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ORIGINAL ARTICLE

Diagnostic Role of β2-Microglobulin in Children with Congestive Heart Failure due to Congenital Heart Disease

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ABSTRACT

Background: Heart failure (HF) is a frequent but challenging complication in children with congenital heart disease (CHD) due to vague symptoms. β2-microglobulin (β2-MG) shows promise as a cardiovascular biomarker, but its role in CHD-related pediatric HF is not well studied. This study aimed to determine the diagnostic value of serum β2-MG in children with HF due to CHD and explore its relationship with cardiac function.

Methods: This case-control study included 48 children: 24 with CHD and HF (case group) and 24 age- and gender-matched healthy controls. All participants underwent comprehensive clinical evaluation, laboratory assessments including serum β2-MG measurement by ELISA, and detailed echocardiographic examination.

Results: Serum β2-MG levels were significantly higher in children with CHD and HF compared to controls (median 1.21 vs. 0.36 ng/ml, $p<0.001$), with levels progressively increasing with HF severity (mild: 0.733, moderate: 1.67, severe: 2.544 ng/ml). Significant negative correlations were observed between β2-MG and ejection fraction ($r=-0.654$, $p<0.001$), and medial E' velocity ($r=-0.782$, $p<0.001$). β2-MG had excellent diagnostic performance for heart failure at a cutoff of ≥0.6485 ng/ml, with 87.5% sensitivity, 91.7% specificity, 89.6% accuracy, and an AUC of 0.919.

Conclusions: Serum β2-MG levels are significantly elevated in children with CHD and HF. It correlates with disease severity and cardiac dysfunction and demonstrates excellent diagnostic performance. These findings suggest that β2-MG may be a useful biomarker for early diagnosis and risk assessment.

Keywords: Congenital heart disease; Heart failure; Biomarker; Echocardiography; Diagnostic value.

INTRODUCTION

Congenital heart disease (CHD) is the most widespread major congenital anomaly, occurring in approximately 1 in 100 live births [1, 2]. Heart failure (HF) is a serious complication in children with CHD, contributing to high morbidity and mortality. Its diagnosis is often difficult due to vague, nonspecific symptoms, particularly in infants and young children. This underscores the need for reliable, objective tools to detect HF in this population [3, 4].

Circulating biomarkers may play a vital role in diagnosing and managing patients presenting with HF, potentially allowing for better prognosis assessment. While several biomarkers have been established for adult HF patients, their application in pediatric populations, especially in the context of CHD, has been limited by factors such as age- and disease-specific variations and lack of standardized reference ranges [5].

β2-microglobulin (β2-MG) is a small protein that constitutes the light chain of major histocompatibility complex class I molecules,

located on the surface of all nucleated cells [6]. The role of serum β2-MG in cardiovascular diseases is gaining increasing attention. Several studies have linked elevated serum β2-MG levels to cardiovascular events and mortality across different patient groups, including those with chronic kidney disease, asymptomatic cardiovascular-related mortality, and left ventricular hypertrophy [7-9].

This study aims to assess the diagnostic value of serum β2-MG in children with CHD and HF and explore its relationship with cardiac function.

METHODS

This case-control study was conducted at Zagazig University Hospital's Cardiology Unit. This study received ethical approval from the Zagazig University Faculty of Medicine's Institutional Review Board (IRB) under approval number ZU-IRB#286/16, which was issued on April 16, 2024, expiring on April 16, 2025. The study followed the ethical criteria mentioned in the Declaration of Helsinki. Informed consent was obtained from all guardians.

The study included 48 children: 24 with CHD and HF (case group) and 24 healthy age—and gender-matched controls.

Eligible participants were aged 1 month to 15 years, regardless of sex. The case group comprised patients diagnosed with CHD by cardiac ultrasound and who met the diagnostic criteria for pediatric HF. We excluded patients with co-infections (including acute upper respiratory tract infections and pulmonary infections), liver diseases, kidney dysfunction, diabetes mellitus, malignant tumors, thyroid diseases, and autoimmune diseases.

All participants underwent a comprehensive evaluation, including full history taking, general examination, and cardiac examination. Grading of severity using the Modified Ross score, which classifies HF into mild, moderate, and severe categories, was performed.

Blood samples were collected for β2-MG and other tests. Echocardiography assessed heart function and Doppler parameters.

Statistical analysis:

Data was analyzed using SPSS version 27. Categorical variables were compared with the chi-square test, and normality was tested with the Shapiro-Wilk test. Quantitative data were compared using the T-test or the Mann-Whitney test, with the Kruskal-Wallis test for multiple groups. ROC analysis identified the β2-microglobulin cutoff for HF diagnosis, and Spearman's correlation assessed associations.

RESULTS

The demographic comparison reveals that both groups were well-matched for gender, age, head circumference, and height, with no significant differences. However, children with CHD and HF had significantly lower weights than controls ($p=0.014$) (Table 1).

Most patients (83.3%) were acyanotic, with ventricular septal defect (VSD) being the most common. Only 16.7% of patients had cyanotic defects (Table 2).

Serum β2-MG levels were significantly higher in children with CHD and HF than in controls ($p<0.001$) (Table 3). A significant relationship was found between β2-MG levels and HF severity ($p<0.001$). Post-hoc comparisons showed significant differences between mild and moderate HF ($p=0.014$), mild and severe HF ($p<0.001$), and between the control group and both moderate ($p<0.001$) and severe HF groups ($p<0.001$) (Table 4).

Significant negative correlations were observed between β2-MG levels and parameters of systolic function (EF, FS), diastolic function (E' medial, E' lateral, A' lateral velocities), LV Posterior Wall in Diastole (LVPWd), and S' lateral velocity. Conversely, significant positive correlations were found with ventricular dimensions (LVIDs, LVIDd), volumes (ESV, EDV), LA/AO ratio, E/A ratio, and E/E' lateral ratio (Table 5).

The ROC curve analysis demonstrated excellent diagnostic performance of β2-MG for identifying congestive HF in children with CHD. A cutoff value of ≥0.6485 ng/ml yielded high sensitivity (87.5%), specificity (91.7%), and overall accuracy (89.6%), with an area under the curve of 0.919 ($p<0.001$) (Table 6).

Table 1: Comparison of demographic and anthropometric characteristics between children with congenital heart disease and healthy controls

Variables	Case group	Control group	χ^2	P
	n=24(%)	n=24(%)		
Gender **Female** **Male**	 14 (58.3%) 10 (41.7%)	 14 (58.3%) 10 (41.7%)	0	>0.999
	Median (IQR)	**Median (IQR)**	Z	P
Age (month)	5(1.63 – 18)	13.5(2 – 28)	-1.056	0.291
Weight (kg)	4.45(2.6 – 9.38)	9.5(4.85 – 13.5)	-2.467	0.014*
	Mean ± SD	**Mean ± SD**	t	P
Head circumference (cm)	41.71 ± 6.02	44.45 ± 5.07	-1.706	0.095
Height (cm)	69.59 ± 22.25	76.9 ± 20.54	-1.182	0.243

Median (Interquartile Range), Mean ± Standard Deviation. Statistical tests: χ^2 = Chi-square test, Z = Mann-Whitney U test, t = Independent samples t-test. Significance: * $p<0.05$ (statistically significant)

Table 2: Types of congenital heart disease

Type of CHD	n=24	%
Acyanotic		
VSD	5	20.8%
ASD	4	16.7%
PDA	4	16.7%
VSD, ASD, PDA	4	16.7%
ASD, PDA	2	8.3%
VSD, ASD	1	4.2%
Cyanotic		
TGA	1	4.2%
DORV	3	12.5%

CHD = Congenital Heart Disease, VSD = Ventricular Septal Defect, ASD = Atrial Septal Defect, PDA = Patent Ductus Arteriosus, TGA = Transposition of Great Arteries, DORV = Double Outlet Right Ventricle

Table 3: β2-microglobulin levels in case versus control groups

Parameter	Case group (n=24)	Control group (n=24)	Z	P-value
β2-microglobulin (ng/ml)	1.21 (0.86 – 1.97)†	0.36 (0.12 – 0.55)†	-4.98	<0.001**

†Values expressed as Median (Interquartile Range). Statistical test: Z = Mann-Whitney U test. Significance: ** $p\leq0.001$ (highly significant)

Table 4: Relationship between HF severity and β2-microglobulin levels

Heart Failure Severity	β2-microglobulin (ng/ml)
Control group (n=24)	0.36 (0.12 – 0.55)†
Mild HF (n=9)	0.733 (0.333 – 0.985)†
Moderate HF (n=8)	1.67 (1.123 – 1.773)†
Severe HF (n=7)	2.544 (2.025 – 2.668)†

Kruskal-Wallis $\chi^2 = 33.286$, $p < 0.001$

Pairwise comparisons:

p_1: 0.014*

p_2: 0.094

p_3: <0.001**

p_4: 0.072

p_5: <0.001**

†Values expressed as Median (Interquartile Range). Statistical test: Kruskal-Wallis test with pairwise comparisons. Significance: * $p<0.05$ (significant), ** $p\leq0.001$ (highly significant). Pairwise comparisons: p_1 = mild vs. moderate; p_2 = moderate vs. severe; p_3 = mild vs. severe; p_4 = control vs. mild; p_5 = control vs. moderate; p_6 = control vs. severe

Table 5: Correlation between β2-microglobulin levels and echocardiographic parameters

Parameter	Correlation coefficient (r)	P-value
Conventional Echocardiography		
Ejection Fraction (EF) (%)	-0.654	<0.001**
Fractional Shortening (FS) (%)	-0.712	<0.001**
LV Internal Dimension in Systole (LVIDs)	0.585	<0.001**
LV Internal Dimension in Diastole (LVIDd) (cm)	0.390	0.006*
LV Posterior Wall in Diastole (LVPWd) (cm)	-0.292	0.044*
Interventricular Septal Thickness in Diastole (IVSD) (cm)	-0.218	0.137
End-Systolic Volume (ESV) (ml)	0.419	0.003*
End-Diastolic Volume (EDV) (ml)	0.336	0.020*
Estimated Systolic Pulmonary Artery Pressure (ESPAP) (mmHg)	0.221	0.131
Left Atrium to Aorta (LA/AO) ratio	0.712	<0.001**
E-wave velocity	0.234	0.109
A-wave velocity	0.390	0.007*
E/A ratio	0.708	<0.001**
Tissue Doppler at Mitral Annulus		
E' medial velocity (cm/s)	-0.782	<0.001**
A' medial velocity (cm/s)	-0.073	0.620
S' medial velocity (cm/s)	-0.098	0.508
E'/A' medial ratio	-0.263	0.071
E/E' medial ratio	0.147	0.320
E' lateral velocity (cm/s)	-0.569	<0.001**
A' lateral velocity (cm/s)	-0.703	<0.001**
S' lateral velocity (cm/s)	-0.375	0.009*
E'/A' lateral ratio	0.056	0.705
E/E' lateral ratio	0.565	<0.001**

Statistical test: Spearman rank correlation coefficient. Significance: * $p<0.05$ (significant), ** $p\leq0.001$ (highly significant)

Table 6: Diagnostic performance of β2-microglobulin for identifying congestive HF

Cutoff value (ng/ml)	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	P-value
≥0.6485	0.919	87.5%	91.7%	91.3%	88.0%	89.6%	<0.001**

AUC = Area Under the Curve, PPV = Positive Predictive Value, NPV = Negative Predictive Value. Statistical test: Receiver Operating Characteristic (ROC) curve analysis. Significance: ** p≤0.001 (highly significant)

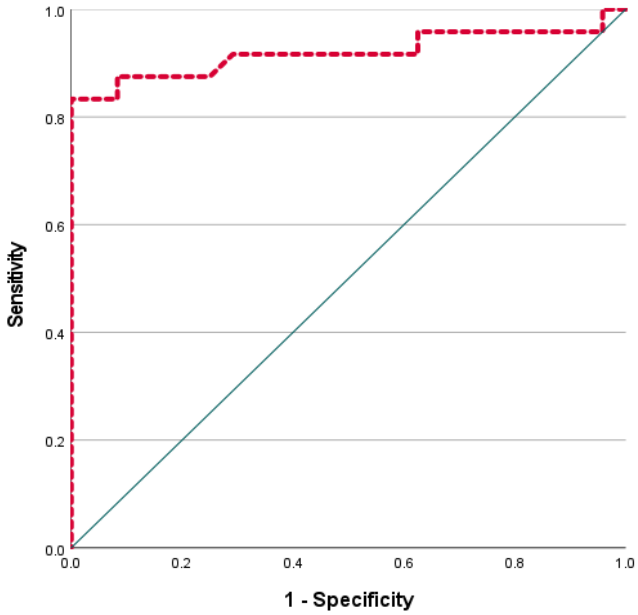

Figure 1: ROC curve showing performance of β2-microglobulin in diagnosis of congestive HF

DISCUSSION

Our study demonstrated highly elevated serum β2-MG levels in children with CHD and HF compared to healthy controls, with a strong correlation between β2-MG concentrations and HF severity. These findings align with Zhou et al., who reported similar elevations in β2-MG levels in children with CHD and chronic HF [10].

The demographic analysis revealed significant weight reduction among children with CHD and HF, consistent with previous studies reporting high malnutrition rates in patients with symptomatic CHD [11, 12], which could be attributed to the nutritional and growth restriction commonly observed in children with CHD and HF. The distribution of CHD types in our cohort aligns with epidemiological patterns reported in recent literature, with VSD, ASD, and PDA being the most frequent types [13]. The predominance of left-to-right shunt lesions contributes to the development of HF in these patients, as these defects cause volume overload in the pulmonary circulation and left heart chambers [14].

The significant correlations with various echocardiographic parameters in this study support the link between β2-MG levels and cardiac function. Negative correlations were found between β2-MG levels and EF, FS, and other markers of left ventricular systolic function, while positive correlations were observed with left ventricular dimensions, end-systolic and end-diastolic volumes, and the left atrial-to-aortic ratio—indicators of cardiac remodeling and dysfunction in heart failure. These results suggest that β2-MG levels reflect not only the clinical severity of heart failure but also the associated structural and functional cardiac abnormalities.

Interestingly, significant correlations were also observed between β2-MG levels and tissue Doppler parameters, particularly E' velocities at the medial and lateral mitral annulus, which are sensitive markers of myocardial relaxation and early indicators of diastolic dysfunction. The

negative correlation with E' velocities and positive correlation with E/E' ratio suggest that β2-MG levels may also reflect diastolic dysfunction, an important component of HF pathophysiology often overlooked in pediatric populations [15].

The diagnostic performance of β2-MG was excellent, with a cutoff value of ≥0.6485 ng/ml showing 87.5% sensitivity, 91.7% specificity, and 89.6% overall accuracy for diagnosing HF in children with CHD. This finding aligns with previous research highlighting the utility of β2-MG as a biomarker in this context. For instance, a study by Zhou et al. assessed the diagnostic value of β2-MG and growth differentiation factor-15 (GDF-15) in infants with CHD and chronic HF. They reported that β2-MG alone had a sensitivity of 82.5% and specificity of 62.0% for diagnosing chronic HF in this population. When combined with GDF-15, the sensitivity remained at 82.5%, but specificity improved to 82.0%, with an area under the curve (AUC) of 0.888, indicating enhanced diagnostic accuracy [10].

The clinical implications of our findings are valuable. β2-MG could serve as a valuable tool for early diagnosis of HF in children with CHD, which is crucial for timely intervention and optimal outcomes. Its correlation with HF severity suggests its potential role in risk stratification and prognostication, which could guide therapeutic decisions and resource allocation. Moreover, the relatively simple and standardized assay for β2-MG measurement makes it feasible for routine clinical implementation, even in resource-limited settings where advanced cardiac imaging may not be readily available.

Limitations of our study include the relatively small sample size and potential influence of subclinical conditions that might affect β2-MG levels despite our exclusion criteria. Future research should include larger, longitudinal studies to validate these findings across different CHD subtypes.

CONCLUSIONS

Serum β2-MG is significantly elevated in children with CHD and HF, correlates with disease severity and cardiac dysfunction, and demonstrates excellent diagnostic performance, potentially serving as a valuable tool for improved management of pediatric HF.

Conflict of Interest: None.

Financial Disclosure: None.

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