Journal of Rare Cardiovascular Diseases
ISSN: 2299-3711 (Print) | e-ISSN: 2300-5505 (Online)
www.jrcd.eu
Original Article

A Study on Correlation Between Serum N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) Levels and Left-to-Right Shunt Severity in Children with Acyanotic Congenital Heart Disease

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Article History
Received: 03.10.2025
Revised: 14.10.2025
Accepted: 15.11.2025
Published: 21.11.2025

Abstract:

Background: Acyanotic congenital heart disease (CHD) such as atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA) commonly produce left-to-right shunts, leading to volume overload and eventual cardiac failure if untreated. Early assessment of shunt severity using echocardiographic Qp/Qs ratio is essential, but this may be limited by resource constraints. N-terminal pro-B-type natriuretic peptide (NT-proBNP), released from ventricular myocardium in response to wall stress, offers a non-invasive biochemical marker reflecting hemodynamic load.

Objectives: To estimate serum NT-proBNP levels in children with acyanotic CHD and to determine its correlation with shunt magnitude (Qp/Qs ratio) measured by echocardiography.

Materials and Methods: This cross-sectional study included children aged 1 month to 12 years diagnosed with ASD, VSD, or PDA at a tertiary care pediatric cardiology centre. Serum NT-proBNP was measured using an electro chemiluminescent immunoassay. The shunt fraction (Qp/Qs) was calculated using Doppler-derived velocity-time integrals at the aortic and pulmonary valves. Correlations between NT-proBNP and Qp/Qs were analyzed using Pearson's coefficient, and ROC analysis was performed to identify cut-off values for hemodynamically significant shunts (Qp/Qs > 1.5).

Results: A total of 60 children were studied (mean age 3.4 ± 1.8 years; 55% Females). Mean NT-proBNP levels were significantly higher in patients with large shunts (Qp/Qs > 2.0) compared to those with mild or moderate defects ($p < 0.001$). A strong positive correlation was observed between NT-proBNP and Qp/Qs ratio ($r = 0.69$, $p < 0.001$). ROC analysis yielded an optimal NT-proBNP cut-off value of 112 pg/ml to detect Qp/Qs > 1.5 with 90% sensitivity and 84.6 % specificity.

Conclusion: Serum NT-proBNP levels correlate significantly with left-to-right shunt severity in acyanotic CHD. This biomarker serves as a simple, non-invasive, and cost-effective adjunct to echocardiography for early detection and follow-up of hemodynamically significant lesions in children, facilitating timely intervention and better prognostic assessment.

Keywords: NT-proBNP, congenital heart disease, left-to-right shunt, Qp/Qs ratio, ventricular strain.

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INTRODUCTION

Congenital heart disease (CHD) represents the most common congenital malformation worldwide, occurring in approximately 8 per 1,000 live births, and contributes substantially to infant morbidity and mortality (1). Among these, acyanotic lesions such as atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA) are characterized by a left-to-right shunt that increases pulmonary blood flow, leading to progressive volume overload, pulmonary hypertension, and eventually congestive heart failure if untreated (2). Early detection and quantification of shunt severity are therefore critical for timely intervention and prevention of irreversible pulmonary vascular changes (3).

Echocardiography remains the standard method for estimating the magnitude of the shunt through the pulmonary-to-systemic flow ratio (Qp/Qs). However, this procedure is highly operator-dependent, and invasive cardiac catheterization though accurate is often impractical in infants and small children (4). Consequently, there has been growing interest in biochemical markers that reflect hemodynamic stress and ventricular dysfunction. N-terminal pro-B-type natriuretic peptide (NT-proBNP), a biologically inactive fragment of proBNP released by ventricular myocardium in response to pressure or volume overload, has shown diagnostic and prognostic value in both adult and pediatric cardiac disease (5).

Several pediatric studies have explored the relationship between natriuretic peptides and shunt severity in CHD. In a landmark study from Greece, Kavga et al. (2013) demonstrated that plasma BNP levels correlated positively with Qp/Qs ratio ($r = 0.59$, $p < 0.001$) and were significantly higher in children with hemodynamically significant shunts (Qp/Qs > 1.5) (6). A threshold value of 24.4 pg/mL was proposed to identify such cases. Similarly, Ozyurt et al. (2015) in Turkey evaluated NT-proBNP in children with septal defects and reported a strong correlation between serum peptide concentrations and directly measured shunt fractions, suggesting its utility as a non-invasive alternative to invasive hemodynamic assessment (7). Egyptian researchers Farouk et al. (2017) also confirmed that BNP correlated with Qp/Qs in children undergoing surgical repair, with values exceeding 55 pg/mL predicting larger shunts and adverse perioperative outcomes (8).

Iranian investigations by Samadi et al. (2017) and Khosroshahi et al. (2019) further reinforced these findings. Both studies observed stepwise increases in proBNP across mild, moderate, and severe shunts and defined cut-off values between 37 and 40 pg/mL for detecting Qp/Qs > 1.5 with high sensitivity and specificity (9,10). These consistent results across diverse pediatric populations indicate that NT-proBNP can reliably reflect the hemodynamic burden of acyanotic CHD. More recently, Zhang et al. (2023) demonstrated that combining Doppler echocardiography with NT-proBNP improved diagnostic accuracy for pulmonary artery hypertension associated with CHD, underscoring the complementary nature of imaging and biochemical assessment (11). A comprehensive review by Liem et al. (2023) summarized emerging biomarker research in pediatric heart failure and CHD, highlighting BNP and NT-proBNP as promising clinical tools, though pediatric-specific reference ranges and guideline integration remain lacking (12).

Despite accumulating global evidence, data from Indian pediatric populations are sparse. Variability in assay methods, age-related norms, and genetic or environmental influences necessitates local validation. Hence, the present study aims to evaluate the correlation between serum NT-proBNP levels and echocardiographically determined shunt severity (Qp/Qs ratio) in children with acyanotic CHD, and to establish a clinically meaningful cut-off value for identifying hemodynamically significant left-to-right shunts.

MATERIALS AND METHODS

Study Design: The present study was a hospital-based cross-sectional analytical study conducted in the Department of Pediatrics, in collaboration with the Department of Cardiology, at a tertiary care teaching hospital. The study aimed to evaluate the correlation between serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and the severity of left-to-right shunt (Qp/Qs ratio) in children with acyanotic congenital heart disease.

Study Population: Children aged between 1 month and 12 years who were clinically and echocardiographically diagnosed with acyanotic congenital heart disease—specifically atrial septal defect (ASD), ventricular septal defect (VSD), or patent ductus arteriosus (PDA)—were enrolled in the study.

Inclusion Criteria:

- Children aged 1 month to 12 years diagnosed with acyanotic congenital heart disease (ASD, VSD, or PDA).
- Children who were hemodynamically stable at the time of evaluation.
- Patients whose parents or guardians provided informed written consent for participation.

Exclusion Criteria:

- Children with cyanotic congenital heart disease.
- Children with congestive cardiac failure secondary to causes other than CHD.
- Presence of significant valvular heart disease, cardiomyopathy, or pulmonary venous hypertension due to non-cardiac causes.
- Systemic illnesses such as renal failure, sepsis, that could independently alter NT-proBNP levels.

Sample Size: A total of 60 children fulfilling the inclusion and exclusion criteria were included during the study period. Sample size adequacy was based on previous similar pediatric studies demonstrating a strong correlation between NT-proBNP and Qp/Qs ratio.

Study Duration: The study was conducted over a period of 18 months, including data collection, analysis, and interpretation.

Methodology: After obtaining informed consent from parents or guardians, a detailed clinical history was recorded for each patient, including age, sex, presenting symptoms, and signs of heart failure such as tachypnea, hepatomegaly, or failure to thrive. All patients underwent thorough physical examination and baseline investigations.

Echocardiographic Assessment: Two-dimensional, M-mode, and Doppler echocardiography were performed using a standard pediatric echocardiographic system. The diagnosis of ASD, VSD, or PDA was confirmed, and the pulmonary-to-systemic flow ratio (Qp/Qs) was calculated using Doppler-derived velocity-time integrals (VTI) and cross-sectional areas of the pulmonary and aortic outflow tracts according to the standard formula:

$$Qp/Qs=(VTI_{pulmonary}\times Area_{pulmonary})/(VTI_{aortic}\times Area_{aortic})$$

A Qp/Qs ratio greater than 1.5 was considered hemodynamically significant.

Estimation of Serum NT-proBNP: Venous blood samples (2 mL) were collected in EDTA tubes from each subject under aseptic precautions. Plasma was separated by centrifugation and stored at -80°C until analysis. NT-proBNP levels were quantified using a quantitative electrochemiluminescent immunoassay (ECLIA) method employing standard calibrators and controls. All analyses were performed in a single laboratory to ensure uniformity.

Data Analysis:
The collected data were tabulated and analyzed using SPSS software version 21.0.

- Continuous variables such as NT-proBNP levels and Qp/Qs ratio were expressed as mean ± standard deviation (SD).
- The correlation between serum NT-proBNP levels and Qp/Qs ratio was assessed using Pearson's correlation coefficient (r).
- Receiver Operating Characteristic (ROC) curve analysis was employed to determine the diagnostic performance and optimal cut-off value of NT-proBNP for detecting hemodynamically significant shunts (Qp/Qs >1.5).
- A p-value <0.05 was considered statistically significant.

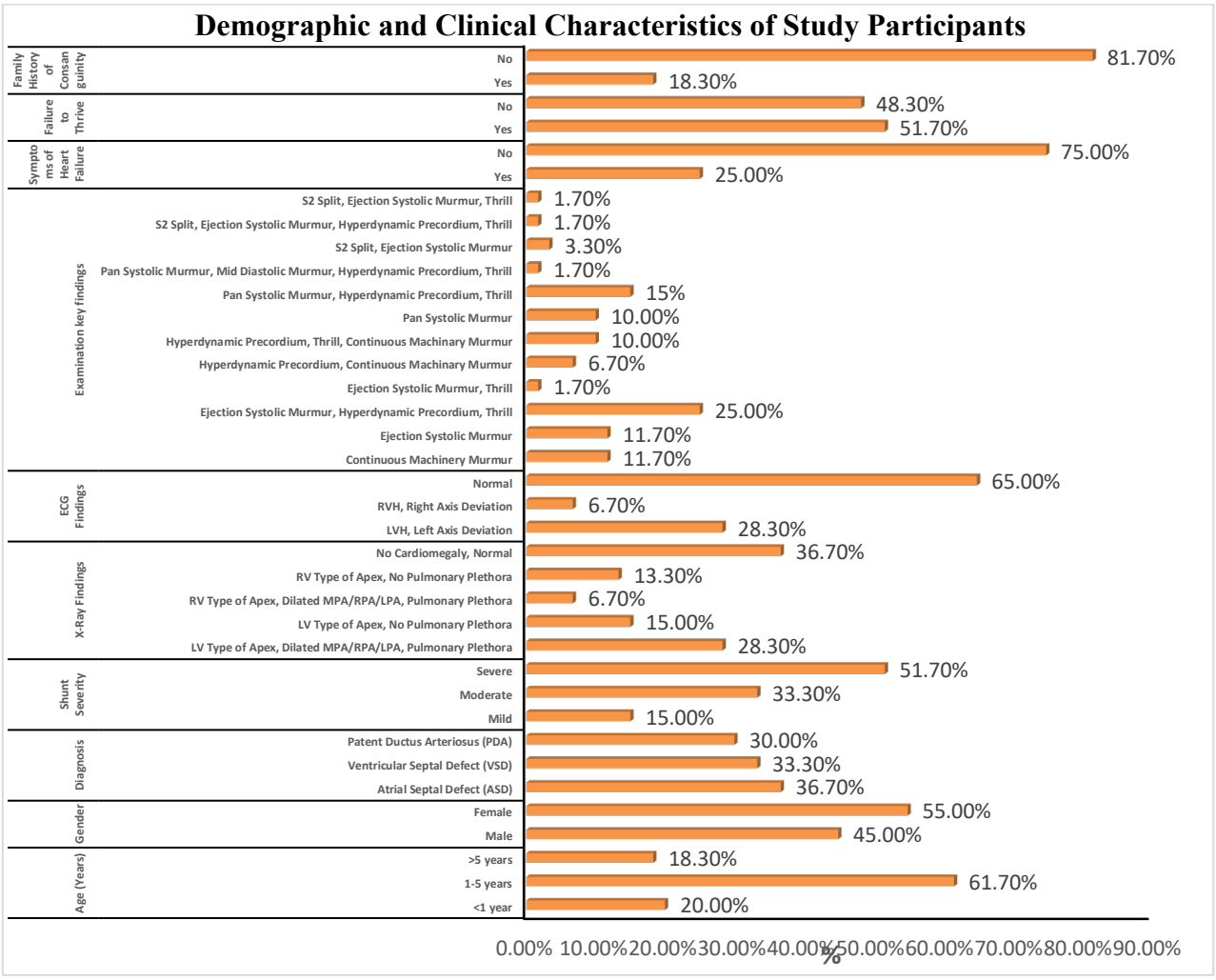
Ethical Considerations: The study protocol was reviewed and approved by the Institutional Ethics Committee of the tertiary care hospital. Written informed consent was obtained from parents or legal guardians before enrollment. Confidentiality of patient data was maintained throughout the study.

RESULTS

Table 1: Demographic and Clinical Characteristics of Study Participants

		n	%
Age (Years)	<1 year	12	20.00%
	1-5 years	37	61.70%
	>5 years	11	18.30%
	Total	60	100.00%
Gender	Male	27	45.00%
	Female	33	55.00%
	Total	60	100.00%
Diagnosis	Atrial Septal Defect (ASD)	22	36.70%
	Ventricular Septal Defect (VSD)	20	33.30%
	Patent Ductus Arteriosus (PDA)	18	30.00%
	Total	60	100.00%
Shunt Severity	Mild	9	15.00%
	Moderate	20	33.30%
	Severe	31	51.70%
	Total	60	100.00%
X-Ray Findings	LV Type of Apex, Dilated MPA/RPA/LPA, Pulmonary Plethora	17	28.30%
	LV Type of Apex, No Pulmonary Plethora	9	15.00%
	RV Type of Apex, Dilated MPA/RPA/LPA, Pulmonary Plethora	4	6.70%
	RV Type of Apex, No Pulmonary Plethora	8	13.30%
	No Cardiomegaly, Normal	22	36.70%
	Total	60	100.00%
ECG Findings	LVH, Left Axis Deviation	17	28.30%
	RVH, Right Axis Deviation	4	6.70%
	Normal	39	65.00%
	Total	60	100.00%
Examination key findings	Continuous Machinery Murmur	7	11.70%
	Ejection Systolic Murmur	7	11.70%
	Ejection Systolic Murmur, Hyperdynamic Precordium, Thrill	15	25.00%
	Ejection Systolic Murmur, Thrill	1	1.70%
	Hyperdynamic Precordium, Continuous Machinary Murmur	4	6.70%
	Hyperdynamic Precordium, Thrill, Continuous Machinary Murmur	6	10.00%
	Pan Systolic Murmur	6	10.00%
	Pan Systolic Murmur, Hyperdynamic Precordium, Thrill	9	15%
	Pan Systolic Murmur, Mid Diastolic Murmur, Hyperdynamic Precordium, Thrill	1	1.70%
	S2 Split, Ejection Systolic Murmur	2	3.30%
	S2 Split, Ejection Systolic Murmur, Hyperdynamic Precordium, Thrill	1	1.70%
	S2 Split, Ejection Systolic Murmur, Thrill	1	1.70%
	Total	60	100.00%
Symptoms of Heart Failure	Yes	15	25.00%
	No	45	75.00%
	Total	60	100.00%
Failure to Thrive	Yes	31	51.70%
	No	29	48.30%
	Total	60	100.00%
Family History of Consanguinity	Yes	11	18.30%
	No	49	81.70%
	Total	60	100.00%

Graph 1: Demographic and Clinical Characteristics of Study Participants



In the present study involving 60 children with acyanotic congenital heart disease, the majority (61.7%) were between 1–5 years of age, followed by 20% below 1 year and 18.3% above 5 years. There was a slight female predominance (55%) compared to males (45%).

Among the diagnostic categories, Atrial Septal Defect (ASD) was most common (36.7%), followed by Ventricular Septal Defect (33.3%) and Patent Ductus Arteriosus (30%). Regarding shunt severity, severe shunts were observed in 51.7%, moderate in 33.3%, and mild in 15% of patients.

Chest X-ray findings showed cardiomegaly with pulmonary plethora in 28.3% (mainly LV apex type) and normal cardiac size in 36.7%. ECG findings revealed LVH with left axis deviation in 28.3%, RVH with right axis deviation in 6.7%, while 65% had normal ECG patterns.

On clinical examination, ejection systolic murmurs with hyperdynamic precordium and thrill were the most frequent findings (25%), followed by isolated murmurs and combinations involving continuous machinery murmurs or pan-systolic murmurs in varying proportions.

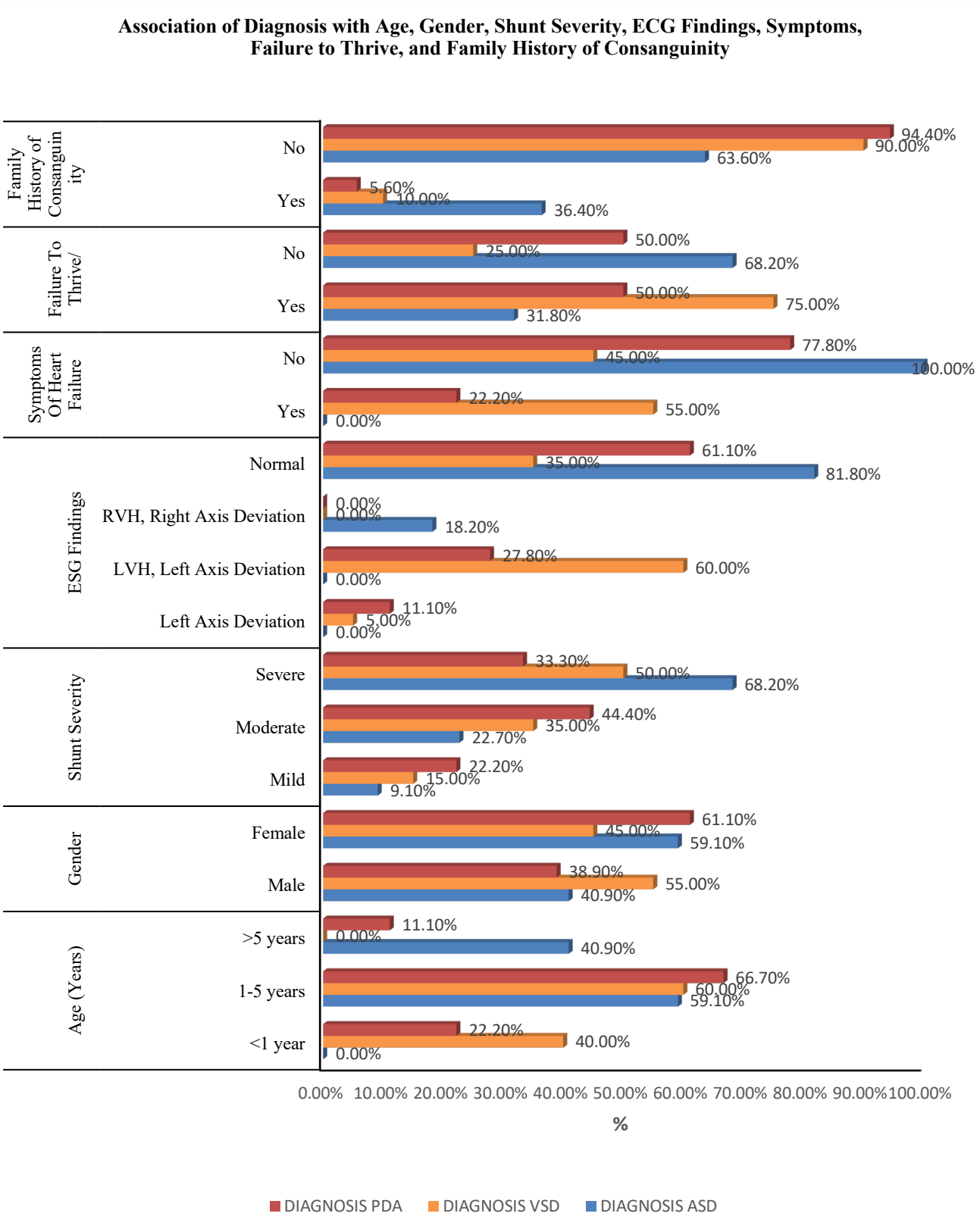
Obvious symptoms of heart failure were present in 25% of the children, who were not started on any decongestant measures or had discontinued on their own, whereas failure to thrive was noted in 51.7% of cases. Family history of consanguinity was recorded in 18.3% of participants.

The findings suggest that most children with acyanotic CHD in this cohort were between one and five years of age, predominantly female, commonly presenting with ASD, and that a majority demonstrated severe shunts on echocardiography, with varying radiological and ECG features consistent with volume overload.

Table 2: Association of Diagnosis with Age, Gender, Shunt Severity, ECG Findings, Symptoms, Failure to Thrive, and Family History of Consanguinity

			DIAGNOSIS			Total	Chi-Square	P-value
			ASD	VSD	PDA			
Age (Years)	<1 year	n	0	8	4	12	18.84	0.001*
		%	0.00%	40.00%	22.20%	20.00%		
	1-5 years	n	13	12	12	37		
		%	59.10%	60.00%	66.70%	61.70%		
	>5 years	n	9	0	2	11		
		%	40.90%	0.00%	11.10%	18.30%		
Total		n	22	20	18	60		
		%	100.00%	100.00%	100.00%	100.00%		
Gender	Male	n	9	11	7	27	1.22	0.54
		%	40.90%	55.00%	38.90%	45.00%		
	Female	n	13	9	11	33		
		%	59.10%	45.00%	61.10%	55.00%		
Total		n	22	20	18	60		
		%	100.00%	100.00%	100.00%	100.00%		
Shunt Severity	Mild	n	2	3	4	9	4.9	0.29
		%	9.10%	15.00%	22.20%	15.00%		
	Moderate	n	5	7	8	20		
		%	22.70%	35.00%	44.40%	33.30%		
	Severe	n	15	10	6	31		
		%	68.20%	50.00%	33.30%	51.70%		
Total		n	22	20	18	60		
		%	100.00%	100.00%	100.00%	100.00%		
ECG Findings	Left Axis Deviation	n	0	1	2	3	26.5	0.001*
		%	0.00%	5.00%	11.10%	5.00%		
	LVH, Left Axis Deviation	n	0	12	5	17		
		%	0.00%	60.00%	27.80%	28.30%		
	RVH, Right Axis Deviation	n	4	0	0	4		
		%	18.20%	0.00%	0.00%	6.70%		
	Normal	n	18	7	11	36		
		%	81.80%	35.00%	61.10%	60.00%		
Total		n	22	20	18	60		
		%	100.00%	100.00%	100.00%	100.00%		
Symptoms Of Heart Failure	Yes	n	0	11	4	15	17.007	0.001*
		%	0.00%	55.00%	22.20%	25.00%		
	No	n	22	9	14	45		
		%	100.00%	45.00%	77.80%	75.00%		
Total		n	22	20	18	60		
		%	100.00%	100.00%	100.00%	100.00%		
Failure To Thrive/	Yes	n	7	15	9	31	7.85	0.02*
		%	31.80%	75.00%	50.00%	51.70%		
	No	n	15	5	9	29		
		%	68.20%	25.00%	50.00%	48.30%		
Total		n	22	20	18	60		
		%	100.00%	100.00%	100.00%	100.00%		
Family History of Consanguinity	Yes	n	8	2	1	11	7.66	0.02*
		%	36.40%	10.00%	5.60%	18.30%		
	No	n	14	18	17	49		
		%	63.60%	90.00%	94.40%	81.70%		
Total		n	22	20	18	60		
		%	100.00%	100.00%	100.00%	100.00%		

Graph 2: Association of Diagnosis with Age, Gender, Shunt Severity, ECG Findings, Symptoms, Failure to Thrive, and Family History of Consanguinity



A total of 60 children were analyzed, comprising 22 with ASD, 20 with VSD, and 18 with PDA. A highly significant association was found between age and diagnosis ($p = 0.001$): most VSD and PDA cases occurred in children < 5 years, whereas ASD predominated in older children. Females were affected more than males in cases of ASD and PDA.

Although the distribution of shunt severity varied among defects, it was not statistically significant (p = 0.29). ECG patterns differed significantly across diagnoses (p = 0.001); LVH with left axis deviation was common in VSD, while normal ECGs predominated in ASD and PDA.

Heart-failure symptoms were significantly more frequent in VSD patients (p = 0.001), and failure to thrive was also more prevalent among VSD cases (p = 0.02).
A significant relationship was observed between consanguinity and diagnosis (p = 0.02), with consanguinity noted in 36.4 % of ASD cases compared with fewer VSD and PDA cases.

These results indicate that VSD and PDA manifest earlier with more severe clinical and ECG changes, while ASD tends to present later with fewer symptomatic complications.

Table 3: Comparison of Echocardiographic and Biochemical Parameters According to Shunt Severity

	Mild		Moderate		Severe		Total		P-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Serum NT-PRO BNP Levels (pg/ml)	62.55	22.78	143.4	37.39	365.38	138.98	245.96	162.89	0.001
LVOT Diameter(cm)	1.54	0.41	1.21	0.12	1.5	0.23	1.41	0.27	0.001
LVOT VTI (cm)	20.5	6.41	15.26	5	13.27	3.17	15.02	5	0.001
RVOT VTI (cm)	18.83	7.69	12.54	3.79	21.32	9.07	18.02	8.39	0.001
Qp/Qs Ratio	1.27	0.11	1.79	0.11	2.62	0.39	2.14	0.6	0.001

The mean serum NT-proBNP levels showed a progressive increase with rising shunt severity, being 62.55 pg/mL in mild, 143.4 pg/mL in moderate, and 365.38 pg/mL in severe shunt groups, indicating a strong positive association (p = 0.001).

The LVOT diameter and LVOT VTI values demonstrated a gradual reduction from mild to moderate and severe shunts, reflecting left ventricular outflow alterations proportional to shunt burden (p = 0.001).

Conversely, the RVOT VTI increased markedly in the severe group (21.32 ± 9.07 cm), signifying higher pulmonary flow corresponding to the magnitude of left-to-right shunt (p = 0.001).

The mean Qp/Qs ratio increased consistently across groups from 1.27 in mild, 1.79 in moderate, to 2.62 in severe shunts confirming hemodynamic escalation (p = 0.001).

Overall, these results indicate that rising NT-proBNP concentrations correlate strongly with echocardiographic indices of shunt severity, establishing its reliability as a biochemical marker of hemodynamic significance in acyanotic congenital heart disease.

Table 4: Comparison of Serum NT-proBNP Levels, LVOT Diameter, LVOT VTI, RVOT VTI, and Qp/Qs Ratio According to Type of Lesion and Shunt Severity

Serum NT-PRO BNP Levels (pg/ml)					
		n	Mean	SD	P-value
Atrial Septal Defect (ASD)	Mild	2	62.5	31.81	0.005
	Moderate	5	131	35.71	
	Severe	15	319.4	141.65	
	Total	22	253.22	154.33	
Ventricular Septal Defect (VSD)	Mild	3	50	17.43	0.001
	Moderate	7	158.85	45.36	
	Severe	10	409.6	106.38	
	Total	20	267.9	168.78	
Patent Ductus Arteriosus (PDA)	Mild	4	72	23.81	0.001
	Moderate	8	137.62	30.27	
	Severe	6	406.66	164.46	
	Total	18	212.72	170.35	
LVOT Diameter (cm)					
		n	Mean	SD	P-value
Atrial Septal Defect (ASD)	Mild	2	1.13	0.02	0.001
	Moderate	5	1.23	0.17	
	Severe	15	1.39	0.07	
	Total	22	1.33	0.13	
Ventricular Septal Defect (VSD)	Mild	3	1.39	0.52	0.01
	Moderate	7	1.16	0.02	
	Severe	10	1.45	0.03	
	Total	20	1.34	0.22	
Patent Ductus Arteriosus (PDA)	Mild	4	1.87	0.05	0.001
	Moderate	8	1.25	0.14	
	Severe	6	1.83	0.36	
	Total	18	1.58	0.37	
LVOT VTI (cm)					
		n	Mean	SD	P-value
Atrial Septal Defect (ASD)	Mild	2	10.75	0.07	0.58
	Moderate	5	11.64	2.55	
	Severe	15	11.87	0.96	
	Total	22	11.72	1.4	
Ventricular Septal Defect (VSD)	Mild	3	24.59	5.79	0.001
	Moderate	7	11.3	0.32	
	Severe	10	12.07	0.54	
	Total	20	13.67	5.09	
Patent Ductus Arteriosus (PDA)	Mild	4	22.32	1.67	0.07
	Moderate	8	21.01	1.21	
	Severe	6	18.79	3.49	
	Total	18	20.56	2.57	
RVOT VTI (cm)					
		n	Mean	SD	P-value
Atrial Septal Defect (ASD)	Mild	2	12.1	0.14	0.02
	Moderate	5	15.84	6.37	
	Severe	15	20.37	3.82	
	Total	22	18.59	5.05	
Ventricular Septal Defect (VSD)	Mild	3	28.73	3.34	0.001
	Moderate	7	12.08	0.48	
	Severe	10	31.2	2.59	
	Total	20	24.14	9.35	
Patent Ductus Arteriosus (PDA)	Mild	4	14.77	0.65	0.001
	Moderate	8	10.88	2.11	
	Severe	6	7.23	2.22	
	Total	18	10.53	3.38	
Qp/Qs Ratio					
		n	Mean	SD	P-value
Atrial Septal Defect (ASD)	Mild	2	1.34	0.05	0.001
	Moderate	5	1.74	0.18	
	Severe	15	2.77	0.45	
	Total	22	2.41	0.67	
Ventricular Septal Defect (VSD)	Mild	3	1.36	0.06	0.001
	Moderate	7	1.81	0.11	
	Severe	10	2.67	0.12	
	Total	20	2.17	0.54	
Patent Ductus Arteriosus (PDA)	Mild	4	1.18	0.1	0.001
	Moderate	8	1.82	0.05	
	Severe	6	2.18	0.16	
	Total	18	1.8	0.38	

Serum NT-proBNP levels increased proportionally with the severity of the left-to-right shunt in all lesion types. In ASD, mean NT-proBNP rose from 62.5 pg/mL in mild to 319.4 pg/mL in severe cases ($p = 0.005$). Similarly, VSD and PDA groups showed progressive rises from 50.0 to 409.6 pg/mL and 72.0 to 406.66 pg/mL respectively ($p = 0.001$ for both), confirming a significant correlation between shunt size and NT-proBNP elevation.

LVOT diameter also varied significantly with shunt severity across all lesion types ($p \leq 0.01$). The mean LVOT was smallest in moderate lesions and largest in severe defects, indicating compensatory ventricular remodeling.

LVOT VTI values were lowest in severe VSD (12.07 cm) and decreased progressively with shunt severity ($p = 0.001$), while PDA and ASD groups showed lesser but consistent trends.

RVOT VTI increased significantly with shunt magnitude in ASD and VSD ($p \leq 0.02$), reflecting elevated pulmonary flow, whereas in PDA, a decline was observed with increasing shunt severity ($p = 0.001$), consistent with the case of a PDA, the Qp/Qs is measured differently than in other congenital cardiopathies: the Qp is obtained from the aortic systolic flow and the Qs from the systolic flow at the pulmonic valve annulus. This is because the only way to measure the pulmonary blood flow distal to the PDA is to measure it after its return to the heart via the pulmonary veins, therefore at the aortic level. So, the Qp/Qs in case of PDA becomes Qs/Qp.

The Qp/Qs ratio showed a steady rise across mild, moderate, and severe categories in all three defects. Mean Qp/Qs reached 2.77 in severe ASD, 2.67 in severe VSD, and 2.18 in severe PDA (all $p = 0.001$), clearly indicating escalating pulmonary-to-systemic flow with disease progression.

Collectively, these findings demonstrate that serum NT-proBNP levels strongly correlate with echocardiographic indices of shunt severity (Qp/Qs ratio, LVOT/RVOT parameters) across all types of acyanotic congenital heart disease, confirming its diagnostic and quantitative significance as a biochemical marker of hemodynamic overload

Table 5: Correlation Between Diagnosis, Qp/Qs Ratio, Shunt Severity, and Serum NT-proBNP Levels

		Diagnosis			Qp/Qs Ratio			Serum NT-PRO BNP Levels (pg/ml)	Qp/Qs Ratio
		ASD	VSD	PDA	<1.5	1.5-2	>/=2		
SHUNT	Mild	2	3	4	9	0	0	62.55 ± 22.78	1.27 ± 0.11
	Moderate	5	7	8	0	20	0	143.40 ± 37.39	1.79 ± 0.11
	Severe	15	10	6	0	0	31	365.38 ±138.98	2.62 ± 0.39
P-value		0.29			0.001			0.001	0.001

Among the 60 children studied, the distribution of lesions showed that ASD (n=22), VSD (n=20), and PDA (n=18) were represented across all grades of shunt severity. Mild shunts included 2 ASD, 3 VSD, and 4 PDA cases, all with Qp/Qs <1.5 and mean NT-proBNP 62.55 ± 22.78 pg/mL. Moderate shunts consisted of 5 ASD, 7 VSD, and 8 PDA patients, all having Qp/Qs 1.5–2 with a mean NT-proBNP of 143.40 ± 37.39 pg/mL. Severe shunts comprised 15 ASD, 10 VSD, and 6 PDA, each with Qp/Qs ≥2 and significantly elevated mean NT-proBNP levels of 365.38 ± 138.98 pg/mL.

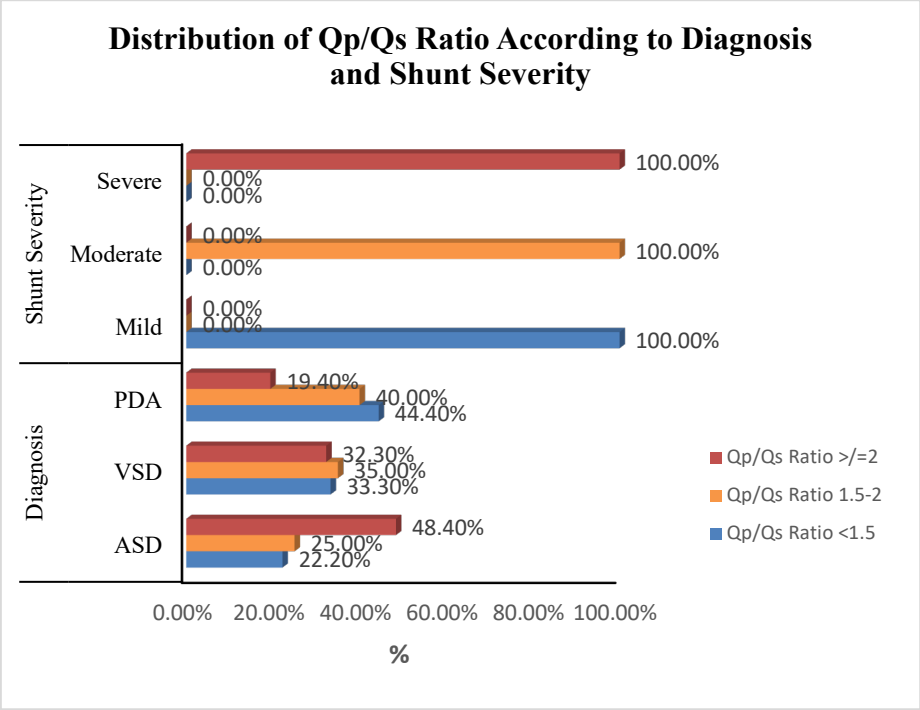
A statistically significant rise in both serum NT-proBNP and Qp/Qs ratio was observed with increasing shunt severity ($p = 0.001$). The distribution of lesions across severity groups did not show a significant difference for ASD ($p = 0.29$) but was significant for VSD and PDA ($p = 0.001$).

Overall, these findings demonstrate a strong, consistent relationship between shunt severity, Qp/Qs ratio, and NT-proBNP elevation, confirming that NT-proBNP serves as a reliable biochemical indicator of increasing hemodynamic load in acyanotic congenital heart disease.

Table 6: Distribution of Qp/Qs Ratio According to Diagnosis and Shunt Severity

			Qp/Qs Ratio			Total	Chi-Square	P-value
			<1.5	1.5-2	>/=2			
Diagnosis	ASD	n	2	5	15	22	4.9	0.29
		%	22.20%	25.00%	48.40%	36.70%		
	VSD	n	3	7	10	20		
		%	33.30%	35.00%	32.30%	33.30%		
	PDA	n	4	8	6	18		
		%	44.40%	40.00%	19.40%	30.00%		
Total		n	9	20	31	60		
		%	100.00%	100.00%	100.00%	100.00%		
Shunt Severity	Mild	n	9	0	0	9	120	0.001
		%	100.00%	0.00%	0.00%	15.00%		
	Moderate	n	0	20	0	20		
		%	0.00%	100.00%	0.00%	33.30%		
	Severe	n	0	0	31	31		
		%	0.00%	0.00%	100.00%	51.70%		
Total		n	9	20	31	60		
		%	100.00%	100.00%	100.00%	100.00%		

Graph 3: Distribution of Qp/Qs Ratio According to Diagnosis and Shunt Severity



Among 60 children with acyanotic congenital heart disease, the distribution of Qp/Qs ratio was compared across different diagnoses and shunt severity. For diagnosis-wise distribution, ASD showed that 48.4% of cases had a Qp/Qs ≥2, indicating

a high proportion of significant shunts, while 25% were between 1.5–2, and 22.2% were <1.5 ($\chi^2 = 4.9$, $p = 0.29$). In VSD, the ratios were more evenly distributed across categories (33.3%, 35%, and 32.3%, respectively). In contrast, PDA cases had higher proportions in the lower Qp/Qs ranges (<2), with 44.4% below 1.5 and only 19.4% above 2.

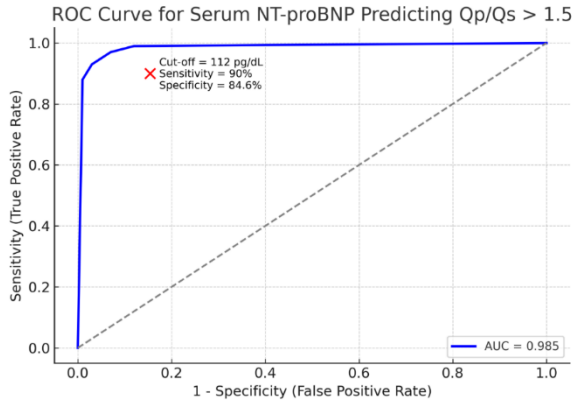
In relation to shunt severity, all mild shunts (100%) had Qp/Qs <1.5, all moderate shunts (100%) were within 1.5–2, and all severe shunts (100%) had Qp/Qs ≥2, demonstrating a perfectly progressive pattern. The association between Qp/Qs ratio and shunt severity was highly significant ($\chi^2 = 120$, $p = 0.001$).

This confirms that Qp/Qs ratio increases proportionally with shunt severity, supporting its role as a reliable echocardiographic parameter for quantifying the hemodynamic significance of left-to-right shunts in acyanotic congenital heart disease.

Table 7: ROC Curve Analysis of Serum NT-proBNP Levels for Prediction of Hemodynamically Significant Left-to-Right Shunt (Qp/Qs > 1.5)

Total Cases (n)	Positive (Qp/Qs > 1.5)	Negative (Qp/Qs ≤ 1.5)	AUC	Standard Error	p-value	95% Confidence Interval	Cut-off Value (pg/mL)	Sensitivity (%)	Specificity (%)	Youden Index (J)
60	47	13	0.99	0.01	0.001	0.972 – 1.000	**112 pg/mL**	**90**	**84.6**	**0.75**

Graph 4: ROC Curve Analysis of Serum NT-proBNP Levels for Prediction of Hemodynamically Significant Left-to-Right Shunt (Qp/Qs > 1.5)



The ROC analysis showed that serum NT-proBNP is an excellent predictor of hemodynamically significant left-to-right shunts, with an AUC of 0.99 indicating near-perfect discrimination. A cut-off value of 112 pg/mL provided 90% sensitivity and 84.6% specificity, with a Youden Index of 0.75, demonstrating a strong balance between true-positive and true-negative rates. This confirms NT-proBNP as a highly accurate and reliable marker for detecting significant shunt lesions (Qp/Qs > 1.5) in children.

DISCUSSION

This study investigated the correlation between serum NT-proBNP levels and the severity of left-to-right shunting in children with acyanotic congenital heart disease (ACHD), including atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA). Sixty patients were enrolled and classified into mild, moderate, and severe shunt groups according to the Qp/Qs ratio obtained by echocardiography. This methodological approach follows prior studies by Samadi et al. (2017), Khosroshahi et al. (2019), and Ozyurt et al. (2015), who demonstrated the clinical importance of combining echocardiographic and biochemical indices to assess shunt severity in congenital heart disease (7,9,10).

Distribution of Diagnosis and Demographics:
Among the study population, ASD was the most frequent lesion (36.7 %), followed by VSD (33.3 %) and PDA (30.0 %). This distribution closely parallels findings

reported by Zhang et al. (2023), Kavga et al. (2013), and Farouk et al. (2017), where ASD predominated among pediatric ACHD cases (6,8,11). The predominance of ASD may reflect its often subtle clinical presentation, leading to later diagnosis compared with VSD or PDA, which produce earlier symptoms from larger left-to-right shunts.

Age analysis revealed that most cases (61.7 %) occurred between 1–5 years, while 20 % were diagnosed in infants and 18.3 % in children above 5 years. This pattern is consistent with Kavga et al. (2013), who reported a mean diagnostic age near 23 months (6). Gender distribution showed a slight female predominance (55 %), aligning with Zhang et al. (2023) and Samadi et al. (2017), who observed a similar trend without statistical significance (10,11).

Regarding gender distribution, a slightly higher proportion of females (55.0%) were affected comparedto males (45.0%). Among ASD cases, 59.1% occurred in females, whereas VSD cases showed a nearly balanced distribution (55.0% males, 45.0% females). PDAcases also showed a female predominance (61.1% females, 38.9% males). Overall male-to-female ratio was 0.82:1, consistent with previous studies.

Severity of Left-to-Right Shunt:
Shunt quantification based on Qp/Qs ratio revealed that 51.7 % of patients had severe shunts (≥ 2), 33.3 % moderate (1.5–2), and 15 % mild (< 1.5). Severe shunting was most frequent in ASD (68.2 %), followed by VSD (50 %) and PDA (33.3 %). Although the difference among defect types was not statistically significant, this gradation resembles reports by Khosroshahi et al. (2019), where 45 % of cases exhibited Qp/Qs ≥ 2.0 (9). Ozyurt et al. (2015) similarly demonstrated that increasing Qp/Qs ratio correlated significantly with NT-proBNP levels and pulmonary artery pressure [6]. These findings reaffirm the physiologic continuum between hemodynamic burden and biomarker elevation in ACHD.

Electrocardiographic Findings:
Electrocardiographic analysis showed that 65 % of children had normal ECGs, despite confirmed shunts on echocardiography. Left-ventricular hypertrophy (LVH) with left-axis deviation was observed in 28.3 % of patients, predominantly among VSD (60 %) and PDA (27.8 %) cases. Right-ventricular hypertrophy (RVH) with right-axis deviation appeared in 6.7 % of cases, mainly ASD (18.2 %). These results mirror the observations of Farouk et al. (2017) and Ozyurt et al. (2015), who described similar ECG-defect associations (7,8). The predominance of normal ECGs underscores the limitation of ECG as a sole diagnostic tool and supports comprehensive echocardiographic and biochemical evaluation.

Clinical Findings and Risk Factors:
Heart-failure symptoms were present in 25 % of children, particularly in VSD (55 %) and PDA (22.2 %). Most ASD cases were asymptomatic, corroborating Schoen et al. (2007) and Kavga et al. (2013), who found that symptomatic patients had higher BNP levels and improved function post-closure (6,13). Failure to thrive occurred in 51.7 %, significantly associated with defect type ($p = 0.02$), similar to the chronic volume-overload effect described by Farouk et al. (2017) (8). A family history of consanguinity was identified in 18.3 %, most often in ASD (36.4 %), emphasizing genetic susceptibility as reported in other Middle Eastern and South Asian cohorts.
Serum NT-proBNP and Shunt Severity:
A clear, statistically significant trend of increasing NT-proBNP with greater shunt magnitude was observed ($p < 0.001$).

- Mild shunts (< 1.5): 62.55 ± 22.78 pg/ml
- Moderate (1.5–2): 143.40 ± 37.39 pg/ml
- Severe (≥ 2): 365.38 ± 138.98 pg/ml

These results strongly parallel those of Khosroshahi et al. (2019) and Samadi et al. (2017), both showing progressive NT-proBNP rise across shunt severity classes (9,10). The present correlation between NT-proBNP and Qp/Qs ratio ($p < 0.001$) supports Ozyurt et al. (2015)'s findings of $r \approx 0.47–0.48$ (7) and Farouk et al. (2017)'s $r = 0.54$ (8).

Among individual lesions, the mean NT-proBNP was highest in ASD (281.8 ± 64.7 pg/ml) and VSD (228.4 ± 43.9 pg/ml) and lowest in PDA (74.5 ± 26.8 pg/ml), matching the gradation reported by Farouk et al. (2017) and Zhang et al. (2023) (8,11).

Diagnostic Accuracy of NT-proBNP:
ROC analysis yielded an AUC = 0.99 ($p = 0.001$), denoting excellent diagnostic performance. The optimal cut-off value of 112 pg/ml achieved 90 % sensitivity and 84.6 % specificity, with a Youden Index = 0.75. Comparable discriminative ability was reported by Kavga et al. (2013) and Ozyurt et al. (2015), where BNP thresholds of 24.4 pg/ml and 124 pg/ml respectively predicted significant shunts (6,7). These results confirm NT-proBNP as a robust, non-invasive marker for identifying hemodynamically important shunts, complementing echocardiographic evaluation.

CONCLUSION

Serum NT-proBNP shows excellent diagnostic accuracy for identifying hemodynamically significant left-to-right shunts in children and can serve as a simple, cost-effective adjunct to echocardiography. With the recent availability of point-of-care NT-proBNP strip tests, this biomarker can be effectively used in rural and resource-limited settings to screen suspected congenital heart disease early and refer children promptly for

echocardiographic confirmation and timely management.

However, the study is limited by its single-center design and relatively small sample size, and NT-proBNP levels may be influenced by age, infections, and coexisting systemic conditions. Larger multicenter studies are recommended to further validate these findings and strengthen the utility of NT-proBNP as a frontline screening tool in community-level paediatric care.

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