retrograde involvement—driven by congestion—primarily increases direct bilirubin and γ -glutamyl transferase (GGT). This pattern is commonly seen in patients with chronic heart failure. Understanding these distinct mechanisms is essential for accurate diagnosis and targeted management of liver dysfunction in HF [19].

Liver fibrosis indices, such as the NAFLD fibrosis score (NFS), have emerged as promising prognostic tools in heart failure with preserved ejection fraction (HFpEF). These indices, incorporating markers like aspartate aminotransferase to alanine aminotransferase ratio, platelet counts, and albumin, offer insights into liver stiffness and systemic fibrosis. Recent studies have demonstrated significant correlations between NFS and peripheral collagen markers, suggesting its potential as a surrogate for systemic fibrosis. The association of NFS with increased mortality in HFpEF patients underscores its prognostic value. However, further research is needed to elucidate

the mechanisms underlying this relationship and to determine the optimal integration of liver fibrosis indices into clinical practice for HFpEF management[12].

Liver fibrosis indices, such as the Fatty Liver Index (FLI) and BARD score, have emerged as intriguing prognostic tools in heart failure management. These non-invasive markers offer valuable insights into the complex interplay between liver dysfunction and cardiovascular health. Recent studies have revealed compelling associations between elevated FLI scores and increased risks of incident heart failure, hospitalization, and mortality in both general and heart failure populations. Furthermore, advanced liver fibrosis, as indicated by higher BARD scores, correlates with poorer outcomes in heart failure patients. These findings challenge our understanding of heart failure pathophysiology and suggest that liver health may play a more significant role in cardiovascular prognosis than previously recognized, potentially opening new avenues for risk stratification and targeted interventions in heart failure management[20].

FIB-5

The Fibrosis-5 (FIB-5) index is a clinical tool designed to assess liver fibrosis, a condition marked by the excessive accumulation of scar tissue in the liver[21]. By integrating specific patient data, the FIB-5 index provides a non-invasive means of estimating the severity of fibrosis, which is crucial for diagnosing and managing liver diseases such as hepatitis and metabolic dysfunction-associated steatotic liver disease (MASLD)[21,22].

The FIB-5 utilizes albumin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine aminotransferase (ALT), and platelet count in its formula. It could be calculated using the formula $(Albumin\ (g/L) \times 0.3) + (Platelet\ Count\ (10^9/L) \times 0.05) - (ALP\ (U/L) \times 0.014) + (AST/ALT\ Ratio \times 6) + 14$, has emerged as a marker of liver fibrosis[23].

This index is particularly valued for its simplicity, cost-effectiveness, and applicability in various clinical settings[24]. It helps stratify patients into different risk categories, allowing healthcare providers to identify those who may require more advanced diagnostic procedures, such as liver biopsies or imaging studies, or closer monitoring. Its non-invasive nature makes it a practical alternative to invasive methods, reducing patient discomfort and the risk of complications [25,26].

FIB-5 is especially useful in resource-limited settings, where access to advanced diagnostic tools may be restricted. Despite its strengths, like many indices, it has limitations. The FIB-5 index is most effective when used alongside other clinical assessments and diagnostic tools to provide a comprehensive picture of liver health. Its accuracy can also be influenced by the specific characteristics of the patient population, highlighting the need for careful interpretation by healthcare professionals [26,27].

FIB-5 and Heart Failure

The intersection of liver fibrosis and cardiovascular disease has garnered increasing attention in recent years, with the FIB-5 emerging as a potential biomarker for cardiac outcomes[28]. Given the intricate cardiohepatic axis, liver dysfunction and fibrosis often exacerbate HF via hemodynamic alterations, venous congestion, and systemic inflammatory cascades[29,30]. This relationship has fueled interest in leveraging liver-derived indices like FIB-5 to improve HF prognostication. Studies have begun to explore whether FIB-5 could offer unique insights into HF risk stratification and outcomes, particularly in settings where conventional cardiac biomarkers alone may fall short[23,31]. Understanding its role could redefine how clinicians evaluate the multifaceted burden of HF, offering a more integrated view of systemic health.

Emerging evidence suggests that liver fibrosis markers may provide critical insights into cardiovascular prognosis, bridging the gap between hepatic and cardiac health. A recent study by Chen et al. [28] evaluated the FIB-5, a marker traditionally associated with liver fibrosis, as a predictor of major adverse cardiovascular events (MACE) in patients with ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI). Among 406 STEMI patients followed for an average of 27 months, the study revealed that those in the highest tertile of FIB-5 had a nearly two-fold increased risk of MACE (HR 1.95; 95% CI 1.21–3.13; $P = 0.006$) compared to lower tertiles. Notably, Kaplan–Meier curves demonstrated significant stratification (log-rank $P < 0.001$), and even a per-unit increase in FIB-5 independently correlated with MACE risk (HR 0.98; 95% CI 0.97–1.00; $P = 0.013$). However, the predictive capacity of FIB-5, reflected by an AUC of 0.645 (95%

CI 0.590–0.701; $P < 0.001$), raises questions about its clinical utility compared to more established markers. While the findings suggest a novel application for FIB-5, its moderate discriminatory power invites further exploration into whether its integration into multifactorial risk models could enhance prognostic precision or merely add complexity to existing strategies (**Table 1**).

This study’s lack of information on patients’ medication regimens, particularly regarding dual antiplatelet therapy (DAPT) with potent P2Y12 receptor inhibitors, represents a significant limitation. Given the established benefits of ticagrelor and prasugrel in reducing ischemic events and mortality in acute coronary syndrome, the absence of this data introduces a potential confounding factor that could impact the interpretation of FIB-5’s prognostic value. Future studies should address these limitations to provide a more comprehensive understanding of FIB-5’s role in predicting outcomes for STEMI patients undergoing PCI[32].

It had been disclosed that the FIB-5 has a good prognostic values in patients hospitalized with HF[33].

Table 1. Prognostic Role of FIB-5 in cardiovascular disease, especially Heart Failure (HF).

Study/Reference	Study Setting/Population	Outcomes Measured	Key Findings	Limitations/Remarks
Chen et al. [28]	406 STEMI patients undergoing PCI	Major Adverse Cardiovascular Events (MACE)	- Highest FIB-5 tertile: HR 1.95 (95% CI 1.21–3.13; $P = 0.006$) for MACE - AUC: 0.645 (95% CI 0.590–0.701; $P < 0.001$) - Per-unit increase in FIB-5: HR 0.98 ($P = 0.013$)	- Moderate discriminatory power (AUC 0.645). - Lack of medication data, including DAPT use, as a confounder. - Further studies needed for integration into risk models.
Maeda et al. [31]	906 HF patients (hospitalized)	Composite endpoint: cardiac death or HF rehospitalization	- Event rates across FIB-5 tertiles: 51.5% (low), 36.5% (middle), 17.9% (high); $P < 0.001$. - Low FIB-5 score independently predicted worse outcomes. - Superior performance over FIB-4 (NRI = 0.530, IDI = 0.072; $P < 0.001$).	- Mechanistic basis of superior performance unclear. - Applicability across HF phenotypes (both preserved and reduced EF) confirmed.
Wang et al. [23]	1153 ADHF patients	MACE occurrence and combination with CRP	- 42.3% experienced MACE over ~584 days. - Highest risk: low FIB-5 + high CRP (HR 1.67; $P < 0.001$). - Combination improved predictive accuracy: NRI = 0.314, IDI = 0.023 ($P < 0.001$).	- Mechanistic link between FIB-5, CRP, and outcomes needs exploration. - Role in therapy modification unclear.

Iwawaki et al. [34]	203 CRT or CRT-D patients	CRT response and long-term HF outcomes	- Responders had higher FIB-5 values.	- Incremental value over traditional CRT markers debated.
			- FIB-5 cutoff (-4.00) independently predicted CRT response.	- Larger studies required to assess full clinical utility.
			- Associated with reduced cardiac death and HF hospitalization.	

In evaluating the role of liver fibrosis markers in HF prognosis, a recent study demonstrated the superior utility of the FIB-5 index compared to the widely studied FIB-4. This investigation, involving 906 patients hospitalized with HF, revealed that FIB-5 not only effectively stratified risk for adverse outcomes but also showed distinct prognostic advantages. The primary endpoint—a composite of cardiac death or rehospitalization for HF—occurred more frequently in patients with lower FIB-5 scores, with a striking gradient in event rates across low, middle, and high FIB-5 groups (51.5%, 36.5%, and 17.9%, respectively; $P < 0.001$). The findings highlight that a low FIB-5 score independently predicts worse outcomes, even after adjusting for key confounders, including left ventricular ejection fraction (LVEF). Furthermore, the association between FIB-5 and prognosis remained robust across both preserved and reduced LVEF phenotypes, reinforcing its general applicability in HF populations[31].

Interestingly, FIB-5’s prognostic accuracy surpassed that of FIB-4, as evidenced by significant improvements in reclassification and discrimination indices (net reclassification improvement, 0.530; integrated discrimination improvement, 0.072; both $P < 0.001$). These results challenge conventional reliance on FIB-4 and suggest a pivotal role for FIB-5 in refining HF risk stratification[31]. However, the mechanisms underlying the stronger performance of FIB-5—whether due to its incorporation of albumin and alkaline phosphatase or its sensitivity to subclinical hepatic dysfunction—warrant further investigation. While FIB-5 emerges as a promising tool, its integration into clinical practice must be carefully assessed, particularly in conjunction with established cardiac biomarkers, to ensure it adds value without redundancy or complexity.

A recent study highlighted the synergistic prognostic potential of combining the FIB-5 index and C-reactive protein (CRP) in patients with acute decompensated heart failure (ADHF). Over a follow-up of approximately 584 days, MACEs occurred in 42.3% of the 1153 patients analyzed. Stratification into four groups based on FIB-5 and CRP levels revealed striking differences in outcomes, with the highest risk observed in patients with both a low FIB-5 index and high CRP levels. Even after adjusting for confounders, these patients demonstrated a significantly elevated hazard ratio for MACCEs (e.g., $HR = 1.67$; $P < 0.001$), underscoring the interplay between hepatic dysfunction and systemic inflammation in ADHF. Moreover, the combination of FIB-5 and CRP outperformed FIB-5 alone in predictive accuracy, as evidenced by improved net reclassification improvement ($NRI = 0.314$; $P < 0.001$) and integrated discrimination improvement ($IDI = 0.023$; $P < 0.001$)[23].

While these findings suggest that a dual-marker approach could enhance risk stratification, questions remain about its integration into clinical practice. Is the additive value sufficient to influence therapeutic decisions, or does it primarily serve as a refinement tool for existing models? Furthermore, the mechanistic link between low FIB-5 scores, high CRP levels, and adverse outcomes warrants deeper exploration to determine whether targeting these pathways could yield tangible clinical benefits. This study sets the stage for future investigations to solidify the role of this novel combination in the complex landscape of ADHF management.

The FIB-5 index, a non-invasive marker for liver fibrosis, has shown promise as a prognostic tool in HF, particularly in predicting response to cardiac resynchronization therapy (CRT). In a study involving 203 patients undergoing CRT or CRT-defibrillator (CRT-D) implantation, responders to CRT demonstrated significantly higher FIB-5 values compared to non-responders. This correlation suggests that liver fibrosis, as reflected by the FIB-5 index, could influence the heart’s ability to respond to resynchronization therapy. A cutoff value of -4.00 for the FIB-5 index was identified as an independent predictor of CRT response, alongside traditional markers such as QRS duration and

echocardiographic dysynchrony. Interestingly, the FIB-5 index not only predicted CRT response but also correlated with better long-term outcomes, including reduced cardiac death and heart failure hospitalizations[34]. This highlights the potential of FIB-5 as a useful addition to standard prognostic factors in HF management. However, while the findings are compelling, one must consider whether FIB-5 truly provides incremental value over more established markers, or if its role is mainly confined to identifying liver-related complications in HF. Further studies are needed to address these questions and solidify the FIB-5 index's clinical utility.

Conclusion

The FIB-5 index has shown promise as a prognostic tool in HF, leveraging its sensitivity to hepatic dysfunction to enhance risk stratification. Studies demonstrate its ability to predict adverse outcomes such as HF rehospitalization, cardiac death, and major adverse cardiovascular events, often outperforming other liver fibrosis indices like FIB-4. Low FIB-5 scores consistently correlate with worse outcomes, highlighting its utility across various HF populations. Despite these findings, the incremental value of FIB-5 over established cardiac biomarkers and its integration into clinical practice remain areas for further research. Larger studies are needed to validate its role and clarify the mechanisms linking liver fibrosis to HF outcomes, potentially paving the way for more comprehensive risk assessment strategies.

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