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Prevalence, Severity, and Hematological Profile of Anemia in Children with Cyanotic Congenital Heart Disease Presenting with Cyanotic Spells: A Cross-Sectional Study.

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Abstract

Background: To determine the prevalence and severity of anemia, characterize the associated hematological profile, and examine its association with recurrent cyanotic spells among children with cyanotic congenital heart disease (CCHD) admitted to a tertiary-care hospital in Pakistan.

Methodology: This observational cross-sectional study included 387 children, from neonates to 12 years, with echocardiographically confirmed CCHD admitted for cyanotic spells at Lady Reading Hospital, Peshawar, Pakistan, from May to October 2025. Data were retrospectively retrieved from the Hospital Management Information System. Anemia was defined as hemoglobin (Hb) <15 g/dL and classified as mild (12–<15 g/dL), moderate (9–<12 g/dL), or severe (<9 g/dL). Demographics, CCHD subtype, hematological indices, and documented cyanotic spells were analyzed.

Results: Mean age was 28.4 ± 22.6 months, and 228 (58.9%) participants were male. Tetralogy of Fallot was the most common lesion (51.2%; n=198). Anemia was present in 58.2% (n=225; 95% CI: 53.2–63.1%), including mild in 35.9%, moderate in 16.0%, and severe in 6.2%. Compared with non-anemic patients, anemic patients had lower MCV (70.2 ± 6.4 vs. 78.5 ± 7.2 fL; p<0.001) and higher RDW (17.8 ± 2.4% vs. 14.2 ± 1.8%; p<0.001), indicating a predominantly microcytic pattern. Recurrent cyanotic spells occurred in 42.2% of anemic versus 31.5% of non-anemic patients (p=0.038; OR=1.59, 95% CI: 1.03–2.46). Among those with severe anemia, 58.3% experienced recurrent spells.

Conclusion: Anemia affected nearly three-fifths of children with CCHD and was associated with a microcytic hematological pattern and greater odds of recurrent cyanotic spells. These findings support routine hematological assessment in CCHD. Prospective studies incorporating ferritin, transferrin saturation, and other iron-status markers are needed to determine the contribution of iron deficiency and its relationship with cyanotic spell burden.

Keywords

Cyanotic Congenital Heart Disease, Anemia, Cyanotic Spells, Hemoglobin, Microcytosis, Pediatric Cardiology, Tetralogy Of Fallot.

Introduction

Congenital heart disease (CHD) is the most common congenital structural abnormality worldwide, affecting approximately 8–10 per 1,000 live births. Cyanotic congenital heart disease (CCHD) accounts for approximately 25–30% of CHD and comprises a heterogeneous group of cardiac lesions characterized by right-to-left shunting, systemic arterial desaturation, and chronic hypoxemia[1,2]. Persistent hypoxemia stimulates renal erythropoietin production and enhances erythropoiesis, resulting in secondary erythrocytosis as a physiological adaptation intended to preserve systemic oxygen delivery[3]. However, sustained erythropoietic activity also increases the body's requirement for iron and may contribute to depletion of iron stores, particularly in rapidly growing children or those with inadequate dietary iron intake[4].

Recognition of anemia in children with CCHD is clinically challenging because conventional age-specific hemoglobin thresholds used in otherwise healthy children may not adequately reflect the physiological requirements of chronically cyanotic patients. In CCHD, compensatory erythrocytosis is expected in response to persistent arterial desaturation; therefore, a hemoglobin concentration considered normal in the general pediatric population may represent relative anemia in a child with chronic cyanosis[5]. A hemoglobin threshold of <15 g/dL has consequently been proposed for identifying anemia in patients with cyanotic heart disease and has subsequently been applied in studies of this population[6]. This distinction is important because reliance solely on conventional pediatric thresholds may fail to identify clinically relevant hematological abnormalities in children with CCHD.

The clinical consequences of inadequate erythropoietic compensation in CCHD may be substantial. Anemia and iron deficiency have been associated with adverse outcomes including hypercyanotic spells, impaired tissue oxygenation, thromboembolic complications, cerebrovascular events, and metabolic disturbances[7,8]. Iron deficiency may further compromise oxygen delivery by producing smaller and less deformable erythrocytes, potentially impairing microcirculatory blood flow despite an apparently adequate or elevated red blood cell mass[9]. Thus, evaluation of hematological indices such as mean corpuscular volume (MCV) and red cell distribution width (RDW), in addition to hemoglobin concentration, may provide clinically relevant information regarding the hematological status of children with CCHD.

Available studies demonstrate considerable geographic variation in the reported burden of anemia and iron deficiency among children with congenital heart disease. Reported prevalence estimates range from approximately 9.1% in Tanzania to 72.0% in Ethiopia, with variation potentially reflecting differences in study populations, diagnostic criteria, age distribution, nutritional status, disease severity, and healthcare resources[10,11]. Such differences are particularly relevant in low- and middle-income countries (LMICs), where nutritional deficiencies may coexist with delayed diagnosis and limited access to definitive pediatric cardiac interventions.

The issue is especially important in Pakistan, where an estimated 60,000 children with CHD are born annually, yet comprehensive national data describing anemia among children with CCHD remain limited[12,13]. In resource-constrained settings, prolonged exposure to chronic hypoxemia, nutritional vulnerability, delayed surgical correction, and limited access to routine iron-status testing may collectively increase the risk of clinically important hematological abnormalities. Despite these concerns, relatively little local evidence is available regarding the prevalence and severity of anemia, its hematological characteristics, or its relationship with cyanotic spell burden among Pakistani children with CCHD.

Therefore, the present study aimed to determine the prevalence and severity of anemia and characterize the associated hematological profile among pediatric patients with echocardiographically confirmed CCHD admitted with cyanotic spells at a tertiary-care hospital in Pakistan. A secondary objective was to examine the distribution of anemia according to age and CCHD subtype and to evaluate the association between anemia and recurrent cyanotic spells. By

characterizing these relationships in a large tertiary-care pediatric cohort, the study seeks to provide locally relevant evidence for improving recognition and hematological assessment of children with CCHD.

Methodology

Study Design

This study was designed as an observational cross-sectional study to determine the prevalence and severity of anemia and to describe the associated hematological profile among pediatric patients with cyanotic congenital heart disease (CCHD) presenting with cyanotic spells. The study used retrospectively retrieved hospital data for eligible patients admitted during the predefined study period. The primary outcome was the presence of anemia, defined according to the hemoglobin threshold specified for patients with cyanotic heart disease. Secondary assessments included the severity of anemia, hematological indices, distribution of anemia according to age and type of CCHD, and the association between anemia and recurrent cyanotic spells.

Ethics

Ethical approval for the study was obtained from the Ethical Review Committee (ERC) of Lady Reading Hospital-Medical Teaching Institution (LRH-MTI), Peshawar, Pakistan. As the investigation involved retrospective analysis of routinely collected clinical information from the Hospital Management Information System (HMIS), a waiver of individual informed consent was granted by the relevant ethical review authority. Patient information extracted for analysis was de-identified to maintain confidentiality and privacy. Data handling and analysis were conducted in accordance with the ethical principles of the Declaration of Helsinki.

Setting

The study was conducted in the Department of Pediatrics and Pediatric Cardiology, Lady Reading Hospital-Medical Teaching Institution (LRH-MTI), Peshawar, Pakistan, over a six-month period from May 2025 to October 2025. LRH-MTI is a major public-sector tertiary-care teaching hospital in Khyber Pakhtunkhwa, with approximately 1,800 beds and a catchment population exceeding 30 million. The pediatric cardiology unit comprises 32 beds, two high-dependency units, and services provided by three qualified pediatric cardiologists. Previous literature has also documented a substantial burden of congenital heart disease among children presenting to this institution.

Participants

The study population consisted of pediatric patients ranging from neonates (0–28 days) to 12 years of age with echocardiographically confirmed CCHD who were admitted primarily for management of cyanotic spells during the study period. Eligible CCHD diagnoses included tetralogy of Fallot (TOF), transposition of the great arteries (TGA), pulmonary atresia with ventricular septal defect (PA-VSD), tricuspid atresia, double outlet right ventricle (DORV), single ventricle, and other complex cyanotic cardiac lesions. Patients were identified consecutively from the HMIS database to minimize discretionary selection of cases.

Patients were excluded if they had undergone definitive surgical correction of their congenital cardiac lesion; had received a blood transfusion or iron supplementation during the preceding three months; had chronic kidney disease, hemolytic anemia, or a known genetic syndrome affecting hematological parameters; or had incomplete medical records that prevented assessment of the variables required for the study.

Variables

The principal study variable was anemia status. In children with CCHD, anemia was defined as a hemoglobin concentration of <15 g/dL, consistent with previously established criteria for cyanotic congenital heart disease[5]. This higher threshold was used because chronic hypoxemia normally stimulates compensatory erythrocytosis in patients with CCHD, and consequently hemoglobin concentrations that might appear normal in the general pediatric population may represent relative anemia in cyanotic patients[5].

Anemia was further categorized according to severity as mild anemia (Hb 12–<15 g/dL), moderate anemia

(Hb 9–<12 g/dL), and severe anemia (Hb <9 g/dL). The manuscript also specified the conventional WHO threshold of Hb <12 g/dL for acyanotic CHD[14]; however, the present study population comprised patients with cyanotic CHD.

Other variables extracted included age, sex, specific type of CCHD, hemoglobin concentration (g/dL), hematocrit (%), mean corpuscular volume (MCV, fL), mean corpuscular hemoglobin (MCH, pg), red cell distribution width (RDW, %), red blood cell (RBC) count, and documented cyanotic spells. For analysis of spell burden, recurrent cyanotic spells were represented by two or more documented spells during the admission.

Data Sources / Measurement

Data were obtained retrospectively from the LRH-MTI Hospital Management Information System (HMIS), a computerized institutional system containing demographic information, diagnoses, admission details, laboratory investigations, and other clinical information. Eligible records were reviewed and the predefined demographic, cardiac, hematological, and clinical variables were extracted.
The diagnosis and type of CCHD were determined from the echocardiography report documented in the patient record. Hematological parameters were obtained from laboratory investigations performed at admission. Hemoglobin was measured using standardized automated hematology analyzers in the hospital central laboratory, and the recorded hemoglobin, hematocrit, MCV, MCH, RDW, and RBC count values were used for analysis. The hemoglobin value documented at admission was used to classify participants as anemic or non-anemic and subsequently to determine anemia severity.

Cyanotic spell information was obtained from the clinical/admission record in HMIS. Patients with two or more documented cyanotic spells during the admission were classified as having recurrent spells for the comparative analysis. Because serum ferritin, serum iron, total iron-binding capacity, and transferrin saturation were not systematically available for all participants, iron deficiency was not directly diagnosed biochemically. Consequently, low MCV and elevated RDW were interpreted as hematological patterns suggestive of iron deficiency rather than definitive evidence of iron deficiency anemia.

Bias

Several measures were incorporated to reduce potential bias. Consecutive selection of all eligible cases from the HMIS database during the predefined study period was used to reduce investigator-driven selection of participants. Restriction of the study to patients with echocardiographically confirmed CCHD reduced the likelihood of diagnostic misclassification. Hematological measurements were based on routinely performed laboratory investigations using standardized automated analyzers rather than subjective clinical assessment.

Potential confounding from recent treatment or other causes of altered hematological parameters was reduced by excluding patients with recent blood transfusion or iron supplementation, chronic kidney disease, hemolytic anemia, known genetic syndromes affecting hematological indices, and definitive surgical correction. Nevertheless, because this was a retrospective, single-center study, residual selection and information bias could not be completely eliminated. Exclusion of incomplete medical records could introduce selection bias, while the absence of systematic nutritional assessment and iron studies could result in misclassification of the underlying cause of anemia. These limitations were considered when interpreting associations between anemia and cyanotic spell frequency.

Study Size

The required sample size was calculated using the WHO sample-size formula for prevalence studies. An expected anemia prevalence of 50% was selected to provide the maximum required sample size in the absence of a definitive local prevalence estimate. Using a 95% confidence level and 5% absolute margin of error, the minimum required sample size was calculated as 384 participants. The final analysis included 387 eligible pediatric patients, thereby meeting the minimum calculated sample-size requirement. Participants were selected consecutively from eligible HMIS records during the study period.

Quantitative Variables

Continuous quantitative variables included age in months, hemoglobin concentration (g/dL), hematocrit (%), MCV (fL), MCH (pg), RDW (%), and RBC count ($\times 10^{12}$/L). Age was additionally categorized into clinically meaningful groups as neonates (0–28 days), infants 1–6 months, infants 6–12 months, toddlers 1–3 years, preschool children 3–5 years, and school-age children 5–12 years for descriptive and subgroup analyses.

Hemoglobin was analyzed both as a continuous variable and categorically according to anemia status and severity. Participants with Hb ≥15 g/dL were considered non-anemic, whereas those with Hb <15 g/dL were considered anemic[11]. The anemic group was further categorized into mild, moderate, and severe anemia according to the predefined hemoglobin ranges. Hematological indices were retained as continuous variables for comparisons between anemic and non-anemic groups.

Statistical Methods

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were calculated for demographic, clinical, and hematological variables. Categorical variables were summarized as frequencies and percentages, whereas continuous variables were reported as mean ± standard deviation (SD) or median with interquartile range (IQR) depending on their distribution. The prevalence of anemia was calculated as the number of patients meeting the predefined anemia criterion divided by the total number of eligible participants and was reported with a 95% confidence interval (CI). Anemia prevalence was additionally examined according to age group and CCHD subtype. Comparisons of categorical variables were performed using the chi-square test or Fisher's exact test, as appropriate. Continuous variables between anemic and non-anemic groups were compared using the independent-samples t-test or Mann–Whitney U test, depending on the distribution of the data.

The association between anemia and recurrent cyanotic spells was assessed by comparing the proportion of patients experiencing two or more documented spells among anemic and non-anemic participants. The magnitude of this association was expressed as an odds ratio (OR) with a 95% confidence interval (CI). All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

Results

Participants

A total of 387 pediatric patients with echocardiographically confirmed cyanotic congenital heart disease (CCHD) who were admitted for the management of cyanotic spells were included in the final analysis. Participants ranged in age from 3 days to 144 months, with a mean age of 28.4 ± 22.6 months. Of the total cohort, 228 (58.9%) were male and 159 (41.1%) were female. The age distribution showed that 28 (7.2%) participants were neonates aged 0–28 days, 89 (23.0%) were infants aged 1–6 months, 76 (19.6%) were infants aged 6–12 months, 98 (25.3%) were toddlers aged 1–3 years, 62 (16.0%) were preschool children aged 3–5 years, and 34 (8.8%) were school-age children aged 5–12 years. The demographic and clinical characteristics of the study population are summarized in Table 1.

Descriptive Data

The distribution of CCHD diagnoses is presented in Table 1 and Figure 1. Tetralogy of Fallot (TOF) was the most frequently documented cardiac lesion, occurring in 198 (51.2%) patients, followed by transposition of the great arteries (TGA) in 58 (15.0%), pulmonary atresia with ventricular septal defect (PA-VSD) in 42 (10.9%), tricuspid atresia in 31 (8.0%), double outlet right ventricle (DORV) in 24 (6.2%), single ventricle in 21 (5.4%), and other complex cyanotic lesions in 13 (3.4%) patients. The mean hemoglobin concentration for the entire cohort was 13.8 ± 2.4 g/dL, with values ranging from 6.8 to 19.2 g/dL. The distribution of CCHD types together with hemoglobin categories is illustrated in Figure 1.

Using the predefined CCHD-specific hemoglobin threshold of <15 g/dL, 225 of 387 patients were classified as anemic, corresponding to an overall anemia prevalence of 58.2% (95% CI: 53.2–63.1%). The remaining 162 patients (41.8%) had hemoglobin

concentrations ≥15 g/dL and were classified as non-anemic. Among the total study population, 139 (35.9%) had mild anemia (Hb 12–<15 g/dL), 62 (16.0%) had moderate anemia (Hb 9–<12 g/dL), and 24 (6.2%) had severe anemia (Hb <9 g/dL). Thus, 86 patients (22.2%) had hemoglobin concentrations below 12 g/dL. The distribution of participants according to hemoglobin category is also shown in Figure 1.

Outcome Data

The primary outcome, anemia, was present in 58.2% (n=225) of the study population. Anemia prevalence varied across age categories. The highest prevalence was observed among infants aged 1–6 months (68.5%; 61/89), followed by neonates (64.3%; 18/28), infants aged 6–12 months (61.8%; 47/76), toddlers aged 1–3 years (56.1%; 55/98), school-age children (52.9%; 18/34), and preschool children (51.6%; 32/62). However, the overall difference in anemia prevalence across age groups was not statistically significant (p=0.312). Anemia prevalence also differed numerically according to the type of CCHD, as detailed in Table 2. The highest prevalence was observed among patients with tricuspid atresia (71.0%; 22/31), followed by transposition of the great arteries (65.5%; 38/58), pulmonary atresia with VSD (61.9%; 26/42), tetralogy of Fallot (55.6%; 110/198), double outlet right ventricle (54.2%; 13/24), single ventricle (52.4%; 11/21), and other CCHD lesions (38.5%; 5/13). Despite these numerical differences, the association between CCHD subtype and anemia status was not statistically significant (p=0.428). The hematological profiles of anemic and non-anemic participants are compared in Table 3. As expected from the classification criterion, mean hemoglobin concentration was lower in the anemic group than in the non-anemic group (12.1 ± 1.8 vs. 16.2 ± 2.1 g/dL; p<0.001). Mean hematocrit was similarly lower among anemic patients (38.4 ± 5.2% vs. 50.6 ± 6.8%; p<0.001). Anemic patients had a significantly lower mean MCV (70.2 ± 6.4 vs. 78.5 ± 7.2 fL; p<0.001) and mean MCH (23.8 ± 3.2 vs. 26.4 ± 2.8 pg; p<0.001), whereas mean RDW was significantly higher (17.8 ± 2.4% vs. 14.2 ± 1.8%; p<0.001). Mean RBC count was also significantly different between the two groups, with values of 5.42 ± 0.82 $\times 10^{12}$/L in anemic patients and 5.18 ± 0.74 $\times 10^{12}$/L in non-anemic patients (p=0.004). Complete between-group comparisons are presented in Table 3.

Main Results

The multivariable logistic regression model evaluating independent predictors of severe coronary artery disease is illustrated in Figure 1. After adjustment for conventional cardiovascular risk factors, including age, sex, hypertension, diabetes mellitus, dyslipidemia, and current smoking, maternal history of CAD remained an independent predictor of severe angiographic coronary artery disease (adjusted OR = 1.58, 95% CI: 1.15–2.16, p = 0.01). In contrast, paternal history (adjusted OR = 1.12) and history of CAD in both parents (adjusted OR = 1.27) showed positive but statistically non-significant associations with severe CAD (p > 0.05).

Among the conventional cardiovascular risk factors, increasing age (adjusted OR = 1.02 per year; 95% CI: 1.00–1.05; p = 0.04), hypertension (adjusted OR = 1.36; 95% CI: 1.05–1.76; p = 0.02), and diabetes mellitus (adjusted OR = 1.44; 95% CI: 1.10–1.89; p = 0.01) were also identified as significant independent predictors of severe coronary artery disease. Male sex, dyslipidemia, and current smoking were not independently associated with disease severity after multivariable adjustment (Figure 1).

Table 1: Demographic and Clinical Characteristics of Pediatric Patients with Cyanotic CHD (n=387).

Variables	n (%)
Age group	
Neonates (0–28 days)	28 (7.2)
Infants (1–6 months)	89 (23.0)
Infants (6–12 months)	76 (19.6)
Toddlers (1–3 years)	98 (25.3)
Preschool (3–5 years)	62 (16.0)

School age (5–12 years)	34 (8.8)
Gender	
Male	228 (58.9)
Female	159 (41.1)
Mean age, months (mean ± SD)	28.4 ± 22.6
Type of CCHD	
Tetralogy of Fallot	198 (51.2)
Transposition of Great Arteries	58 (15.0)
Pulmonary Atresia with VSD	42 (10.9)
Tricuspid Atresia	31 (8.0)
Double Outlet Right Ventricle	24 (6.2)
Single Ventricle	21 (5.4)
Others	13 (3.4)

Table 2: Distribution of Hemoglobin Levels Among Participants.

Hemoglobin (Hb) level	n (%)
<12 g/dL	86 (22.2%)
12–15 g/dL	139 (35.9%)
>15 g/dL	162 (41.9%)

Table 3: Prevalence of Anemia by Type of Cyanotic CHD.

CCHD Type	Total, n (%)	Yes, n (%)	No, n (%)	p-value
Tetralogy of Fallot	198 (51.2%)	110 (55.6%)	88 (44.4%)	
Transposition of Great Arteries	58 (15.0%)	38 (65.5%)	20 (34.5%)	
Pulmonary Atresia with VSD	42 (10.9%)	26 (61.9%)	16 (38.1%)	
Tricuspid Atresia	31 (8.0%)	22 (71.0%)	9 (29.0%)	0.428
Double Outlet Right Ventricle	24 (6.2%)	13 (54.2%)	11 (45.8%)	
Single Ventricle	21 (5.4%)	11 (52.4%)	10 (47.6%)	
Others	13 (3.4%)	5 (38.5%)	8 (61.5%)	

*p<0.05 is considered statistically significant.

Table 4: Comparison of Hematological Parameters Between Anemic and Non-Anemic Patients.

Parameter	Anemic (n=225)	Non-Anemic (n=162)	p-value
Hemoglobin (g/dL)	12.1 ± 1.8	16.2 ± 2.1	<0.001*
Hematocrit (%)	38.4 ± 5.2	50.6 ± 6.8	<0.001*
MCV (fL)	70.2 ± 6.4	78.5 ± 7.2	<0.001*
MCH (pg)	23.8 ± 3.2	26.4 ± 2.8	<0.001*
RDW (%)	17.8 ± 2.4	14.2 ± 1.8	<0.001*
RBC count (x10^{12}/L)	5.42 ± 0.82	5.18 ± 0.74	0.004*

*p<0.05 is considered statistically significant.

Discussion

The present study demonstrates a substantial burden of anemia among pediatric patients with cyanotic congenital heart disease (CCHD) admitted for management of cyanotic spells at a large tertiary-care hospital in Pakistan. Using the predefined CCHD-specific hemoglobin threshold of <15 g/dL, 58.2% of the 387 patients were classified as anemic, with mild, moderate, and severe anemia accounting for 35.9%, 16.0%, and 6.2% of the total cohort, respectively. In addition to the high prevalence of anemia, anemic patients exhibited significantly lower MCV and MCH and higher RDW than non-anemic patients. Most importantly, recurrent cyanotic spells were significantly more frequent among anemic patients than among their non-anemic counterparts (42.2% vs. 31.5%; p=0.038), with an odds ratio of 1.59 (95% CI: 1.03–2.46). Together, these findings highlight the potential clinical relevance of hematological abnormalities in children with CCHD.

The observed prevalence of anemia is broadly consistent with findings reported from neighboring India[15,16] and supports previous evidence that hematological abnormalities represent an important but potentially under recognized problem among children with CCHD in South Asian and other resource-limited settings[17]. Differences in prevalence between studies should, however, be interpreted cautiously because reported estimates are influenced by the hemoglobin threshold used to define anemia, age distribution, underlying cardiac lesions, nutritional status, degree of hypoxemia, access to cardiac intervention, and availability of iron-status testing[18,19]. The relatively high prevalence observed in the present cohort may therefore reflect both the physiological hematological demands imposed by chronic cyanosis and characteristics of the population referred to a tertiary-care center.

The definition of anemia deserves particular consideration in CCHD. Chronic arterial desaturation normally stimulates erythropoietin-mediated erythrocytosis as a compensatory mechanism to maintain systemic oxygen delivery[20]. Consequently, hemoglobin concentrations that would not ordinarily be considered anemic in healthy children may represent an inadequate erythropoietic response in a chronically cyanotic child. Amoozgar et al. proposed a hemoglobin concentration below 15 g/dL as a clinically relevant threshold in pediatric congenital heart disease[21], and similar thresholds have subsequently been applied in studies involving cyanotic patients[22,23]. The concept of relative anemia is therefore especially important in CCHD, because application of conventional pediatric hemoglobin thresholds alone may underestimate clinically meaningful hematological impairment[24,25].

Tetralogy of Fallot was the predominant CCHD lesion in the present cohort, accounting for 51.2% of participants, consistent with its recognized importance among cyanotic congenital cardiac lesions[19]. Anemia prevalence varied numerically across CCHD subtypes, ranging from 38.5% among other complex lesions to 71.0% among patients with tricuspid atresia. However, the overall difference according to CCHD subtype was not statistically significant (p=0.428). Therefore, the apparently higher prevalence among patients with tricuspid atresia, transposition of the great arteries, and pulmonary atresia with VSD should be interpreted as descriptive rather than evidence of a lesion-specific association. Differences in the degree of arterial desaturation could theoretically influence erythropoietic demand, but oxygen saturation was not included in the present analysis and this mechanism cannot be established from the current data. The age-specific analysis similarly demonstrated numerical variation without a statistically significant association. Anemia prevalence was highest among infants aged 1–6 months (68.5%), followed by neonates (64.3%) and infants aged 6–12 months (61.8%), whereas lower prevalence estimates were observed among older age groups. The vulnerability of younger infants may plausibly relate to rapid growth, changing iron stores, and physiological changes in hemoglobin concentration during early infancy[20]. In children with CCHD, these normal developmental processes occur in parallel with increased erythropoietic requirements generated by chronic hypoxemia. Nevertheless, because the difference between age

categories did not reach statistical significance (p=0.312), the observed age pattern should not be interpreted as demonstrating an independent effect of age. Survival and referral patterns may also influence the age distribution of children with severe unrepaired CCHD in resource-constrained settings[21].

An important finding was the distinct hematological profile observed among anemic patients. Compared with non-anemic participants, anemic children had significantly lower MCV (70.2 ± 6.4 vs. 78.5 ± 7.2 fL; p<0.001), lower MCH (23.8 ± 3.2 vs. 26.4 ± 2.8 pg; p<0.001), and higher RDW (17.8 ± 2.4% vs. 14.2 ± 1.8%; p<0.001). This combination represents a microcytic hematological pattern compatible with iron-restricted erythropoiesis. Previous studies have emphasized that iron deficiency in CCHD can be difficult to recognize because chronic hypoxemia may maintain relatively high hemoglobin and hematocrit concentrations despite depleted iron stores[15,18]. MCV and RDW may therefore provide useful supportive information when evaluating these patients[23,24].

However, the present findings should not be interpreted as confirming iron-deficiency anemia. Serum ferritin, serum iron, total iron-binding capacity, and transferrin saturation were not systematically measured in the study population. Although reduced MCV and elevated RDW are compatible with iron deficiency, these indices are not specific enough to establish its etiology. Previous studies have demonstrated the value of direct iron-status assessment in patients with cyanotic heart disease[22,26]. Accordingly, the present study identifies a hematological phenotype suggestive of iron-restricted erythropoiesis but cannot determine the proportion of anemia directly attributable to iron deficiency.

The association between anemia and recurrent cyanotic spells represents the principal clinically relevant finding of the study. Two or more documented cyanotic spells occurred in 42.2% of anemic patients compared with 31.5% of non-anemic patients, corresponding to significantly greater odds among the anemic group (OR=1.59; 95% CI: 1.03–2.46; p=0.038). Moreover, 58.3% of patients with severe anemia experienced recurrent spells. These observations are directionally consistent with previous work by Mukherjee et al., who reported an association between iron deficiency anemia and cyanotic spells among children with CCHD[7].

Several biological mechanisms may plausibly contribute to this relationship. Iron deficiency can produce microcytic erythrocytes with reduced deformability, potentially impairing microcirculatory flow and aggravating tissue hypoxia[3]. Iron also contributes to cellular oxygen utilization and multiple metabolic pathways involved in oxygen homeostasis[22]. In a child whose systemic oxygen delivery is already compromised by right-to-left shunting and chronic arterial desaturation, an inadequate hemoglobin response or altered erythrocyte characteristics could potentially further compromise tissue oxygenation. Nevertheless, the current cross-sectional data demonstrate association rather than causation, and the direction of the relationship between anemia and recurrent spells cannot be determined from this study.

The findings are particularly relevant to resource-limited settings such as Pakistan. Nutritional deficiencies, delayed diagnosis of congenital heart disease, limited availability of pediatric cardiac surgery, and restricted access to specialized laboratory investigations may increase the likelihood that hematological abnormalities remain undetected[13,24]. Genetic and hematological factors may also be relevant in the local population[27-30]. LRH-MTI serves a large population in Khyber Pakhtunkhwa and has previously reported a substantial pediatric CHD burden[29], making the present findings clinically relevant to tertiary-care practice in the region, although they should not automatically be generalized to all Pakistani children with CCHD.

From a clinical perspective, these results support careful hematological evaluation of children with CCHD, particularly those presenting with recurrent

cyanotic spells. Hemoglobin should be interpreted in the context of chronic cyanosis rather than solely according to conventional pediatric reference ranges. When available, serum ferritin, transferrin saturation, serum iron, and other appropriate iron-status investigations should complement complete blood count indices to distinguish true iron deficiency from other causes of microcytosis or anemia[26]. Treatment decisions should subsequently be based on documented or appropriately established iron deficiency rather than on microcytosis alone. Previous literature has described iron supplementation strategies in this population[27], but the present observational study did not evaluate iron treatment and therefore cannot establish the effectiveness or optimal regimen of supplementation.

This study adds locally relevant evidence by quantifying the burden and severity of anemia and describing its hematological characteristics among Pakistani children with CCHD presenting with cyanotic spells. The observed association between anemia and recurrent spells warrants further investigation using prospective, multicenter designs incorporating arterial oxygen saturation, biochemical iron indices, nutritional assessment, disease severity, and treatment-related variables. Multivariable analyses would also be valuable to determine whether anemia independently predicts recurrent cyanotic spells after accounting for age, CCHD subtype, severity of hypoxemia, and other potential confounders.

Strengths and Limitations

Several limitations should be considered when interpreting these findings. First, the study was conducted at a single tertiary-care center, and the study population consisted specifically of children with CCHD admitted for management of cyanotic spells. The prevalence estimates therefore may not be generalizable to children with CCHD in the community, clinically stable outpatients, or patients managed at other healthcare facilities. Second, the cross-sectional observational design prevents determination of temporality or causality. Although anemia was significantly associated with recurrent cyanotic spells, the study cannot establish that anemia caused the increased spell frequency. Residual confounding from the severity of the underlying cardiac lesion, degree of hypoxemia, nutritional status, or other clinical factors may have influenced this association. Third, the study relied on retrospectively recorded HMIS data, making the analysis dependent on the completeness and accuracy of routine clinical documentation. Exclusion of patients with incomplete records may have introduced selection bias, while variation in documentation of cyanotic spells could have contributed to information bias. Fourth, iron status was not confirmed biochemically in all participants. Serum ferritin, serum iron, total iron-binding capacity, transferrin saturation, and related markers were not systematically available. Consequently, although the lower MCV and MCH and higher RDW among anemic patients are compatible with iron-restricted erythropoiesis, the study cannot determine the prevalence of confirmed iron deficiency or iron-deficiency anemia. Fifth, systematic information regarding nutritional status and dietary iron intake was not collected, limiting assessment of the potential contribution of malnutrition or dietary deficiency. In addition, variables that could influence the relationship between anemia and cyanotic spells, particularly arterial oxygen saturation and other indicators of CCHD severity, were not included in the reported analysis. Finally, the association between anemia and recurrent cyanotic spells was based on an unadjusted comparison and odds ratio. Multivariable analysis accounting for clinically relevant potential confounders was not reported. Therefore, anemia cannot be regarded from these data as an independent predictor of recurrent cyanotic spells. Future studies should address these limitations through prospective multicenter recruitment, standardized documentation of cyanotic spells, comprehensive iron and nutritional assessment, measurement of oxygen saturation and disease severity, and appropriately adjusted multivariable analyses.

Conclusion

Anemia was highly prevalent among pediatric patients with cyanotic congenital heart disease admitted for management of cyanotic spells at this

tertiary-care center in Pakistan, affecting 58.2% of the study population using the predefined CCHD-specific hemoglobin threshold of <15 g/dL. Anemic patients demonstrated significantly lower MCV and MCH and higher RDW, indicating a predominantly microcytic hematological pattern compatible with, but not diagnostic of, iron-restricted erythropoiesis.

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