The Potential Role of microRNA-122 in Cardiac Failure: A Molecular Insight into Pathogenesis and Prognosis

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Abstract:

Cardiac failure remains a leading cause of morbidity and mortality worldwide, with a growing need for early diagnostic and prognostic tools. MicroRNAs (miRNAs) have emerged as promising biomarkers due to their stability in circulation and regulatory roles in various disease processes. miRNA-122, primarily found in the liver, is increasingly being studied for its potential role in heart-related diseases. This review explores the emerging evidence on the role of miR-122 in cardiac failure, emphasizing its potential as a biomarker and pathophysiological mediator Patients suffering from heart failure have been found to have elevated levels of circulating miR-12 and are associated with inflammation, cardiomyocyte apoptosis, hypertrophy, and fibrosis. The liver–heart axis may contribute to this elevation, suggesting a bidirectional relationship. We also discuss how miR-122 compares with established cardiac biomarkers and its potential utility in diagnosis, prognosis, and therapeutic targeting. Future studies are needed to validate these findings and clarify whether modulating miR-122 levels could offer novel treatment strategies in cardiac failure.

Keywords: miR-122, cardiac failure, microRNA, biomarker, heart disease, inflammation, fibrosis, liver-heart axis

Introduction:

Heart failure, or HF, is a complicated clinical illness caused by structural or functional cardiac abnormalities that affect the heart's capacity to pump blood effectively. It remains a major public health concern, with high rates of hospitalizations, morbidity, and mortality worldwide (1). Traditional biomarkers such as B-type natriuretic peptide (BNP) and troponins have been instrumental in diagnosing and managing HF. However, these markers often lack specificity in early disease stages or in patients with co-existing conditions, highlighting the need for more sensitive and specific molecular markers. In recent years, **microRNAs (miRNAs)** have emerged as promising candidates in this regard. These ~22 nucleotide-long non-coding RNAs help regulate gene activity, and are increasingly recognized for their role in cardiac biology (2). Numerous physiological and pathological processes are impacted by them, including as cell division, apoptosis, differentiation, inflammation, and fibrosis—all of which are central to the development and progression of heart failure (3,4).

Among the numerous miRNAs identified, microRNA-122 (miR-122) is of particular interest. It is highly expressed in the liver and has traditionally been studied in the context of hepatic function and diseases such as hepatitis, cirrhosis, and hepatocellular carcinoma (5). However, circulating miR-122 has also been detected in non-hepatic conditions, including cardiovascular conditions, including heart failure, atherosclerosis, and myocardial infarction, suggesting broader biological relevance (6,7). Recent studies have shown that miR-122 may play a significant role in cardiac pathophysiology, possibly through the regulation of lipid metabolism, inflammation, oxidative stress, and myocardial cell apoptosis. Dysregulation of lipid handling and metabolic pathways—processes in which miR-122 is deeply involved—has been increasingly recognized as a contributor to heart failure, particularly in patients with metabolic syndrome or diabetes (8,9).

Furthermore, miR-122 is detectable in the circulation, is stable under various conditions (due to its packaging in exosomes or binding to proteins like Argonaute-2), and shows disease-specific expression patterns. These features make it a strong candidate for a non-invasive biomarker for early diagnosis, prognosis, and treatment monitoring in HF patients (10). Despite these promising findings, the precise mechanisms by which miR-122 influences cardiac function remain to be fully elucidated. Moreover, clinical studies examining its role in heart

failure are still limited and sometimes inconsistent. Therefore, a comprehensive review of available evidence is warranted. This review aims to explore the potential role of miR-122 in cardiac failure, summarizing its known biological functions, alterations in expression in heart failure patients, underlying mechanisms, and its diagnostic and prognostic implications. We also highlight the current limitations and future directions for integrating miR-122 into clinical practice.

Cardiac Failure: A Brief Overview

Cardiac failure, commonly referred to as **heart failure (HF)**, is a progressive clinical syndrome characterized by the heart's inability to pump blood efficiently, either due to impaired contractility or compromised ventricular filling. This results in insufficient blood flow to meet the metabolic demands of peripheral tissues, leading to symptoms such as fatigue, dyspnea, fluid retention, and reduced exercise tolerance (11).

Heart failure is typically classified into subtypes based on **left ventricular ejection fraction (LVEF)**:

- **HFrEF** (heart failure with reduced ejection fraction; LVEF < 40%),
- **HFpEF** (heart failure with preserved ejection fraction; LVEF ≥ 50%),
- **HFmrEF** (heart failure with mildly reduced ejection fraction; LVEF 41–49%) (12).

The pathogenesis of heart failure is multifactorial, involving hemodynamic stress, myocardial injury, neurohormonal activation, and structural remodeling**.** Conditions such as coronary artery disease, hypertension, myocardial infarction, cardiomyopathies, and valvular disorders are major contributors to its development. The activation of compensatory mechanisms, particularly the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system**,** initially helps maintain perfusion but eventually contributes to adverse cardiac remodeling and disease progression (13). Globally, heart failure represents a significant public health burden, with an estimated prevalence exceeding 64 million individuals. The incidence continues to rise due to aging populations, lifestyle factors, and improved survival following acute cardiovascular events (1). Despite major advances in pharmacological therapies (e.g., ACE inhibitors, beta-blockers, SGLT2 inhibitors) and device interventions, the condition remains associated with high morbidity, frequent hospitalizations, and a 5-year mortality rate of approximately 50% in advanced stages (14). Given the clinical heterogeneity and poor prognosis of HF, there is a growing emphasis on the identification of novel molecular biomarkers that can enable earlier diagnosis, precise risk stratification, and targeted therapies.

In this context, microRNAs (miRNAs) have attracted considerable interest due to their regulatory roles in key pathophysiological processes involved in HF—including inflammation, fibrosis, hypertrophy, oxidative stress, and apoptosis.

Importance of Finding New Biomarkers in Cardiac Failure:

Heart failure (HF) is a chronic and progressive condition with high clinical and economic burdens, often associated with delayed diagnosis, unpredictable progression, and variable therapeutic response. While current clinical biomarkers such as B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) have significantly improved the diagnosis and management of HF, they also have well-recognized limitations. These peptides are influenced by non-cardiac factors such as renal function, age, obesity, and atrial fibrillation, which may affect their sensitivity and specificity in various patient populations (13,15). Moreover, conventional biomarkers primarily reflect hemodynamic stress rather than the underlying molecular mechanisms driving the disease, such as inflammation, fibrosis, apoptosis, oxidative stress, and myocardial remodeling. As heart failure is a multifactorial syndrome with diverse etiologies, there is a growing need for novel biomarkers that offer better pathophysiological insight, aid in early detection, and facilitate personalized risk stratification and therapeutic monitoring (16).

In this context, microRNAs (miRNAs) have emerged as promising non-invasive biomarkers. These small, non-coding RNAs regulate gene expression post-transcriptionally and are involved in numerous biological processes relevant to cardiovascular pathology. Importantly, miRNAs are stable in circulation, resistant to degradation, and show disease- and tissue-specific expression patterns. Their levels in plasma or serum can reflect real-time pathophysiological changes in the myocardium or other organs affected in HF, such as the kidney and liver (10,17). Identifying new biomarkers such as miR-122 not only has the potential to improve diagnostic accuracy but may also help predict disease progression, identify therapeutic targets, and monitor treatment efficacy. This is particularly crucial in patients with HFpEF, where traditional biomarkers often fall short, and no definitive treatment has yet been established (18). The integration of novel biomarkers into clinical practice may ultimately lead to a more personalized approach to managing HF, improving outcomes and reducing healthcare costs.

Introduction to microRNAs and miR-122:

MicroRNAs are a class of small (~21–23 nucleotides), non-coding RNA molecules that play a fundamental role in post-transcriptional gene regulation. They exert their biological effects by binding to the 3′ untranslated region (UTR) of target messenger RNAs, leading to mRNA degradation or translational repression (2). Since their discovery in the early 1990s, miRNAs have been recognized as crucial regulators of gene networks across a variety of biological processes including cell proliferation, differentiation, apoptosis, stress response, metabolism, and inflammation (4,19). In the cardiovascular system, miRNAs are involved in the regulation of cardiac development, hypertrophy, fibrosis, angiogenesis, and electrical conduction. Dysregulation of specific miRNAs has been implicated in numerous cardiac diseases such as myocardial infarction, atherosclerosis, arrhythmias, and heart failure (20). The discovery that miRNAs can be released into the bloodstream in stable forms — either packaged in exosomes, microvesicles, or bound to protein complexes like Argonaute-2 — has led to intense interest in their potential as non-invasive biomarkers for cardiovascular disease (10).

Among the many miRNAs studied, miR-122 is of particular interest. It is one of the most abundantly expressed miRNAs in the liver, accounting for over 70% of total hepatic miRNA content. It plays a central role in lipid metabolism, cholesterol synthesis, and hepatocyte differentiation (5,8). Although traditionally associated with liver-specific functions and liver diseases, recent studies have identified miR-122 in the circulation of patients with cardiovascular diseases, including acute coronary syndromes, atherosclerosis, and heart failure (6,7). The emerging role of miR-122 in cardiovascular pathophysiology may be linked to its regulatory effects on lipid metabolism, systemic inflammation, and oxidative stress, all of which are key contributors to cardiac dysfunction. Its elevated expression in circulation may reflect extra-hepatic injury responses, particularly in heart failure patients with concurrent metabolic syndrome or liver congestion. Due to its tissue specificity, stability in plasma, and altered expression in disease states, miR-122 is being actively explored as a potential biomarker for diagnosis, prognosis, and monitoring in heart failure and other cardiovascular conditions.

Role of miR-122 in Heart Failure:

Recent studies suggest that microRNA-122 (miR-122), though traditionally recognized as a liver-specific miRNA, may also play a significant role in the pathogenesis and development of heart failure. The altered expression of miR-122 in the circulation of heart failure patients indicates a potential systemic regulatory function extending beyond hepatic metabolism (6).

1. miR-122 and Cardiac Pathophysiology:

miR-122 is involved in the regulation of key biological processes relevant to cardiac function, including:

- **Lipid and cholesterol metabolism**: Dyslipidemia is a well-established risk factor for heart failure, especially in patients with ischemic heart disease. miR-122 suppresses genes involved in cholesterol biosynthesis (e.g., HMGCR), and its dysregulation may contribute to atherosclerotic burden **and** myocardial remodeling (8).
- **Inflammation and oxidative stress**: Elevated levels of circulating miR-122 may reflect systemic inflammation, a core feature of HF, particularly in HF with preserved ejection fraction (HFpEF). Studies suggest that miR-122 can regulate pro-inflammatory cytokines via targeting of genes such as **SOCS1**, a negative regulator of the JAK/STAT pathway (7).
- **Cardiac fibrosis and remodeling**: Although direct cardiac expression of miR-122 is low under physiological conditions, its levels increase in pathological states. Animal models of pressure overload-induced cardiac hypertrophy have shown upregulation of miR-122 in heart tissue**,** which may exacerbate myocardial fibrosis through TGF-β signaling pathways (21).

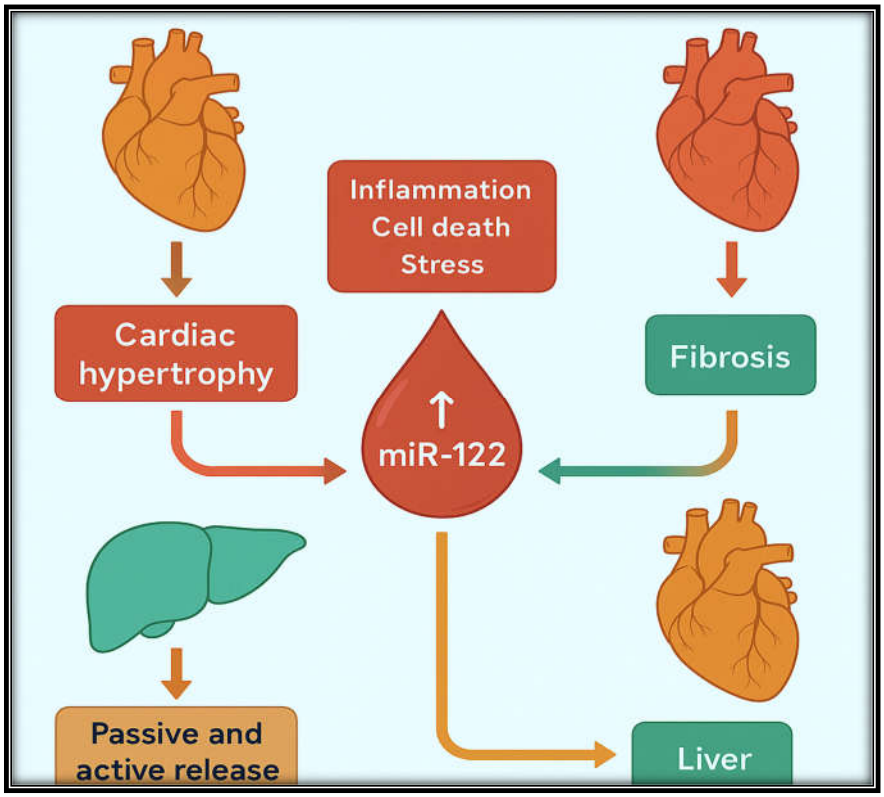

Figure:1 shows how miR-122, mainly produced by the liver, increases in the blood during heart failure. It may worsen heart damage by promoting inflammation, cell death, hypertrophy, and fibrosis. The diagram also highlights the liver–heart link, where liver congestion in heart failure raises miR-122 levels, creating a cycle that further harms the heart. This supports the role of miR-122 as a potential biomarker and therapeutic target in cardiac failure.

2. Diagnostic and Prognostic Potential:

Several clinical studies have demonstrated that plasma levels of miR-122 are significantly elevated in patients with chronic and acute decompensated heart failure compared to healthy controls. The studies reported that circulating miR-122 was markedly higher in elderly patients with HF and correlated with NT-proBNP levels, left ventricular dysfunction, and adverse outcomes (6). Other study found that miR-122 had a good diagnostic performance (AUC > 0.80) in distinguishing acute heart failure patients from non-HF individuals, suggesting its use as a complementary biomarker (7). Moreover, elevated miR-122 may serve as an independent predictor of mortality and hospital readmission, reflecting both cardiac and systemic stress, including subclinical hepatic dysfunction — a common comorbidity in HF known as cardiohepatic syndrome (22).

3. **Therapeutic Implications:**

Given its functional roles and consistent elevation in HF, miR-122 is being considered not only as a biomarker but also as a therapeutic target. Antagonism of miR-122 (e.g., via antisense oligonucleotides) has been shown to improve lipid profiles, reduce inflammation, and potentially modulate cardiac remodeling in preclinical models. However, further studies are needed to evaluate its safety, specificity, and cardiac effects in human trials.

miR-122 Levels in Cardiac Failure:

1. **Changes in miR-122 Levels in Heart Failure Patients:**

Multiple studies have consistently demonstrated that circulating levels of miR-122 are significantly increased in patients with heart failure compared to healthy controls. Although miR-122 is primarily expressed in the liver, its presence in the bloodstream during cardiac dysfunction suggests it may serve as an indirect biomarker of myocardial injury or systemic metabolic stress.

The increase in miR-122 may reflect:

- Hepatic congestion due to elevated central venous pressure in HF.
- Systemic inflammation and oxidative stress associated with cardiac decompensation.
- Cross-talk between the liver and heart, where hepatic stress contributes to cardiovascular pathology.

This increase in miR-122 is not just a bystander effect but may be part of a pathophysiological response**,** contributing to lipid dysregulation, vascular inflammation, and myocardial remodeling.

2. **Elevated miR-122 levels in Heart Failure:**

The study investigated elderly patients with chronic heart failure and found significantly higher circulating miR-122 levels compared to age-matched healthy individuals. Importantly, miR-122 levels correlated positively with NT-proBNP, a well-established HF marker, and with echocardiographic parameters of ventricular dysfunction (6). Other studies reported that plasma miR-122 levels were elevated in patients admitted with acute heart failure**.** Receiver operating characteristic (ROC) curve analysis demonstrated good diagnostic accuracy (AUC ~0.82), suggesting

potential use of miR-122 as a non-invasive biomarker for acute HF (7). Other study found that miR-122 levels were higher in patients with dilated cardiomyopathy-related HF, and these levels were associated with worse New York Heart Association (NYHA) functional class, indicating a potential role in disease staging (23).

3. **Association with Disease Severity:**

Several findings highlight the link between miR-122 levels and HF severity:

- **Positive correlation with NT-proBNP**: NT-proBNP is released in response to ventricular stretch. High miR-122 levels often accompany elevated NT-proBNP, indicating advanced hemodynamic stress.
- **Association with NYHA class**: Higher miR-122 levels have been observed in NYHA Class III–IV patients compared to Class I–II, suggesting that miR-122 may reflect **clinical worsening**.
- **Relationship with liver function markers**: In HF patients with hepatic congestion or cardiohepatic syndrome, miR-122 levels often parallel increases in ALT and AST, reinforcing its utility as a dual marker of both liver and heart strain.

Collectively, these associations position miR-122 not only as a diagnostic tool but also as a prognostic biomarker capable of reflecting disease burden and guiding risk stratification in heart failure.

Use of miR-122 as a Biomarker in Heart Failure:

MicroRNAs (miRNAs) are emerging as promising non-invasive biomarkers for various cardiovascular diseases, including heart failure (HF). Among them, miR-122, primarily liver-derived, has gained attention due to its altered levels in HF patients and its association with clinical outcomes.

1. **miR-122 Help in Early Diagnosis**

Recent evidence highlights the potential of miR-122 as an early diagnostic biomarker in heart failure (HF). Elevated circulating levels of miR-122 have been observed in patients with acute HF, even in the absence of clear clinical symptoms. For instance, studies reported significantly higher miR-122 levels in acute HF patients, with a diagnostic AUC of approximately 0.82 in ROC analysis, indicating good discriminatory ability (7). Importantly, miR-122 may be

particularly valuable in populations where HF diagnosis is challenging—such as the elderly or those with multiple comorbidities, where typical signs may overlap with other chronic diseases. Since miR-122 is released in response to liver congestion and systemic inflammation, it could reflect early multisystem stress before overt cardiac dysfunction becomes clinically apparent. These findings suggest that miR-122 may complement existing diagnostic tools and improve early detection, especially in patients at high risk or with atypical presentations.

2. Prognostic value of miR-122 in heart failure:

Emerging evidence suggests that miR-122 holds significant prognostic value in heart failure (HF). Elevated plasma levels of miR-122 have been associated with markers of advanced disease and poorer clinical outcomes. Studies demonstrated that patients with high circulating miR-122 levels had a lower left ventricular ejection fraction (LVEF), higher NYHA functional class, elevated NT-proBNP levels, and an increased risk of hospital readmission and mortality(6). miR-122 may serve as a dual marker reflecting both cardiac dysfunction and hepatic congestion, two common features of advanced HF. This makes it particularly useful for assessing multi-organ involvement, which is a major determinant of prognosis in these patients. Incorporating miR-122 measurement into clinical practice may improve risk stratification and support personalized management strategies, enabling earlier intervention in high-risk individuals.

3. Comparison with Other Known Heart Failure Biomarkers:

Biomarker	Primary Source	Function	Use	Limitations
NT-proBNP	Cardiomyocytes	Released in response to stretch	Gold standard for HF diagnosis	Influenced by age, obesity, renal function

Troponin	Cardiomyocytes	Marker of myocardial injury	Useful in acute HF with ischemia	May be elevated in other conditions
miR-122	Liver (mainly)	Reflects systemic stress, inflammation, hepatic congestion	Early detection, prognosis, multi-organ stress	Not specific to cardiac origin

While NT-proBNP and troponin remain the cornerstone markers, miR-122 offers additional information — particularly for patients with coexisting hepatic dysfunction or metabolic stress. Its non-cardiac origin can be seen as both a limitation and an advantage**,** depending on the clinical context.

Conclusion:

miR-122 holds potential as a complementary biomarker in heart failure, with roles in early detection**,** especially in complex or comorbid presentations, Prognostication**,** predicting functional decline and adverse outcomes, multi-organ monitoring**,** capturing systemic effects of HF not visible with traditional markers. However, translating it from bench to bedside will require rigorous mechanistic studies**,** large-scale clinical validation**,** and advances in targeted delivery technologies**.** Its future role in personalized cardiovascular care remains an exciting frontier.

Acknowledgement:

I would like to acknowledge Mahatma Gandhi Medical College and Research Institute, SBV University, Department of Biochemistry and Department of Cardiology for the support while conducting the research.

Ethical oversight:

The study design was approved by IHEC.

Informed Consent Statement: The Consent was obtained from all patient's attender involved in the study.

Conflicts of Interest: The authors declared that there is no conflict of interest in the study.

Author Contributions: All authors have contributed to the study's conception and design, as well as the analysis have read and agreed to the published version of the manuscript.

Funding: The author thanks the ICMR-SRF category for the fellowship.

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