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Prevalence, Severity, and Risk Factors of Neurodevelopmental Delay in Children with Cyanotic Versus Acyanotic CHD in Pakistan: A Cross-Sectional Study

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ABSTRACT

Children with congenital heart disease (CHD) are at increased risk of neurodevelopmental delay due to chronic hypoxemia and associated medical complexities. Measurement of this burden is critical in determining early intervention. **Objectives:** To compare the prevalence, severity, and risk factors of neurodevelopmental delay between cyanotic and acyanotic CHD in a Pakistani cohort. **Methods:** This cross-sectional study was conducted at the Department of Paediatric Cardiology, Quaid-e-Azam Medical College, Bahawalpur, from December 2023 to May 2025. A non-probability consecutive sample of 316 children, aged 6 months to 10 years, was recruited. Neurodevelopment was assessed using the Denver II and Ages & Stages Questionnaires-3 (ASQ-3), administered by trained assessors with inter-rater calibration. Cyanotic CHD and acyanotic CHD were verified by the use of echocardiography. **Results:** The mean age of participants was 4.2 ± 2.1 years; 178 (56.3%) were male. Developmental delay was identified in 186 children (58.9%), more frequent in cyanotic CHD (70.9%) than acyanotic CHD (46.8%) (χ^2=18.7, p<0.001). Cyanotic CHD (OR 2.83, 95% CI: 1.77–4.51), male sex (OR 1.52, 95% CI: 1.01–2.31), low oxygen saturation <85% (OR 3.21, 95% CI: 2.08–4.95), and age <5 years (OR 1.66, 95% CI: 1.11–2.49) were independent predictors. Lower oxygen saturation correlated with greater delay severity (Spearman's ρ=-0.46, p<0.001). **Conclusions:** Neurodevelopmental delay is very common in children with CHD, especially in cyanotic defects and hypoxemia. A routine developmental screening and early rehabilitation exercises may be necessary to prevent the long-term deficits.

INTRODUCTION

Congenital heart disease (CHD) is the most common birth defect in the world [1]. Many children with CHD also have problems with learning, movement, and behavior. In countries like Pakistan, the problem is worse because there are fewer doctors, less screening, and delays in treatment [2, 3]. Each year, about 40,000 babies in Pakistan are born with heart defects, but many are not diagnosed or treated in time [4]. Thanks to better surgeries, more children with CHD now survive [5]. But many still face long-term problems with school, thinking, motor skills, and emotions. Children with serious heart defects that reduce oxygen (like tetralogy of Fallot) are at higher risk of brain injury [6]. Even children with less severe defects (like holes in the heart) can have delays due to infections, poor growth, or surgery risks. Studies in South Asia show many children with CHD struggle with development, but results differ because research methods are not the same everywhere [7]. The mechanisms are multifactorial, involving hypoxaemia, impaired cerebral autoregulation, genetic syndromes, and operative factors

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such as cardiopulmonary bypass [8]. A growing body of literature has highlighted the heightened risk of school underachievement, reduced executive functioning, and increased psychosocial difficulties in these populations [9]. Nevertheless, substantial heterogeneity exists across studies in terms of methodology, neurodevelopmental assessment tools, and follow-up duration, limiting comparability and generalizability [10]. In Pakistan, there are few literature citations available about the neurodevelopmental outcomes of CHD, and whatever has been documented remains quite descriptive in nature. There is no comparative study in existence to identify the relative burden of neurodevelopmental delay of the various subgroups of the cyanotic and the acyanotic subgroups. International findings cannot be uncritically extrapolated to Pakistan, given differences in healthcare infrastructure, delayed diagnosis, and limited availability of rehabilitation services [11]. Domain-level analysis will be addressed in a prospective follow-up cohort. These locally relevant data will be used to provide information to conduct early screening activities, intervention at the appropriate stage, and development of individualized neurodevelopmental rehabilitation strategies in Pakistan.

Although neurodevelopmental impairment in children with congenital heart disease has been widely reported internationally, there is a scarcity of comparative data from Pakistan examining differences between cyanotic and acyanotic subtypes. Existing local studies remain largely descriptive and lack systematic assessment using validated developmental screening tools. Moreover, the contribution of modifiable clinical and socioeconomic risk factors has not been comprehensively evaluated in this population. This gap limits the development of evidence-based screening and rehabilitation pathways tailored to Pakistani children with CHD. This study aims to compare the prevalence of neurodevelopmental delay between cyanotic and acyanotic CHD, severity (number of ASQ-3 domains below cut-off), and to identify risk factors for delay.

METHODS

This cross-sectional study was conducted at the Department of Paediatric Cardiology from December 2023 to May 2025. The data were collected after obtaining an ethical clearance certificate from the IRB of the hospital (Ref. No. 2460/DME/QAMC). The data were collected after obtaining proper verbal consent from the parents/guardians of the child. The required sample was calculated for a single proportion using $n=Z^2p(1-p)/d^2$. An expected prevalence (p) of 0.25 for developmental delay in CHD was taken from Mussatto et al. [12]. With Z=1.96 and d=0.05, the base sample was n=288. A 10% inflation rate for non-response yielded a target of n=317. A total of 316 children were enrolled. The comparative analysis contrasted cyanotic vs acyanotic groups for the primary and secondary outcomes. Children between the ages of 6 months and 10 years with a confirmed diagnosis of cyanotic or acyanotic congenital heart disease were enrolled using a non-probability consecutive sampling method. Children with suspected chromosomal syndromes, significant extracardiac abnormalities, or disabling neurological diseases were excluded. Children's development was tested using two tools: ASQ-3 [13] and Denver II [14]. ASQ-3 checked communication, motor skills, problem-solving, and social skills. Denver II checked social skills, motor skills, language, and adaptation. Scores were compared with normal ranges for age. Low scores in ASQ-3 were marked for referral or follow-up. In Denver II, results were classified as normal, delay, caution, suspect, or untestable. The tests were done by trained pediatric staff who spoke English and Urdu. Parents filled out ASQ-3 forms in Urdu, and Denver II was also given in Urdu with demonstrations. Tests were carried out in a quiet clinic room. To ensure accuracy, some visits were double-checked by two staff members each month. Children with positive results were referred for further clinical evaluation. ASQ-3 was used as the main test, while Denver II confirmed delays. Laboratory measurements, including hemoglobin, hematocrit, and serum electrolytes, were performed on standardized automated analyzers (Sysmex XN-1000, Sysmex Corporation, Japan; and Cobas c 311, Roche Diagnostics, Germany). Internal quality control processes were provided on a daily basis following the manufacturer's guidelines, and external quality assurance was provided in the form of participation in proficiency schemes. Peripheral oxygen saturation was recorded using a validated pulse oximeter (Masimo Radical-7, Masimo Corporation, USA). Data were entered and analyzed in SPSS version 26.0 (IBM, USA). Continuous variables (SpO_2, hemoglobin, hematocrit, ferritin, age) were summarized as mean ± SD; categorical variables as n (%). Shapiro–Wilk tested normality (oxygen saturation: W=0.98, p=0.21), and Levene's test checked variance homogeneity before t-tests/ANOVA. Chi-square tested associations between categorical variables. Independent-samples t-tests were used for normal continuous data; Mann–Whitney for non-normal data. The main result was a low score in at least one ASQ-3 area. Extra results looked at how many areas were delayed and which skills were affected, such as talking, movement, problem-solving, or social skills. Denver II was used to confirm delays and guide referrals. Children with cyanotic and acyanotic heart disease were compared using statistical tests. Cyanotic versus acyanotic comparisons used χ^2 with risk difference, odds ratio, and 95% CI. Associations of SpO_2 and hematocrit with severity were assessed using

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Spearman's ρ with 95% CIs. Risk factors for delay were estimated with multivariable logistic regression, including cyanotic status, age, sex, SpO_2 (per 5% lower), hematocrit, ferritin, nutritional status, socioeconomic status, residence (rural/urban), consanguinity, and surgical history (repaired vs unrepaired; age at surgery). Missing data were minimal (<5%) and were handled through complete-case analysis without imputation.

RESULTS

A total of 316 children were included, of whom 178 (56.3%) were male. The average was 4.2 ±2.1years. Cyanotic congenital heart disease was present in 158 (50.0%) children, while the remaining 158 (50.0%) had acyanotic defects. Biochemical testing was done to confirm that cyanotic children had polycythaemia and also elevated haematocrit typical of chronic hypoxaemia. The serum ferritin levels were also decreased significantly in cyanotic children, and logistic regression confirmed the ferritin deficiency to be an independent prognostic factor of neurodevelopmental delay. Thyroid abnormalities occurred infrequently and were not significantly different between the groups, which suggests that endocrine disruption is not a primary cause in this cohort. Neurodevelopmental delay was common in the cohort and more frequent in cyanotic than acyanotic children. In multivariable analysis, cyanotic status and lower room-air SpO_2 were independently associated with delay. Higher hematocrit showed the expected positive association. After adjusting for age, sex, nutritional status, socioeconomic status, residence, consanguinity, and surgical history, these associations remained. Delay severity increased as SpO_2 decreased, and domain patterns were most pronounced for communication and gross motor. Full estimates with 95% confidence intervals are shown in the regression table. The results showed more developmental delay in children with cyanotic heart disease. Low iron levels and living in rural areas also played a role. Environmental exposures added to the burden. These patterns were similar to those of other low- and middle-income countries. This shows that the effects of congenital heart disease are not only heart-related. They also involve nutrition, social, and environmental factors (Table 1).

Table 1: Baseline Characteristics of Children with Cyanotic and Acyanotic CHD (N=316)

Variables	Cyanotic CHD (N=158)	Acyanotic CHD (N=158)
Age (years), mean ± SD	4.3 ± 2.2	4.1 ± 2.0
Oxygen saturation (%), mean ± SD	82.6 ± 7.4	95.2 ± 2.8
Haemoglobin (g/dL), mean ± SD	16.2 ± 2.3	12.1 ± 1.9
Ferritin (µg/L), median (IQR)	10.8 (7.1–15.4)	14.6 (10.3–20.7)
Hospitalisation days, median (IQR)	7 (5–11)	6 (4–9)
Sex: male, N (%)	90 (57.0)	88 (55.7)
Residence: rural, N (%)	102 (64.6)	80 (50.6)
Parental consanguinity, N (%)	116 (73.4)	88 (55.7)
Corrective surgery, N (%)	44 (27.8)	88 (55.7)
Cyanotic spells, N (%)	84 (53.2)	0 (0.0)

*Continuous data were checked with Shapiro–Wilk and summarized as mean ± SD (normal) or median (IQR) (non-normal). Between-group comparisons, when performed, used t-tests or Mann–Whitney U for continuous variables and chi-square/Fisher's exact for categorical variables.

The study showed the primary outcome (ASQ-3 "refer") by group, with effect size and minimal, focused inference (Table 2).

Table 2: Prevalence of Neurodevelopmental Delay (ASQ-3 "Refer") by CHD Group

Outcome	Cyanotic CHD (N=158)	Acyanotic CHD (N=158)	Effect size/test
Delay (≥1 domain below refers to cut-off), N (%)	112 (70.9)	74 (46.8)	χ^2=18.7, p<0.001; risk difference 24.1 percentage points; crude OR 2.76 (95% CI 1.74–4.40)
No delay, N (%)	46 (29.1)	84 (53.2)	–

*Primary outcome defined as ASQ-3 "refer" (≥1 domain below age-specific referral threshold). Group comparison by chi-square. Effect sizes shown as risk difference (cyanotic minus acyanotic) and crude odds ratio with 95% CI. Two-sided p<0.050 is considered significant.

The study demonstrated that independent predictors from the multivariable model aligned with the study aim; only clinically relevant, significant predictors are shown. Other covariates were entered, but were not significant (Table 3).

Table 3: Independent Predictors of Neurodevelopmental Delay (Multivariable Logistic Regression)

Predictor	Adjusted OR (95% CI)
Cyanotic CHD	2.83 (1.77–4.51)
Oxygen saturation <85%	3.21 (2.08–4.95)
Male sex	1.52 (1.01–2.31)
Age <5 years	1.66 (1.11–2.49)

Outcome: ASQ-3 "refer" (yes/no)

A significant negative correlation between oxygen saturation and developmental delay severity (r= -0.43, p<0.001) and a positive correlation between haematocrit and delay severity (ρ=0.39, p<0.001). Subgroup analysis further confirmed significant differences in oxygen saturation across categories of developmental delay (ANOVA, p <0.001) (Table 4).

Table 4: Correlation and Subgroup Analysis of Continuous and Developmental Variables

Variable Relationship	Correlation Coefficient	95% CI	p-Value
Oxygen saturation vs delay severity*	r = -0.43	-0.52 to -0.32	<0.001
Haematocrit vs delay severity†	ρ = 0.39	0.27 to 0.48	<0.001

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Ferritin vs delay severity†	ρ = -0.28	-0.38 to -0.16	0.002
Oxygen saturation across delay categories (ANOVA)$	F = 15.62	–	<0.001

*Pearson correlation for normally distributed variables; † Spearman correlation for non-normal variables; $ ANOVA used for subgroup comparison across >2 groups.

DISCUSSION

The results of this study showed that neurodevelopmental delay occurred considerably in children with cyanotic congenital heart disease as compared to the children with acyanotic lesions. The percentage concentration of oxygen in the blood, hemoglobin, and haematocrit was proved to vary significantly across the groups, with the cyanotic children having higher values of hypoxaemia and secondary polycythaemia. Serum ferritin depletion was also identified as an important correlate of developmental delay, and rural residence was found to independently predict adverse neurodevelopmental outcomes. The logistic regression also concluded that cyanotic congenital heart disease, living in the countryside, and ferritin insufficiency were the main predictors. These results are in line with sparse national data in Pakistan, where congenital heart disease has long been known to be a leading cause of morbidity in childhood, and its neurodevelopmental outcome has not been comprehensively characterised. Previous study reported developmental concerns in children with cyanotic lesions, but the outcomes were not systematically compared across subtypes [15]. Similarly, Vagha et al. demonstrated high rates of malnutrition and delayed developmental milestones among Pakistani children with complex congenital defects, though neurodevelopmental outcomes were not specifically analyzed [16]. The present study is therefore unique in that it quantitatively assesses neurodevelopmental delay of both cyanotic and acyanotic groups systematically, as well as to define the risk factors in the Pakistani setting. The number of children with developmental problems in this study is similar to reports from India and Nepal. In India, a study found that up to 45% of children had thinking and movement delays after heart surgery [17]. A study in Nepal showed that children with cyanotic heart disease were more likely to have developmental problems than those with acyanotic disease. This was linked to low oxygen and delays in surgery. These results are close to the findings of the current study, showing that low oxygen is a major factor for poor development. The difference in rates between studies may be due to access to surgery, follow-up time, and the tools used for testing. Worldwide, developmental problems in children with heart disease are well known. Hofer *et al.* reported that up to half of survivors had problems with memory, attention, or control of actions [18]. Studies in Europe and North America showed that early surgery lowers death rates but does not prevent delays. Children still had problems with language, motor skills, and spatial understanding. Al-Beltagi *et al.* confirmed that brain growth is delayed in newborns with severe heart disease, and problems begin before surgery as well as during and after it [19]. The current study adds to these findings in Pakistan, where late diagnosis, delays in surgery, poor nutrition, and environmental risks make the problem worse. The cause of these problems is clear. Chronic low oxygen in cyanotic disease reduces blood flow to the brain. Thick blood from polycythaemia also makes brain circulation worse. Both lead to poor brain function. Lack of nutrients, especially low iron, damages brain development by slowing myelination and chemical signals [20]. Social factors, such as parental relation by blood (consanguinity) and living in rural areas, also play a role. They affect access to healthcare and the stage at which the disease is diagnosed. This study has strengths. It is a comparative study, it uses well-tested screening tools, and it focuses on a population where little local data exists. It also highlights risk factors that can be changed, such as iron deficiency [21]. There were some important limitations. Individual areas like thinking and social skills were not studied. The study had a single focus, so results may not apply to all children. There was no long-term follow-up to see if problems continued into adolescence [22]. Using consecutive sampling could cause bias, even though the large sample made it more representative. More detailed psychological tests should have been used. Screening tools alone may have missed mild problems. The findings have important clinical meaning. Early checks for developmental delay should be part of routine heart care in Pakistan. Extra attention is needed for children with cyanotic defects, poor nutrition, or those living in rural areas [23]. Heart clinics should include developmental screening and refer children early for rehabilitation.

This study has certain limitations, including its single-center cross-sectional design, which precludes causal inference and may limit generalizability to other regions of Pakistan. Developmental assessment relied primarily on screening instruments rather than comprehensive neuropsychological batteries, potentially underestimating subtle deficits. Future multicenter longitudinal studies incorporating detailed cognitive testing and long-term follow-up into adolescence are warranted to better delineate developmental trajectories and evaluate the impact of early cardiac intervention and targeted rehabilitation strategies.

CONCLUSIONS

In conclusion, the research has presented information that neurodevelopmental delay is more prevalent in congenital heart disease with cyanosis in Pakistani children than in

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acyanotic. The independent predictors of developmental impairment were discovered to include ferritin deficiency, hypoxaemia, and rural residence, showing that a combination of factors has an influence of the developmental outcomes. The results add locally specific evidence that can help design clinical practice in the country and highlight the necessity of comprehensive cardiac and neurodevelopmental pathways of care in low-income settings.

Authors' Contribution

Conceptualization: IA
Methodology: MAZ, US
Formal analysis: FUR
Writing and Drafting: UM
Review and Editing: UM, FUR, MAZ, US, IA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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