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Role of Biomarkers in the Early Detection of Heart Failure in Children

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Article Details

ABSTRACT

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Pediatric heart failure (HF) remains a major cause of morbidity and mortality and often presents with nonspecific clinical manifestations, making timely diagnosis and management challenging. Early detection is critical to prevent irreversible myocardial damage and to initiate appropriate therapeutic interventions. In recent years, the identification and validation of cardiac biomarkers have significantly advanced the diagnosis and prognostic evaluation of pediatric heart failure. This study aims to provide a comprehensive overview of key biomarkers used for the early detection and monitoring of heart failure in children. An extensive review of recent literature was conducted to evaluate diagnostic, prognostic, and inflammatory biomarkers associated with pediatric HF. Established biomarkers such as natriuretic peptides, including B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), along with cardiac troponins (cTnI and cTnT), demonstrate strong diagnostic and prognostic value by reflecting myocardial stress and injury. Emerging biomarkers, including Galectin-3, Growth Differentiation Factor-15 (GDF-15), and myeloperoxidase (MPO), provide additional insights into underlying pathophysiological mechanisms such as inflammation, oxidative stress, and myocardial fibrosis. The combined use of multiple biomarkers enhances diagnostic sensitivity and supports effective therapy monitoring. Incorporating biomarker profiling into clinical practice improves early diagnosis, risk stratification, and treatment monitoring in pediatric heart failure. Future research should focus on integrating biomarker data with advanced imaging modalities and machine learning approaches to improve diagnostic accuracy and facilitate personalized treatment strategies for children with heart failure.

INTRODUCTION:

Heart failure (HF) in children is a complex clinical syndrome characterized by the inability of the heart to meet the metabolic demands of the growing body (Lee et al., 2025). Pediatric heart failure remains a significant cause of morbidity, mortality, and prolonged hospitalization among children with congenital or acquired cardiac conditions (Burstein et al., 2019). Unlike adults, heart failure in children arises more commonly from congenital structural abnormalities, cardiomyopathies, or post-infectious myocardial injury, resulting in distinct pathophysiological mechanisms (Shaddy et al., 2018). Early detection of pediatric heart failure is crucial, as timely therapeutic intervention can improve clinical outcomes and prevent irreversible myocardial damage. However, early diagnosis remains challenging because clinical manifestations in pediatric patients such as fatigue, feeding difficulties, and tachypnea are often nonspecific and may overlap with symptoms of other childhood illnesses (El Radhi, 2023).

HF biomarkers play a particularly important role in pediatric populations by enabling early detection and risk stratification in children with systemic illnesses and an increased risk of cardiac dysfunction (Castiglione et al., 2022). An ideal biomarker should possess high sensitivity and specificity, allow simultaneous analysis of multiple samples, provide rapid results, be cost-effective, and offer potential therapeutic relevance (Ahmad et al., 2023). Biomarkers reflecting myocardial stress, injury, and remodeling include B-type natriuretic peptide (BNP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), cardiac troponins (cTnI), and growth differentiation factor-15 (GDF-15). These circulating biomarkers have demonstrated promising diagnostic and prognostic utility in both acute and chronic pediatric heart failure. Elevated levels of natriuretic peptides, for instance, are strongly associated with adverse clinical outcomes, reduced ejection fraction, and increased ventricular wall stress (Castiglione et al., 2022).

Recent studies have identified novel biomarkers, including galectin-2, soluble ST2 (sST2), high-sensitivity C-reactive protein (hsCRP), and microRNAs, which reflect inflammatory, fibrotic, and molecular remodeling processes involved in cardiac and hepatic dysfunction. Despite these advances, no widely accepted biomarker panel or validated cutoff values specifically tailored for pediatric populations are currently available (Lim et al., 2023). Interpretation of biomarker levels in children is further complicated by physiological and clinical factors such as growth, age, renal function, and coexisting illnesses, underscoring the need for age-specific reference ranges and standardized diagnostic protocols (Van Donge et al., 2019).

Causes of Heart Failure in Infants and Children

HF in children can be divided into two groups. Over-circulation failure and pump failure.

Over Circulation Failure

Over-circulation refers to conditions that lead to volume overload of the cardiac chambers, in which left ventricular (LV) function is typically preserved or may even be hypercontractile. Pulmonary venous or arterial hypertension may be present to a variable degree (Jayaprasad, 2016). Conditions associated with increased pulmonary blood flow are Left to right shunts like ventricular septal defects, patent ductus arteriosus, aortopulmonary window, and atrioventricular defect. Admixture lesions like total anomalous pulmonary venous connection, truncus arteriosus and single ventricle. Parallel circulation in transposition of arteries. Conditions causing increased cardiac output Anemia, systemic arteriovenous fistula, and beriberi (Rao, 2019).

Pump Failure

Pulmonary venous or arterial hypertension may be present to a variable degree. Causes of pump failure include both congenital and acquired conditions (Jones et al., 2023). LV or systemic ventricle function is abnormal and most patients have pulmonary venous hypertension in that group. The causes of pediatric heart failure can be grouped into several categories, including congenital, inflammatory, cardiomyopathy

and other specific conditions. Congenital causes involve structural heart defects that obstruct normal blood flow, such as left ventricular outflow tract obstruction (aortic stenosis), coarctation of the aorta, right ventricular outflow tract obstruction in pulmonary stenosis, and abnormal origin of the left coronary artery from the pulmonary artery. Ventricular dysfunction may also occur following surgical correction of congenital heart defects. Inflammatory causes include infections or inflammation of the heart muscle, such as viral myocarditis, HIV-related cardiomyopathy, and Chagas disease. Dilated cardiomyopathies arise from idiopathic, familial, neuromuscular, or metabolic origins, leading to enlargement and weakening of the heart chambers (Simpson and Miller, 2021).

Diagnostic Methods

Diagnostic methods are employed to identify the underlying causes and evaluate the severity of cardiac dysfunction in children. Diagnosis involves multiple modalities, including electrocardiography, echocardiography, chest radiography, cardiac magnetic resonance imaging (MRI), artificial intelligence–based tools, and the assessment of cardiac biomarkers. These diagnostic approaches are illustrated in Figure 1.

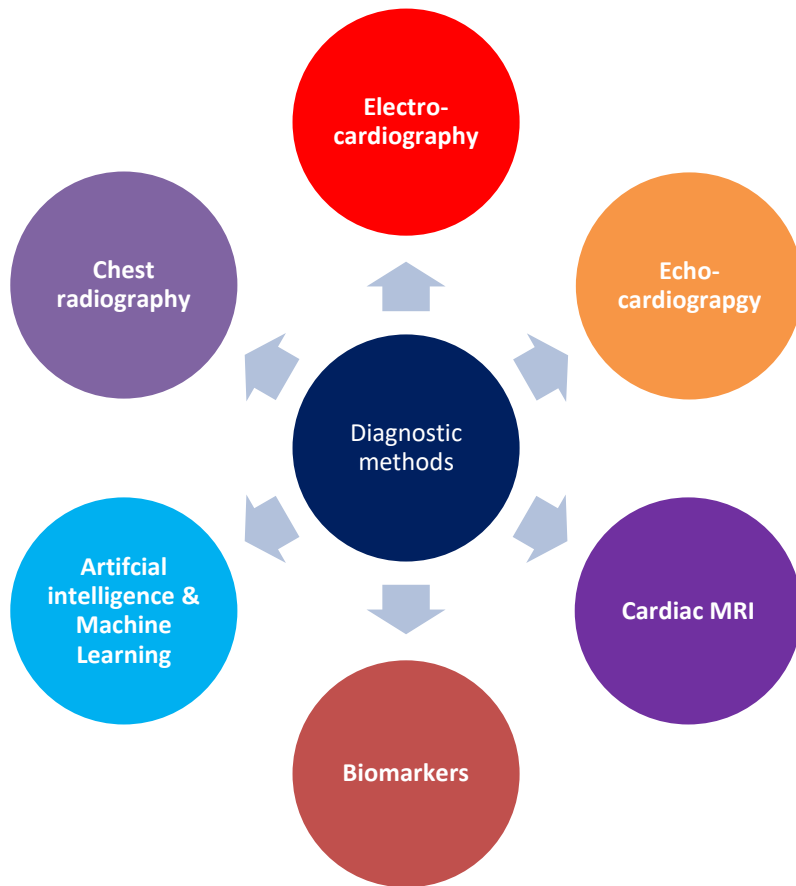


Figure 1. Diagnostic methods for the detection of heart failure in children

Electrocardiography

Children's ECG characteristics might vary and include atrioventricular conduction delays, low voltage QRS complexes in the limb leads, sinus tachycardia, nonspecific ST-T-wave alterations, T-wave inversion, and ST-segment elevation. The ST-segment alterations may indicate a diffuse or clearly defined coronary distribution pattern of myocardial damage or infarction. Pathologic Q waves can appear with time and cardiac injury; in one investigation, PCR was used to specifically diagnose parvovirus B19 myocarditis. Additionally, ST-segment elevation and PR depression may indicate the presence of pericarditis (Das and

Zipes, 2021). The presenting symptoms may include atrioventricular block, supraventricular tachycardias, ventricular tachycardia and fibrillation, and atrial fibrillation or flutter. When a patient with new-onset third-degree heart block, myocarditis should always be ruled out (Beijnink et al., 2021).

Echocardiography

In order to rule out any structural illness, transthoracic echocardiography is recommended in all pediatric heart failure situations. For comparisons in the future, baseline echocardiogram will be necessary. The current definition of LV systolic dysfunction in children is an ejection fraction (EF) of less than 55%. Additionally, echocardiography is helpful for screening individuals with neuromuscular problems, storage disorders, cancer patients receiving anthracycline chemotherapy, etc. First-degree relatives of patients with different hereditary types of cardiomyopathy must undergo periodic echocardiographic examination. For HF patients, periodic echocardiography follow-up is helpful for tracking the course of the disease and evaluating the effectiveness of treatment (Jayaprasad, 2016).

Chest Radiography

In order to determine the size of the heart and to look for further indicators of heart failure, such as pulmonary oedema, septal lines (also known as Kerley B lines), and pleural effusions, chest radiography is recommended for all children with suspected heart failure (Siwik et al., 2023). Children and teenagers experiencing severe chest pain are frequently examined with chest radiography. Chest radiography was performed on 35.6–72.0% of pediatric patients with chest discomfort in earlier investigations. Pneumonia/bronchitis, pneumomediastinum, pneumothorax, pneumopericardium, and cardiomegaly were common positive findings on chest radiography. Nevertheless, chest radiography's sensitivity was only 11.0–17.2% (Pissara et al., 2022).

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance is recommended for the research of complex CHDs or for tissue characterisation. As a result, it can be used for diagnosis, risk assessment, and continued treatment of individuals with particular types of cardiomyopathies (Mitchel et al., 2016). Relatively recent mapping sequences still need histologic validation, despite the fact that cardiac MRI-defined myocardial infarction parameters including infarct size, oedema, microvascular damage, and replacement fibrosis have solid histologic evidence (Beijnink et al., 2021).

Role of Artificial Intelligence and Machine Learning

The evolution in cardiovascular diseases requires advancements in the treatment and diagnostic techniques, thus AI is now being rapidly incorporated in the field of cardiovascular medicine. AI has the potential to revolutionize the medical diagnosis, treatment, risk prediction, clinical care, and drug discovery through the interpretation of vast databases more efficiently as compared to the human brain (Yasmin et al., 2021). Machine learning methods can handle temporal, large-volume, and multi-modality data e.g., sound, language, tabular electronic health record (EHR), imaging, and metabolomic data (Averbuch et al., 2022).

Biomarkers

Biomarkers are measurable indicators of disease, biological processes, or therapeutic response, providing crucial information for the early diagnosis, monitoring of disease progression, and evaluation of treatment efficacy. A variety of biomarkers have been identified in pediatric heart failure, reflecting myocardial stress, injury, inflammation, fibrosis, neurohormonal activation, oxidative stress, renal function, metabolism, and anthropometric factors, as described below and summarized in Table 1.

B-type Natriuretic Peptide (BNP)

Ventricular myocytes, mostly from the left ventricle, generate and release B-type natriuretic peptide (BNP) in response to pressure or volume excess of the ventricle (stretch) (Cantinotti, 2016). Human BNP is a 32-amino acid polypeptide with two cysteine residues joined by a disulphide bond and a 17-amino acid ring structure (Ludwikowska et al., 2024). In clinical applications, high BNP levels serve as a marker of ventricular wall stress and malfunction and are utilised to identify heart failure in both adults and children at an early stage. It has been demonstrated that BNP can distinguish between cardiac and non-cardiac causes of respiratory distress in children (Sulu et al., 2023).

N-terminal pro-B-type Natriuretic Peptide (NT-proBNP)

When proBNP is cleaved, it produces the active 32–amino-acid BNP and the 76–amino-acid inactive fragment NT-proBNP. Due to its longer half-life and greater stability, NT-proBNP serves as a more sensitive biomarker for detecting chronic or early-stage heart failure in children (Liu et al., 2021). NT-proBNP levels are less impacted by some treatments (such the usage of ARNI) since it is not immediately broken down by the enzyme neprilysin. As a result, it may be a more accurate measure of underlying cardiac strain in pediatric populations (Sbolli and deFilippi, 2020).

Cardiac Troponin (cTnI, cTnT)

When myocardial cells are damaged, cardiac troponins I and (T regulatory proteins of the cardiomyocyte contractile apparatus) are released into the bloodstream. In order to better identify extremely low troponin concentrations, high-sensitivity tests are being utilised more often to treat congenital cardiac disease and myocarditis in babies and neonates. Detectable or increasing troponin concentrations in children have been linked to severe systemic sickness, surgical cardiac damage, and myocardial injury from myocarditis; nevertheless, interpretation necessitates pediatric-specific reference ranges and clinical correlation. Thus, when combined with clinical evaluation and imaging, troponin serves as a sensitive biomarker of cardiac damage and has diagnostic and prognostic significance in pediatric heart illness (Clerico et al., 2021; Ferraro et al., 2024).

C-Reactive Protein (CRP / hs-CRP)

A common indicator of systemic inflammation, C-reactive protein is an acute-phase protein that the liver produces in reaction to cytokines like interleukin-6 (Schwuchow-Thonke et al., 2021). Recent research has demonstrated a correlation between myocardial inflammation, unfavorable remodeling, and prognosis in patients with cardiomyopathy and heart failure and high-sensitivity CRP (hs-CRP) tests, which are capable of detecting low-grade inflammation (Mitsis et al., 2025). Elevated hs-CRP may indicate the severity of congenital heart disease in children and can supplement cardiac biomarkers in risk stratification, according to pediatric research and pediatric-focused analyses. Therefore, when combined with other data, hs-CRP is a non-specific but therapeutically valuable inflammatory biomarker that provides predictive information in both adult and pediatric heart failure (Schwuchow-Thonke et al., 2021).

Galectin-3

Activated macrophages and fibroblasts generate galectin-3, a β -galactoside-binding lectin that stimulates inflammatory signalling, fibroblast activation, and myocardial fibrosis (Saleh et al., 2020). Higher galectin-3 concentrations in pediatric patients with congenital heart disease are correlated with heart-failure state and may help diagnose decompensation early, according to prospective data from 2020 (Zaborska et al., 2023). Galectin-3 primarily reflects the fibrotic/remodeling axis of cardiac illness and can supplement myocyte damage indicators in the evaluation of pediatric heart failure (BaniHani et al., 2025).

Neprilysin and the Natriuretic Peptide System

In order to reduce the beneficial cardiovascular effects of endogenous natriuretic peptides, such as BNP, the enzyme neprilysin is essential (Nakagawa and Saito, 2022). NT-proBNP, which is not a neprilysin substrate, is therefore function as an independent marker of cardiac status. In therapeutic contexts (such as with neprilysin inhibitors), BNP concentrations may initially rise (because breakdown is blocked) but may then decrease with effective therapy (Ludwikowska et al., 2024).

Myeloperoxidase (MPO)

A heme enzyme manufactured by neutrophils, myeloperoxidase produces reactive oxidant species and connects inflammation to oxidative tissue damage in the heart and blood vessels (El Kazzi et al., 2020). MPO is a predictive biomarker and a possible therapeutic target in heart failure, according to recent translational and clinical studies, which highlight MPO's function in increasing oxidative stress and maladaptive remodelling (Profire et al., 2025). The pathophysiologic evidence supports MPO as a marker of oxidative/inflammatory heart damage that may supplement other biomarkers in children with inflammatory or ischaemic myocardial illness, even if pediatric MPO-specific outcome data are currently few (Lin et al., 2024).

Cystatin C

Serum cystatin C is a sensitive indicator of renal function and early decreases in GFR because it is a low-molecular-weight cysteine protease inhibitor that is generated by all nucleated cells and primarily removed via glomerular filtration. In the context of pediatric cardiac surgery, research indicates that cystatin C increases prior to creatinine and is predictive of acute kidney damage and worse postoperative outcomes in children with congenital heart disease (Zakaria et al., 2022). Cystatin C's diagnostic utility for early postoperative AKI in pediatric cardiac surgery is further supported by systematic reviews and meta-analyses, which further highlight its prognostic significance for cardio-renal interactions. Thus, in children with heart disease, cystatin C is a helpful cardio-renal biomarker that can identify subclinical renal involvement that influences treatment and prognosis (Griva et al., 2025).

Adiponectin

Adiponectin is an adipocyte-derived hormone with insulin-sensitizing, anti-inflammatory and vasoprotective properties that modulates metabolic and inflammatory pathways relevant to cardiovascular disease (Jung and Jung, 2021). Complex relationships between circulating adiponectin and cardiovascular outcomes have been reported by recent large-scale observational and genetic analyses; some studies have linked elevated adiponectin to an increased risk of heart failure or death in advanced disease (Nielsen et al., 2024). In pediatric cardiology, focused investigations remain rare, but existing data show that altered adiponectin levels reflect metabolic dysregulation that can accompany congenital heart disease and may connect with cardiac dysfunction in children (Orlando et al., 2019).

Body Mass Index (BMI)-Dependent BNP Adjustment

Body mass index (BMI) exhibits a substantial inverse association with circulating BNP and NT-proBNP levels: greater BMI (obesity) is related with lower natriuretic peptide levels, either due to enhanced clearance or changed synthesis (Suthahar et al., 2021). In pediatric clinical practice this means that lower cut-off points of BNP (and NT-proBNP) may be required in obese children to maintain sensitivity, while higher cut-offs may improve specificity in lean children. Careful adjustment for BMI therefore enhances diagnostic accuracy of these biomarkers in children (Zrinski and Lenicek, 2025).

Type of Biomarker	Biomarker Name	Biological Source Mechanism	Clinical Significance	Occurs Before Indicates	References
Diagnostic Biomarker	B-type Natriuretic Peptide (BNP)	Secreted by ventricular myocytes in response to pressure or volume overload	Indicates ventricular wall stress and left ventricular dysfunction	Elevates before or during symptomatic heart failure	(Sulu et al., 2023)
Diagnostic Prognostic Biomarker	N-terminal proBNP (NT-proBNP)	Cleaved from proBNP; released by ventricles during myocardial strain	Strongly correlates with heart failure severity and prognosis	Rises early before clinical signs, useful for early detection	(Liu et al., 2021)
Prognostic Biomarker	Cardiac Troponins (cTnI, cTnT)	Released from damaged cardiac myocytes	Indicates myocardial injury or necrosis; helps assess disease severity	Increases during acute or worsening heart failure	(Ferraro et al., 2024)
Inflammatory Biomarker	C-reactive Protein (CRP)	Produced by hepatocytes during systemic inflammation	Reflects inflammation contributing to heart failure progression	Elevates before or during HF exacerbation	(Clerico et al., 2021)
Fibrosis Biomarker	Galectin-3	Expressed by macrophages and fibroblasts during cardiac remodeling	Marker of fibrosis and long-term ventricular dysfunction	Rises before chronic HF progression	(Saleh et al., 2020)
Neurohormonal Biomarker	Neprilysin (Neutral Endopeptidase, NEP)	Membrane-bound enzyme that degrades natriuretic peptides and vasoactive substances	High levels reduce BNP activity, associated with worse cardiac remodeling and HF severity	Increases before clinical worsening, used to guide ARNI (sacubitril/valsartan) therapy	(Nakagawa and Saito, 2022)
Oxidative Stress Biomarker	Myeloperoxidase (MPO)	Released by activated neutrophils; promotes	Reflects endothelial dysfunction and	Increases early, before significant structural cardiac damage	(El Kazzi et al., 2020)

		oxidative damage	myocardial stress		
Renal Function Biomarker	Cystatin C	Produced by nucleated cells; filtered by kidneys	Detects subclinical renal dysfunction secondary to HF	Rises before serum creatinine, showing early kidney impairment	(Zakaria et al., 2022)
Metabolic Biomarker	Adiponectin	Secreted by adipose tissue; regulates glucose and lipid metabolism	Low levels linked with inflammation and poor HF outcomes	Decreases before metabolic and vascular complications	(Jung et al., 2021)
Anthropometric / Prognostic Biomarker	Body Mass Index (BMI)	Ratio of body weight to height; reflects nutritional and metabolic status	Low BMI = malnutrition (poor prognosis); high BMI = increased cardiac load	Changes before clinical deterioration, indicates risk or progression of HF	(Suthahar et al., 2021)

Table 1 Mechanisms and clinical significance of different types of Biomarkers

Conclusion

Biomarkers offer a non-invasive insight into cardiac function, injury, and remodeling, playing a crucial role in the early detection and management of heart failure in pediatric patients. While BNP and NT-proBNP remain the most clinically validated markers for identifying early myocardial stress, cardiac troponins provide valuable information on myocardial necrosis. Inflammatory and fibrotic biomarkers, such as Galectin-3, MPO, and GDF-15, further enhance diagnostic capability by revealing the molecular pathways driving disease progression beyond traditional hemodynamic assessment. Looking ahead, multi-biomarker panels integrated with advanced imaging techniques, genetic profiling, and artificial intelligence based predictive models hold great promise for the management of pediatric heart failure. These approaches can improve diagnostic accuracy, guide timely therapeutic interventions, and ultimately enhance both the quality of life and survival outcomes for children with heart failure.

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