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Galectin-3: Heart failure biomarker in pediatric heart defects

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Abstract

Galectin-3 *(Gal-3), a β-galactoside-binding lectin, has emerged as a potential diagnostic and prognostic biomarker for various diseases, including certain heart and kidney diseases, as well as cancer. Its significance is particularly notable in the context of congenital heart defects (CHD), which are the most prevalent congenital malformations, occurring in 6 to 8 out of every 1000 live births. Symptoms of heart failure (HF) in patients with congenital heart defects can manifest early in life, but in some cases, the disease progresses gradually, leading to a progressive decline in quality of life and the development of various complications. This variability underscores the need for early biomarkers to detect HF development in pediatric patients. Gal-3 plays a key role in myocardial remodeling, making it a promising candidate for advancing the diagnosis and management of HF in CHD patients. It is especially relevant in pediatric care, where early detection and intervention can significantly alter disease progression and patient outcomes. This review aims to consolidate current knowledge on the utility of Gal-3 in predicting HF among pediatric patients with CHD, highlighting its potential to transform the diagnostic and therapeutic approach in this vulnerable patient population.* (Cardiol J 2025; 32, 2: 175–188)

Keywords: galectin-3, congenital heart defects, heart failure, biomarkers

Introduction

Congenital heart defects (CHD), the most common congenital defects in children, contribute to abnormal growth and development, impairing the cardiovascular system's functioning. In pediatric patients with these defects, cardiac muscle failure (HF, heart failure) may develop, which represents a major complication and poses a serious threat to health and life [1].

Heart failure is a complex pathological condition in which the heart is unable to supply adequate blood to the tissues for proper oxygenation and nutrition. Congenital heart defects affect both the structure and function of the heart, leading to hemodynamic disturbances and increased strain on the cardiac muscle, gradually impairing its efficiency. Consequently, this leads to decreased physical capacity, diminished quality of life, limitations in daily activities, and, in severe cases, direct threats to the lives of pediatric patients [1–3].

Heart failure in children with CHD can have multifactorial origins, depending on the severity and type of heart defect. It may result from shunt lesions, obstructive lesions, severe valve disease or other more complex structural heart defects. While HF symptoms might be evident in the first days of a patient's life in some cases, the disease might progress slowly, manifesting gradually over time in others [1–3].

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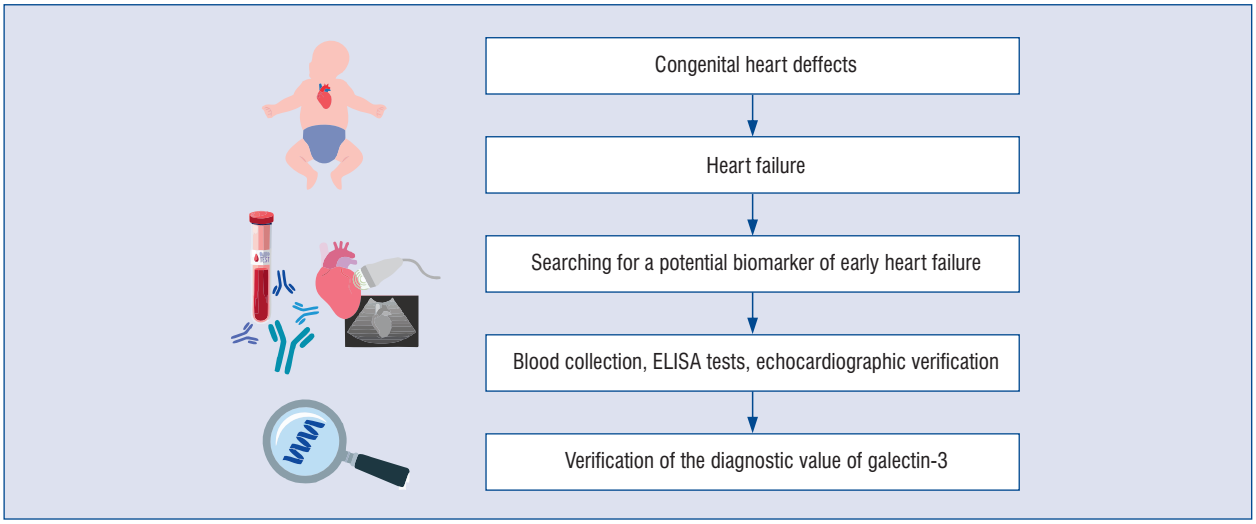

Central illustration. Diagnostic workflow for galectin-3 as a biomarker in pediatric heart failure. This illustration outlines the step-by-step process of identifying and verifying galectin-3 (Gal-3) as a biomarker for early heart failure (HF) in children with congenital heart defects (CHD). The workflow begins with CHD, the search for potential biomarkers of early HF is initiated. The process involves blood collection, ELISA tests, and echocardiographic verification to assess biomarker levels and their correlation with HF. Finally, the diagnostic value of Gal-3 is verified, highlighting its potential role in early detection and management of pediatric HF

Early and prompt diagnosis, along with appropriate HF treatment in children with CHD, pose a challenge for specialists in pediatrics and pediatric cardiology. A multi-stage approach, encompassing pharmacological therapy and surgical interventions, is often necessary to improve cardiac function and the quality of life for pediatric patients. Early detection can significantly impact the prognosis for children with HF [1, 2, 4].

The gold standard diagnostic tool for HF is an echocardiogram. However, due to the need for specialized equipment and experienced specialists, the lack of availability of equipment and shortage of pediatric cardiologists in various regions worldwide might lead to delayed or incorrect diagnoses [5]. Benavidez et al. [6] in a retrospective cohort study, highlighted those diagnostic errors in echocardiography significantly influenced clinical management in up to 66% of pediatric patients with CHD. The analysis also indicated that up to 77% of these errors were potentially preventable. A study conducted in 2015 evaluated the accuracy of diagnoses based on echocardiograms performed by non-specialized centers for children with CHD. It was found that only 8% of patients underwent echocardiography performed by a pediatric cardiology specialist. Diagnostic errors were observed in 38% of children, and in 23% of the cases, this directly affected the implementation of inappropriate therapeutic measures [7].

Biomarkers might be useful in diagnosing and monitoring HF in children. Usually, they would be used as a complement to echocardiography. Sometimes they could help determine patients that would need a more thorough follow up, which might be especially helpful in non-specialized centers or regions with few pediatric cardiologists. Some of biomarkers, such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) are already commonly used [8]. However, researchers continuously seek other effective biomarkers. One of them, that could significantly influence HF diagnosis and monitoring in future is galectin-3 (Gal-3). The advantages and possibilities of introducing this biomarker are summarized in the Central illustration.

The impact of galectin-3 on physiological cellular processes

Galectins belong to the lectin group, possessing one or several carbohydrate-binding domains (CRD, C-type carbohydrate recognition domain) that bind to β-galactosides. Currently, 15 types of galectins have been identified among mammals, classified into three groups based on the organization of their domains. These include prototype galectins (with a single CRD), galectins with tandem repeats (with two CRDs), and chimera-type galectins (with a single CRD connected to a flexible N-terminal domain), among which the best-known to date is Gal-3 [9].

Gal-3 is a protein with a molecular mass of 35 kDa, encoded in the human body by a single gene *LGALS3* located on chromosome 14. Its N-terminal domain is of fundamental importance for constructing polymeric structures, undergoing proteolysis by matrix metalloproteinases, and interacting with other intracellular proteins [10].

The proper secretion process of Gal-3 and its penetration into the cell nucleus depend on the presence of the initial sequence of 12 amino acids [11]. Meanwhile, the C-terminal CRD domain of Gal-3 is responsible for binding to glycoconjugates containing N-acetyllactosamine, allowing it to form bonds with proteins in the presence or absence of carbohydrates.

Gal-3 is predominantly located in the cytoplasm and also within cell nuclei, where it is transported. Additionally, it can undergo secretion onto cell surfaces or into body fluids. Due to its numerous localizations, this protein is responsible for many biological functions. Through its interaction with anti-apoptotic proteins, Gal-3 plays a significant role in the process of programmed cell death. Moreover, it activates pre-mRNA splicing in the cell nucleus and supervises gene transcription. Furthermore, it is responsible for intercellular interactions, including interactions between epithelial cells and the extracellular matrix, thus playing a significant role in the extracellular space. This protein also plays a crucial role in various biological processes, such as cell growth, differentiation, transformation, angiogenesis, the development of inflammation and fibrosis. Additionally, several renowned research centers have confirmed that Gal-3 is a significant factor involved in the pathogenesis of cardiovascular remodeling and various autoimmune and inflammatory processes [12].

Gal-3 is present in many tissues, including all types of immune cells such as macrophages, monocytes, dendritic cells, eosinophils, mast cells, NK cells, as well as T and B lymphocytes, and in epithelial cells, endothelial cells, and sensory neurons [13]. The expression of the gene responsible for encoding Gal-3 in tissues is mainly regulated during embryonic development, where a more specific pattern of protein expression dominates in epithelial cells, kidneys, chondrocytes, and hepatocytes. Studies conducted on rodents have shown that in mice lacking *LGALS3* gene expression, there was no increase in mortality, nor a higher percentage of developmental defects. The only noted negative consequence was a faster aging process [14]. Figure 1 illustrates selected cellular processes influenced by Gal-3.

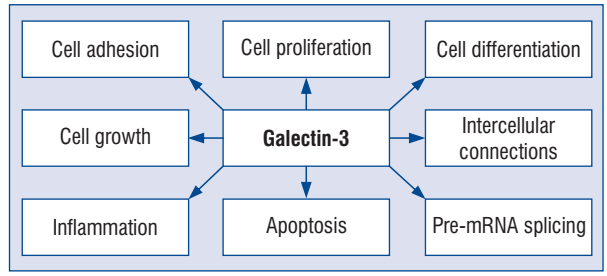

Figure 1. The impact of galectin-3 on cell physiology. This figure illustrates the multifaceted roles of galectin-3 (Gal-3) in cellular processes. Gal-3 influences critical aspects of cell physiology, including cell adhesion, proliferation, differentiation and growth. It also plays a role in maintaining intercellular connections and regulating pre-mRNA splicing. Furthermore, Gal-3 is involved in the processes of inflammation and apoptosis, highlighting its importance in both normal cellular function and pathological conditions. These diverse effects underscore its central role in cellular homeostasis and its potential as a biomarker in disease progression

Gal-3 can serve as a sensitive biomarker, independent of age, body mass, gender, or circadian rhythm. A slight increase in its concentration is observed during periods of increased activity, returning to baseline levels after a few hours [15]. Thanks to these properties, this marker has found application in the diagnosis and prediction of various diseases, making it a potential therapeutic target in treatment. Both an increase and decrease in Gal-3 levels can indicate an ongoing pathological process, such as cardiovascular disease, tumor formation, infectious conditions, or abnormalities associated with kidney or liver function [16].

Pathophysiological mechanisms of increased galectin-3 levels in congenital heart disease

As previously mentioned, CHD can significantly affect heart function and the development of HF. The pathophysiological mechanisms through which CHD contributes to increased levels of Gal-3 include several key processes:

— Chronic pressure and volume overload: CHD, such as aortic valve stenosis or pulmonary artery stenosis, lead to chronic pressure overload in the heart. Other defects, such as patent ductus arteriosus or atrial septal defect, lead to volume overload [17]. Both conditions can cause stretching and damage to the heart walls, stimulating the release of Gal-3. Gal-3, by stimulating fibroblast proliferation and collagen production, plays a key

role in this process, leading to further stiffening of the heart muscle and progression of heart failure [18]. Additionally, in these conditions, levels of other heart failure biomarkers, such as NT-proBNP, may also rise, indicating hemodynamic stress and heart overload [17].

— Fibroblast activation and fibrosis: Chronic heart overload leads to the activation of fibroblasts in the heart muscle. Gal-3 plays a crucial role in the transformation of fibroblasts into myofibroblasts, which are the main cells involved in heart fibrosis. Myofibroblasts produce collagen and other extracellular matrix components, leading to heart fibrosis and further increasing Gal-3 levels [19]. Studies have shown that the recombinant form of Gal-3 can induce the transformation of inactive fibroblasts into myofibroblasts, leading to the proliferation of cardiac fibroblasts and stimulating the synthesis of transforming growth factor-beta, collagen production, and the expression of cyclin D1 [19, 20]. Other biomarkers, such as suppression of tumorigenicity 2 (ST2) and matrix metalloproteinase-9 (MMP-9), can also rise in response to fibrosis and remodeling processes [21].

— Inflammatory response stimulation: CHD are often associated with chronic inflammation. Gal-3 is a protein involved in the inflammatory response, binding to immune cells such as macrophages. Activation of macrophages by Gal-3 leads to the release of pro-inflammatory cytokines, such as interleukin-4 (IL-4) and interleukin-13 (IL-13), which further exacerbate inflammatory processes and fibrosis. MacKinnon et al. revealed that the binding of Gal-3 to the membrane protein CD98 on macrophages activates the phosphoinositide 3-kinase (PI3K) pathway and alternative activation. This stimulation results in increased expression of IL-4, IL-13, and the accumulation of extracellular matrix components, particularly collagen [22, 23]. In these conditions, levels of C-reactive protein (CRP) and Tumor necrosis factor-α (TNF-α), markers of inflammation may also increase [24].

— Endothelial dysfunction: CHD can cause damage and dysfunction of endothelial cells in blood vessels, leading to disturbances in the production of nitric oxide and other vascular mediators. Endothelial dysfunction is associated with elevated Gal-3 levels, which promote inflammatory and fibrotic processes within the vessel walls and heart muscle [25]. Other biomarkers, such as asymmetric dimethylarginine (ADMA) and the von Willebrand factor, can also indicate endothelial dysfunction [26].

— Oxidative stress: Hemodynamic disturbances associated with CHD can lead to increased oxidative stress in heart cells. Gal-3 can increase the expression of enzymes such as nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase, leading to the production of reactive oxygen species (ROS). ROS cause cellular damage, enhance inflammatory states, and promote fibrosis, contributing to further increases in Gal-3 levels. Reports indicate Gal-3's ability to increase the expression of NADPH oxidase 4 (NOX4) in heart cells and to regulate levels of ROS originating from NOX4 during the cardiac fibrosis process [27]. In a study published in 2018 by Ibarrola et al. [28], it was demonstrated that Gal-3 can cause cardiac damage by promoting oxidative stress in human cardiac fibroblasts and in animal and human heart disease models. It was also shown that Gal-3 reduces the level of the protective enzyme fumarate hydratase, increases fumarate production, and stimulates the release of the oxidative stress mediator, which is present in the cardiac muscle of HF patients and correlates with left ventricular dysfunction [29, 30].

These pathophysiological mechanisms demonstrate how CHD can lead to elevated levels of Gal-3 through complex interactions between mechanical overload, inflammation, oxidative stress, and fibrosis processes. All these processes contribute to the progression of HF and highlight the importance of Gal-3 and other biomarkers in assessing and managing patients with CHD. Figure 2 illustrates pathways involved in HF development with the involvement of Gal-3.

Development based on extensive research, it can be speculated that Gal-3 may serve as a potential biomarker, which is promising in predicting and diagnosing HF [31, 32]. The aim of this review is to present the current knowledge on Gal-3 as a potential HF biomarker in pediatric patients with CHD.

Methods

A literature review was performed using the "PRISMA" criteria [33]. A review of the scientific literature was conducted on May 15, 2023, using online databases: PubMed and Scopus. "galectin 3 AND heart failure pediatric patients congenital

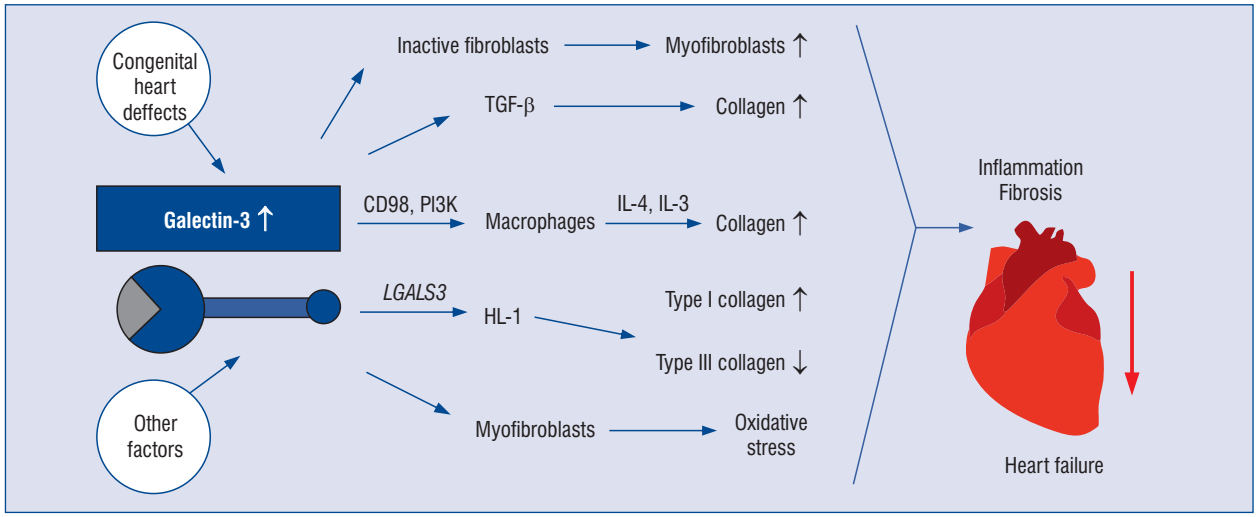

Figure 2. The impact of galectin-3 in the pathomechanism of heart failure development. The key molecular pathways and factors involved in HF progression related to Gal-3. TGF-β promotes the activation of inactive fibroblasts into myofibroblasts, leading to increased collagen production. CD98 and PI3K stimulate macrophages, which release IL-4 and IL-13, further enhancing collagen synthesis. The gene LGALS3, encoding Gal-3, plays a central role in these processes, including the activation of HL-1 cardiac muscle cells. Additional factors contribute to oxidative stress, type I and type III collagen production, and the transition to myofibroblasts, culminating in inflammation, fibrosis, and HF; CD98 — cluster of differentiation 98; Gal-3 — galectin-3; HF — heart failure; HL-1 — cardiac muscle cell line I; IL-4 — interleukin-4; IL-13 — interleukin-13; LGALS3 — a gene encoding galectin-3; PI3K — phosphoinositide 3-kinase; TGF-β — transforming growth factor beta

heart defects (*i*) OR pediatric heart failure (*ii*) OR Congenital heart defects pediatric patients (*iii*)" were formulated as a research question for the review. Thirty-five (n = 35) records from the PubMed database and thirty-two (n = 32) records from the SCOPUS database were obtained. Thirty-four (n = 34) duplicates were removed.

Two authors independently reviewed thirty-three (n = 33) records selected in stage one. The inclusion criteria were: Polish or English language of the study (*a*), studies associated with utility of Gal-3 as a biomarker for HF in pediatric patients due to CHD (*b*). Studies older than 10 years (*c*), conducted on animal models (*d*) and in the form of reviews, conference reports or letters to the editor (*e*) were established as exclusion criteria. For further review authors included ten (n = 10) available reports which met the mentioned criteria. The study selection process is illustrated in **Supplementary Figure 1**, which presents a PRISMA flowchart detailing the identification of studies via databases.

The risk of bias in the analyzed studies was assessed using the Critical Appraisal Skills Programme (CASP) [34]. Two independent researchers conducted a bias risk assessment to ensure objectivity and accuracy of the results. Each researcher analyzed the studies against key CASP criteria, such as clearly formulated research questions, cohort recruitment, accuracy in measuring exposure and outcomes, identification and consideration of confounding factors, and completeness of observation. The results of the bias risk assessment are presented in **Supplementary Table 1**.

Results

The review of studies indicates that Gal-3 is a sensitive and specific biomarker for early diagnosis and assessing the severity of HF in pediatric patients with CHD, significantly predicting rehospitalization and mortality risks, although it does not show a significant correlation with HF development in cases of tetralogy of Fallot (ToF) and aortic coarctation (CoA). The results of the review have been summarized and presented collectively in Table 1. The proposed cut-off points and concentrations of Gal-3 suggesting the diagnosis of HF are also presented in Table 1. The values should be interpreted with caution, taking into consideration other factors that may influence Gal-3 concentrations, which is further discussed below.

Table 1. Summary of studies on galectin-3 and heart failure in pediatric patients

Publication (authors and year)	Study design	N (control/ /patients)	Age (median/ range)	Diagnosis	Outcome category	Final outcome	Biomarkers	Correlation (yes/no)	Additional information
Saleh et al., 2020 [35]	C	40/75	3.7 ± 2.89 years	CHD with and without HF	Ross classification, Gal-3, EF, HF	HF symptoms, reduced EF	Gal-3	YES (r = 0.69, p = 0.018)	Gal-3 cutoff ≥ 10.4 ng/dL, AUC = 0.96; no significant correlation with mortality (p = 0.08)
Elhewala et al., 2020 [36]	CC	40/20	15.48 ± 10.072 months	CHD	Ross classification, Gal-3	HF progression, clinical severity	Gal-3	YES (sensitivity 80%, specificity 100%)	Average galectin-3: 25.93 ± 14.35 ng/dL in pediatric HF patients
Parker et al., 2020 [37]	C	145 (cohort)	Aged 18 years or younger	CHD post-surgery	ST2, Gal-3, GFAP, RACHS-1	Postoperative complications (365-day)	Gal-3, ST2, GFAP	YES (AUROC = 0.805, p = 0.036)	Median: 23.34 ± 12.82 ng/dL; IQR: 14.35–37.16 ng/dL; worse prognosis, rehospitalization risk. Composite endpoint: rehospitalization, heart failure, mortality. Further studies needed
Cura et al., 2022 [38]	CC	22/22	Infants	VSD	Gal-3, NT-proBNP, aldosterone	LV remodeling	Gal-3, NT-proBNP	YES (p = 0.015)	Galectin-3 cutoff > 3.62 ng/mL, sensitivity 59.1%, specificity 86.4%
Brown et al., 2019 [43]	C	162 (cohort)	Aged 18 years or younger	CHD post-surgery	Gal-3, NT-proBNP	Rehospitalization, mortality (30-day post-surgery)	Gal-3, NT-proBNP	YES (p < 0.05)	Median: 24.49 ng/dL; IQR: 15.38–37.01 ng/dL; worse prognosis, rehospitalization. Composite endpoint: rehospitalization and mortality 30 days post-surgery
van den Bosch et al., 2021 [46]	MC	133 (cohort)	19.2 years/ (14.6–25.7)	CHD post-Fontan surgery	Gal-3, NT-proBNP, ST2	Composite endpoint (death, arrhythmia, VO2 max ≤ 65%)	Gal-3, NT-proBNP, ST2	NO (Gal-3 p = 0.9)	NT-proBNP (p = 0.004) and ST2 (p = 0.04) significant
Van den Bosch et al., 2022 [49]	MC	137 (cohort)	19.2 years/ (14.6–25.7)	CHD post-ToF repair	Gal-3, NT-proBNP, ST2	Composite endpoint (death, arrhythmia, VO2 max ≤ 65%)	Gal-3, NT-proBNP, ST2	NO (Gal-3 p = 0.09)	NT-proBNP and ST2 significant (p = 0.04). Composite endpoint includes non-HF outcomes
Di Lorenzo et al., 2022 [50]	CS	60 (no controls)	15 years	ToF post-surgery	Gal-3, MMP-1, CMR	RV and LV remodeling	Gal-3, MMP-1	NO (Gal-3 p > 0.05)	MMP-1 correlated with remodeling (p < 0.05)
Frank et al., 2019 [55]	C	27 (cohort)	Mean 0.70 years	CoA post-surgery	Gal-3, ET-1, ST2	LV remodeling and mass	Gal-3, ET-1, ST2	NO (Gal-3 p > 0.05)	ET-1 and ST2 correlated with LV remodeling (p < 0.05)

AUC — area under the curve; AUROC — area under the receiver operating characteristic curve; C — cohort study; CC — case-control study; CHD — congenital heart disease; CMR — cardiac magnetic resonance; CS — cross-sectional; EF — ejection fraction; ET-1 — endothelin-1; Gal-3 — galectin-3; GFAP — glial fibrillary acidic protein; HF — heart failure; LV — left ventricle; MC — multicenter cohort study; MMP-1 — matrix metalloproteinase-1; NT-proBNP — N-terminal pro-B-type natriuretic peptide; OR — odds ratio; RACHS-1 — risk adjustment for congenital heart surgery-1; RV — right ventricle; ST2 — suppression of tumorigenicity 2; VO2 max — maximum oxygen consumption; VSD — ventricular septal defect

Discussion

The predictive value of galectin-3 in predicting the development of heart failure in pediatric patients with congenital heart defects

Saleh et al. [35], recognizing the severity of HF development in pediatric patients with CHD, conducted a cohort study at Menoufia University to verify the clinical and diagnostic utility of Gal-3 as a biomarker. The study involved three groups: pediatric patients with CHD and HF symptoms with reduced ejection fraction (n = 45), children with CHD but without HF symptoms and normal ejection fraction (n = 30), and a control group without cardiac conditions (n = 40). The findings revealed a significant increase in Gal-3 levels in the first group compared to the other subgroups ($p < 0.001$). Additionally, Gal-3 levels showed a positive correlation with the Ross classification ($r = 0.69$, $p = 0.018$) and a negative correlation with ejection fraction ($r = -0.61$, $p < 0.001$). Further statistical analysis demonstrated that Gal-3 provided superior prognostic value for early HF diagnosis in CHD patients compared to the Ross classification. A Gal-3 cutoff concentration of ≥ 10.4 ng/dL exhibited high sensitivity (96.7%) and specificity (90%), with a positive predictive value of 93.2% and an area under the curve (AUC) of 0.96, yielding an overall accuracy of 93%. Despite these strong diagnostic results, the study did not find a statistically significant correlation between serum Gal-3 levels and HF-related mortality ($p = 0.08$). However, the authors emphasized that Gal-3 measurement could serve as a valuable prognostic tool for enhancing the early detection of HF in pediatric patients [35].

While Gal-3 demonstrated impressive sensitivity and specificity, the study also highlighted the importance of careful interpretation of these results in clinical settings. The test's specificity — its ability to accurately identify individuals without HF — can be influenced by broader clinical factors, such as infections or inflammation, which may elevate Gal-3 levels [9]. This potential for false positives introduces complexity into the use of Gal-3 as a diagnostic tool. Clinicians must account for these variables, ensuring that Gal-3 results are considered in conjunction with other clinical assessments to avoid misinterpretation and over-diagnosis.

A team led by Elhewala [36] in 2020 conducted a similar study to assess the diagnostic utility of Gal-3 in predicting the development of HF in pediatric patients with CHD. Their analysis demonstrated significantly higher Gal-3 levels in CHD patients compared to controls (18.62 ± 13.056 ng/dL vs. 4.67 ± 1.97 ng/dL). A statistically significant positive correlation was observed between Gal-3 levels and the Ross classification, indicating that higher Gal-3 levels were associated with more severe HF progression. The study showed that Gal-3 had high predictive value, with sensitivity reaching 80% and specificity at 100% for detecting heart muscle impairment in progressing HF cases. The authors suggested that Gal-3 could be an important supplementary tool for diagnosing HF in children with CHD, as it also serves as a marker for disease severity.

However, the findings from Elhewala's team also emphasize the importance of contextualizing these results in real-world clinical practice. While the study reported perfect specificity, meaning that the test was highly effective in identifying patients without HF, the accuracy of such tests can be challenged by factors outside controlled environments. The factors mentioned earlier could elevate Gal-3 levels independently of HF, leading to false positives. This underscores the necessity of considering pre-existing conditions and the patient's overall clinical presentation. Though the pre-test probability does not change the fundamental sensitivity or specificity of the biomarker, it plays a crucial role in how the test results are interpreted. Therefore, Gal-3 should not be viewed as a standalone diagnostic marker but as part of a broader diagnostic toolkit, ensuring that clinicians avoid overdiagnosing or overtreating conditions based solely on Gal-3 levels. In 2020, Parker et al. [37] conducted a prospective cohort study (n = 145) assessing the application of innovative biomarkers such as ST2, Gal-3, and glial fibrillary acidic protein (GFAP) in predicting clinical complications in pediatric patients after at least one CHD operation. The Risk Adjustment for Congenital Heart Surgery-1 (RACHS-1) model enriched with ST2 and Gal-3 values showed a statistically significant improvement in the predictive model performance from area under the ROC curve (AUROC) = 0.719 to AUROC = 0.805 ($p = 0.036$). The authors emphasized the necessity for further multicenter studies to confirm the diagnostic effectiveness of Gal-3 [37].

Understanding the potential diagnostic and therapeutic uses of Gal-3, Cura et al. [38] published a study in 2022 aimed at verifying the association of this biomarker with left ventricular dilation in 22 infants with ventricular septal defects. The

study also measured levels of aldosterone and NT-proBNP, comparing results with a healthy control group. They found a statistically significant difference in Gal-3 concentration, with a median of 4.0 ng/mL in pediatric CHD patients and 2.5 ng/mL in healthy children ($p = 0.015$). NT-proBNP also demonstrated strong diagnostic utility ($p = 0.003$), while aldosterone levels showed no significant difference between the groups ($p = 0.8$). No statistically significant difference was noted between the predictive capabilities of Gal-3 and NT-proBNP ($p = 0.6$). At a cutoff of > 3.62 ng/mL, Gal-3 showed a sensitivity of 59.1% and specificity of 86.4%, which were comparable to NT-proBNP's sensitivity (90.9%) and specificity (63.6%). The researchers concluded that Gal-3 levels increased independently with left ventricular enlargement, suggesting that Gal-3 has diagnostic potential similar to NT-proBNP [38]. Although Gal-3 demonstrated acceptable specificity (86.4%) in this study, the authors pointed out that its real-world diagnostic performance could be influenced by factors as mentioned earlier, which may elevate Gal-3 levels regardless of heart failure progression. Therefore, while Gal-3 presents promise as a biomarker, it should be used alongside other clinical data, and its application in complex cases requires careful consideration. Further research is needed to confirm its broader clinical utility and therapeutic potential in pediatric heart failure cases.

The predictive value of galectin-3 in predicting the development of heart failure in pediatric patients with congenital heart defects after cardiac surgery

Rehospitalization within 30 days post-surgery is experienced by 10 to 20% of children undergoing CHD surgery, with 4% of these surgeries resulting in death [39]. This constitutes a significant emotional and financial burden and is a notable issue for the healthcare system [40]. In recent years, scientists have discovered and developed predictive models that aid clinicians in identifying patients at the highest risk of complications after CHD surgeries in children with progressive HF. Unfortunately, there are few studies dedicated to predicting rehospitalization or mortality after such surgeries, especially concerning biomarker analysis compared to clinical data [41, 42]. Therefore, in 2019, Brown et al. [43] decided to conduct a study to assess the relationship between new biomarker levels before and after surgery and 30-day unplanned rehospitalization or mortality in a cohort of 162 pediatric patients, post-CHD surgery with progressive HF. Blood samples were collected to measure the concentrations of 4 examined biomarkers, including Gal-3. The analysis, using three predictive models developed by the research team, aimed to determine which serum biomarker concentration could serve as a potential prognostic marker. The introduction of new clinically available biomarkers showed a statistically significant increase in the effectiveness of predictive models, with AUC increasing from 0.617 to 0.802 ($p = 0.003$). The study revealed that pre- and post-operative log-transformed Gal-3 concentrations correlated with 30-day unplanned rehospitalization or mortality after CHD surgery in children ($p < 0.05$). Importantly, the researchers focused on a short-term postoperative period, assessing outcomes within the first 30 days after surgery. Interestingly, such correlation was not observed in case of NT-proBNP concentrations. Thus, the use of Gal-3 may enhance the ability to predict the risk of 30-day readmission or mortality after pediatric cardiothoracic surgeries.

In another previously cited study from the USA, researchers observed a statistically significant association between preoperative Gal-3 levels and a twofold increased risk of rehospitalization or death within a year following CHD operations ($p < 0.05$) [37]. The same research team conducted a study in 2019 involving 244 children undergoing CHD-related cardiothoracic procedures hospitalized at Johns Hopkins Children's Center in the USA. To predict the development of postoperative complications, the authors decided to use commonly known markers of cardiomyocyte fibrosis, namely Gal-3 and ST2. Biomarker concentrations were measured both before and after cardiothoracic surgery in heparinized plasma. The analysis of the results showed that the postoperative middle tertile of Gal-3 concentration was significantly associated with rehospitalization in the 30-day postoperative period, progressive HF and mortality [odds ratio (OR): 6.17; 95% confidence interval (CI): 1.50–25.43], similar to the highest tertile of both pre- and post-operative ST2 concentrations. The study indicates that elevated postoperative Gal-3 levels are significantly associated with increased rehospitalization or mortality risk in the postoperative period for pediatric patients. The scientists also confirmed the predictive effectiveness of ST2 protein. Moreover, the findings demonstrate the potential utility of Gal-3 as a marker in classifying the risk of developing cardiac complications and in improving postoperative care quality [44].

Patients undergoing Fontan surgery are at high risk of developing multiple complications, including HF [45]. To understand which biomarkers can aid in predicting the development of these complications, van den Bosch et al. [46] conducted a multicentred study in 2021 involving 133 pediatric patients who underwent Fontan surgery. The study focused on long-term outcomes, with a median follow-up of 17.3 years after surgery, and the median age at the time of biomarker assessment 19.2 years (range 14.6–25.7 years). Researchers aimed to verify the predictive value of 10 biomarkers, including Gal-3. However, no statistically significant correlation was found between Gal-3 levels and the development of HF in pediatric patients after Fontan surgery ($p = 0.9$). The study also used a composite endpoint that included cardiac death, arrhythmias, hospitalization for arrhythmias, or a VO2 max ≤ 65% of predicted. Importantly, not all components of this composite endpoint may be relevant to the review, as VO2 max reduction, though useful for prognosis, may not directly reflect hard clinical outcomes like death or hospitalization. Nevertheless, the scientists confirmed that certain biomarkers, particularly NT-proBNP ($p = 0.004$) and ST2 ($p = 0.04$), may play a significant role in long-term clinical observation and risk stratification in these patients [46].

Tetralogy of Fallot (ToF) is among the most common CHD, with current survival rates reaching 95% in patients at 10 years old and over 90% in those at 25 years old. However, patients still often experience long-term problems, mainly associated with residual pulmonary valve insufficiency. Additionally, frequent occurrences of right ventricular dilation, ventricular dysfunction, and arrhythmias are observed during long-term follow-ups [47, 48].Despite significant progress in diagnosing and predicting HF, there is still a lack of sufficient research on biomarkers in young patients with CHD, particularly in ToF cases. In 2022, van den Bosch et al. [49], conducted a study focused on the long-term outcomes of 137 patients who underwent ToF repair surgery. The study assessed patients with a median of 17.3 years after surgery and followed them for a median of 8.7 years, aimed to evaluate the predictive value of several biomarkers. Importantly, the median age of patients at the time of biomarker assessment was 19.2 years (ranging from 14.6 to 25.7 years), meaning biomarkers were measured in young adults and older adolescents, long after their surgical interventions. The study found no statistically significant correlation between Gal-3 levels ($p = 0.09$) and the development of HF in ToF patients [49]. However again, it is important to highlight that the study used a composite endpoint, which included cardiac death, arrhythmias, hospitalization for arrhythmias, or a VO2 max ≤ 65% of predicted. While VO2 max is an important prognostic indicator, it may not directly reflect harder clinical outcomes, such as death or hospitalization, which should be considered when interpreting the study's conclusions. In 2022, Di Lorenzo et al. [50] conducted a study on 60 pediatric patients who underwent cardiac surgery for ToF, aiming to compare the concentrations of selected markers, including Gal-3, with cardiac muscle remodeling observed through cardiac magnetic resonance (CMR). The analysis did not show a statistically significant correlation between Gal-3 levels and changes in the cardiac muscle ($p > 0.05$). However, higher levels of another biomarker — matrix metalloproteinase-1 (MMP-1) — were strongly correlated with a higher left and right ventricular mass index ($p < 0.05$), indicating ongoing remodeling processes. The study focused on long-term outcomes after ToF repair, with patients being evaluated a median of 15 years post-surgery, and the median age of the participants at the time of biomarker assessment was 15 years. While Gal-3 did not show statistically significant correlations with clinical or imaging markers of ventricular remodeling, MMP-1 emerged as a promising indicator, particularly in relation to ventricular mass and the right ventricular mass-to-volume ratio.

Isolated coarctation of aorta (CoA) occurs in about 8% of all CHD cases, and most patients with severe CoA require an operation to reduce the left ventricular (LV) strain caused by high pressure [51]. Additionally, children affected by the disease are at risk of long-term complications, including chronic hypertension, cardiac mechanical disorders, and LV hypertrophy, present in as many as 50–65% of cases [52]. Heart remodeling is noticeable in many patients already during the first operation [53]. The presence of echocardiographic indicators of LV remodeling at the time of diagnosis suggests the possibility of activating significant pathological pathways earlier [54]. Mechanisms behind early LV remodeling and the variable process of reversed remodeling in this population remain unexplored. A better understanding of such pathways and patterns of their activation represents a promising perspective for understanding disease progression mechanisms, improving prognostic accuracy, and delineating targeted therapy in the future. In 2019, Frank et al. [55] conducted a study to evaluate the role of several promising biomarkers in a pediatric cohort of 27 patients with CoA undergoing surgery.

Biomarker concentrations were measured in heparinized plasma before and after surgery. The study found no statistically significant correlation between Gal-3 levels ($p > 0.05$) and the development of HF or persistent LV abnormalities. Additionally, no association was observed between preoperative levels of other biomarkers and factors such as the type of surgical procedure, use of preoperative prostaglandin or milrinone infusion, or prenatal diagnosis of CoA. Focusing on long-term outcomes, the study followed patients for about a year post-surgery. The average age at surgery was 0.70 years, ranging from neonates to children up to 18 years. Endothelin-1 (ET-1) was significantly associated with increased LV mass index and relative wall thickness at follow-up ($p < 0.05$), indicating its potential as a marker for persistent LV remodeling. Lower ST-2 levels were also linked to LV abnormalities, enhancing the predictive accuracy when combined with ET-1. In contrast, BNP and norepinephrine (NE) showed expected changes based on the patients' condition but did not correlate with long-term LV remodeling. Overall, while Gal-3 lacked predictive value, ET-1 and ST-2 emerged as key markers for assessing long-term risks in post-CoA repair patients, warranting further research [54].

Limitations of the studies

The limitations of the studies can be characterized as follows:

- Small sample size: The study was conducted at a single facility and involved a rare condition, resulting in a limited number of cases. This small sample size hindered detailed multivariate analyses to fully assess all potential confounding factors [43, 44, 50, 55].
- Clinical heterogeneity: There was significant diversity in clinical presentations and ages among patients, which could introduce additional variables affecting biomarker levels independently or in conjunction with LV pressure load [46, 50, 55].
- Low incidence of persistent LV abnormalities: The incidence of persistent LV abnormalities was lower than previously reported, reducing the statistical power of the study. This discrepancy might be due to differences in observation periods or classification methods [55].
- Observational study design: The prospective and longitudinal design of the study is limited by its observational nature, which prevents drawing definitive conclusions about causality between biomarkers and myocardial changes [44, 46, 55].
- Single center study: Conducting the study at a single center may limit the generalizability of the findings. The results might not be fully representative of the broader population with CHD, as practices, patient demographics, and care standards can vary between different institutions [36, 43].
- Need for further research: To validate these findings and gain a better understanding of the mechanisms leading to persistent LV changes, further studies involving larger cohorts and multiple centers are needed [36, 37, 44, 46, 55].

These limitations indicate the need for further, more comprehensive research to fully understand and confirm these findings.

Comparison of other potential biomarkers of HF investigated in pediatric patients with congenital heart defects

The studies analyzed various biomarkers for diagnosing HF in patients with CHD, including Gal-3, NT-proBNP, ST2, Insulin-like growth factor-binding protein 7 (IGFBP-7), MMP1, and matrix metalloproteinase-2 (MMP2). Elevated ST2 levels, both pre- and post-surgery, were linked to a higher risk of rehospitalization or death within a year. High pre-surgery Gal-3 levels also indicated a similar risk. NT-proBNP, although a recognized marker in adults, was not associated with increased risk in this study. In terms of diagnostic accuracy, Gal-3 had a sensitivity of (59.1%) and a specificity of (86.4%) at a threshold of 3.62 ng/mL, while NT-proBNP, with a threshold of 96.42 pg/mL, showed a sensitivity of (90.9%) and specificity of (63.6%) [43].

The significant associations between ST2 and Gal-3 levels both before and after pediatric heart surgeries and the risk of rehospitalization or mortality within 30 days were confirmed. Even after considering clinical factors and new preoperative biomarkers, a significant correlation between preoperative ST2 levels and subsequent readmission or mortality remained significant. NT-proBNP did not show an association with 30-day readmission or mortality in this study. Higher levels of ST2 and Gal-3 both before and after surgeries were associated with the risk of rehospitalization or mortality. Even after adjustment, higher levels of these biomarkers in the highest tertiles often correlated with a greater probability of readmission or mortality. Patients with lower levels of these biomarkers had significantly lower risk of 30-day readmission or mortality [43].

Comparison between NT-proBNP and galectin-3: Limits and practical usefulness in clinical diseases

NT-proBNP is a biomarker released from the heart in response to ventricular stretching and volume overload [56]. It is widely used for diagnosing and managing HF, with well-established thresholds aiding in prognosis and therapeutic decision-making. However, NT-proBNP has its limitations. It lacks specificity as its levels can be elevated in conditions other than HF, such as renal dysfunction, acute coronary syndromes, and pulmonary hypertension, complicating differential diagnosis. Additionally, NT-proBNP levels increase with age and can be affected by gender, necessitating age- and gender-specific reference ranges. Impaired renal function significantly impacts NT-proBNP levels, often leading to false positives due to the role of kidneys in NT-proBNP clearance. Moreover, while effective in acute HF settings, NT-proBNP is less specific for chronic, stable HF and may not accurately reflect disease progression or response to treatment [8, 57, 58].

In contrast, as previously described, Gal-3 is a novel biomarker involved in inflammation, fibrosis, and remodeling processes [9, 16]. It is considered valuable for HF and other fibrotic diseases, reflecting myocardial fibrosis and remodeling more directly than NT-proBNP. Gal-3 levels can be elevated in various conditions, including chronic inflammatory diseases, liver cirrhosis, and some cancers, potentially leading to false positives [9, 10, 13, 16]. There is also a lack of standardized cut-off values for Gal-3, and its use is not as deeply integrated into clinical practice guidelines as NT-proBNP. Additionally, Gal-3 may not be as useful in acute HF settings where rapid changes in hemodynamics need quick and reliable assessment [59].

In clinical practice, NT-proBNP is well-validated for both diagnosing and prognosing HF. Its levels correlate with HF severity, guide treatment, and predict outcomes [58, 59]. Gal-3, on the other hand, provides additional prognostic information, particularly in chronic HF, by reflecting fibrosis and inflammation. It may help in identifying patients at risk of disease progression and adverse outcomes [60]. In patients with renal disease, NT-proBNP levels are often elevated, complicating interpretation and requiring adjustments for renal function. Gal-3 is less affected by renal function compared to NT-proBNP, making it a potentially more reliable marker in patients with concurrent renal disease. In acute coronary syndromes (ACS), NT-proBNP's elevated levels can indicate myocardial strain, providing prognostic information [8, 61, 62]. Gal-3 can indicate adverse remodeling post-ACS, offering insights into long-term prognosis and potential therapeutic targets [60].

While NT-proBNP is not specific for fibrotic processes, Gal-3 is directly involved in fibrotic pathways, making it valuable for diseases characterized by fibrosis, such as liver cirrhosis and certain cancers [10]. Despite NT-proBNP's established role in cardiology, its limitations, especially in patients with renal dysfunction and other comorbidities, highlight the need for complementary markers like Gal-3 [58–60]. Gal-3 offers additional insights into fibrosis and inflammation, providing prognostic value in HF and other fibrotic diseases [9, 10, 60].

Understanding the context in which these biomarkers are utilized is crucial. In situations where stability and consistency in assessment are crucial, Gal-3 might outperform NT-proBNP [37, 43]. On the other hand, the responsiveness of NT-proBNP to various physiological states makes it an irreplaceable tool in diagnosing various heart conditions, albeit requiring more complex considerations in its interpretation.

Conclusions

In relation to studies concerning the use of Gal-3 as a biomarker in CHD, the findings suggest that its prognostic value in diagnosing HF is complex and requires further research. Most studies confirmed that Gal-3 can be sensitive and specific biomarker of HF in pediatric patients with CHD, especially among non-operated patients and those with simple heart defects, such as ventricular septal defects. Some research emphasized a higher prognostic value of Gal-3 in comparison to well established and commonly used NT-proBNP [29, 35]. In contrast, published results suggest that in patients undergoing surgery for complex CHD, the effectiveness of Gal-3 in predicting HF may be lower. To fully verify the diagnostic utility of Gal-3 in early HF detection, more multicenter studies with larger cohorts focusing on specific CHDs are needed.

A key limitation of both this review and the current knowledge is the lack of standardized metrics across studies, hindering result comparisons. Standardizing data presentation would improve outcome comparisons. This challenge, due to varied methodologies, should be seen as a limitation in the field, not in just this review. Addressing it would clarify Gal-3's role as a biomarker in CHD.

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Supplementary material: Suppl. Table 1; Suppl. Figure 1.

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