Hematological and Other Laboratory Indices Abnormalities in Children with Congenital Cyanotic Heart Disease Attending Assiut University Hospitals: A Prospective Hospital-Based Study

Running Title: *Hematologic Abnormalities in Children with Cyanotic Congenital Heart Disease*

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Abstract

Introduction: Congenital heart defects are the most common developmental anomalies and are a leading non-infectious cause of mortality in newborns, affecting up to 6–8 per 1,000 infants. In most cases, the cause is unknown. Erythrocytosis, thrombocytopenia, platelet function defects, and coagulation factor deficiencies are the main hematologic disorders found in patients with cyanotic congenital heart diseases (CCHD).

Objective: To determine the hematological and laboratory indices abnormalities in congenital cyanotic heart diseases.

Methods: This Prospective cross-sectional observational study was done at the Pediatric Cardiology Unit of Assiut University Hospitals over one year from (January 2023 to December 2023) it included 50 patients who have been diagnosed with cyanotic congenital heart disease through echocardiography, but those with other types of congenital heart disease, congenital anomalies, other chronic diseases, and Post-operative patients were excluded.

Results: Erythrocytosis, thrombocytopenia, platelet function defects, and coagulation factors deficiencies were the main hematologic disorders in patients with cyanotic congenital heart disease (CCHD). Most (74% of the patients) had normal white blood cell counts, but many (68%) had abnormal red blood cell counts (erythrocytosis), and 94% of the subjects had iron deficiency and low MCH/MCHC levels (indicators of microcytic anemia). Many (68% of the patients) had elevated uric acid levels, a potential risk factor for gout. Most had abnormally low creatinine and BUN levels (92% of the cases), which may require further investigations.

Conclusion: Erythrocytosis, thrombocytopenia, platelet function defects, and coagulation factors deficiencies were the main hematologic disorders in patients with cyanotic congenital heart disease (CCHD).

Keywords: Cyanotic congenital heart diseases; Erythrocytosis; Thrombocytopenia; Platelet function defects.

Introduction:

Congenital heart defects are the most common developmental anomaly and are the most common non-infectious causes of mortality in newborns; they affect up to 6-8/1000 infants, and in most cases, the cause is unknown**[1].** Erythrocytosis, thrombocytopenia, platelet function defects, and coagulation factors deficiencies are the main hematologic disorders in patients with cyanotic congenital heart diseases (CCHD). Erythrocytosis is an isolated increase in the number of red blood cells. Primary erythrocytosis is an increased red cell mass that surfaces in the absence of a definable

stimulus, whereas secondary erythrocytosis refers to an isolated increase in the red cell mass in response to such stimulus as low systemic arterial oxygen saturation in the context of cyanotic congenital heart disease **[2]**. Polycythemia is mainly caused by the capillary diameter being significantly smaller than the red cell diameter, and this mismatch could cause viscosity to increase at the capillary level. In patients with CCHD, platelets are shown to have both qualitative and quantitative abnormalities **[3]**. A significant association has been reported between thrombocytopenia and high hematocrit in cyanotic patients. Immature reticulated platelets represent the youngest platelets released into circulation by regenerated marrow megakaryocytes and are the analog of the red cell reticulocyte **[4]**.

Aim of the Work:

To determine the hematological abnormalities in congenital cyanotic heart diseases.

Patient and Methods:

This Prospective cross-sectional observational study was done at the Pediatric Cardiology Unit of Assiut University Hospitals over one year from (January 2023 to December 2023).

Inclusion Criteria:

- Children who have been diagnosed with cyanotic congenital heart disease through echocardiography.

Exclusion Criteria:

- Children with other types of congenital heart diseases.
- Children with other congenital anomalies.
- Children with other chronic diseases.
- Post-operative patients.

Methods:

The study included 50 patients with cyanotic heart disease. Every patient was subjected to the following steps:

- **History**: Name, Age, Sex and Consanguinity, Onset of Cyanosis, Permanent or Potential, and What Increase and decrease of the cyanosis.
- **Clinical Examination:** focused on identifying the site of the heart's apex, listening to the heart's sound and heart murmurs, and detecting the site of the murmur.

Investigations: Included:

Echocardiography, Complete Blood Count, Coagulation Profile, Serum Iron, Total Iron Binding Capacity, Serum Ferritin and Serum Creatinine, Blood Urea Nitrogen, Serum Uric Acid.

Statistical Analysis:

SPSS 22 (SPSS Inc., Chicago, IL, USA) was used for statistical calculations. Non-normally distributed data are presented as mean ± SD, median, range, frequencies, and relative frequencies (percentages) when applicable. Kruskal Wallis or Mann Whitney U tests were used to compare quantitative variables since the data were not regularly distributed. Wilcoxon sign rank test compared paired quantitative data. To compare categorical data, the Chi-square ($\chi 2$) test was used. For anticipated frequencies less than 5, an exact test was employed. The P-value is always 2-tailed and is significant at 0.05.

Ethical Considerations:

- Approval from the Ethics of Scientific Research Committee, Faculty of Medicine Assiut University was obtained (**IRB: 17101859)**.
- Verbal and written consents were obtained from all the patient's caregivers.
- The privacy and confidentiality of all information obtained was observed without intervention in the prescribed treatment.

Results:

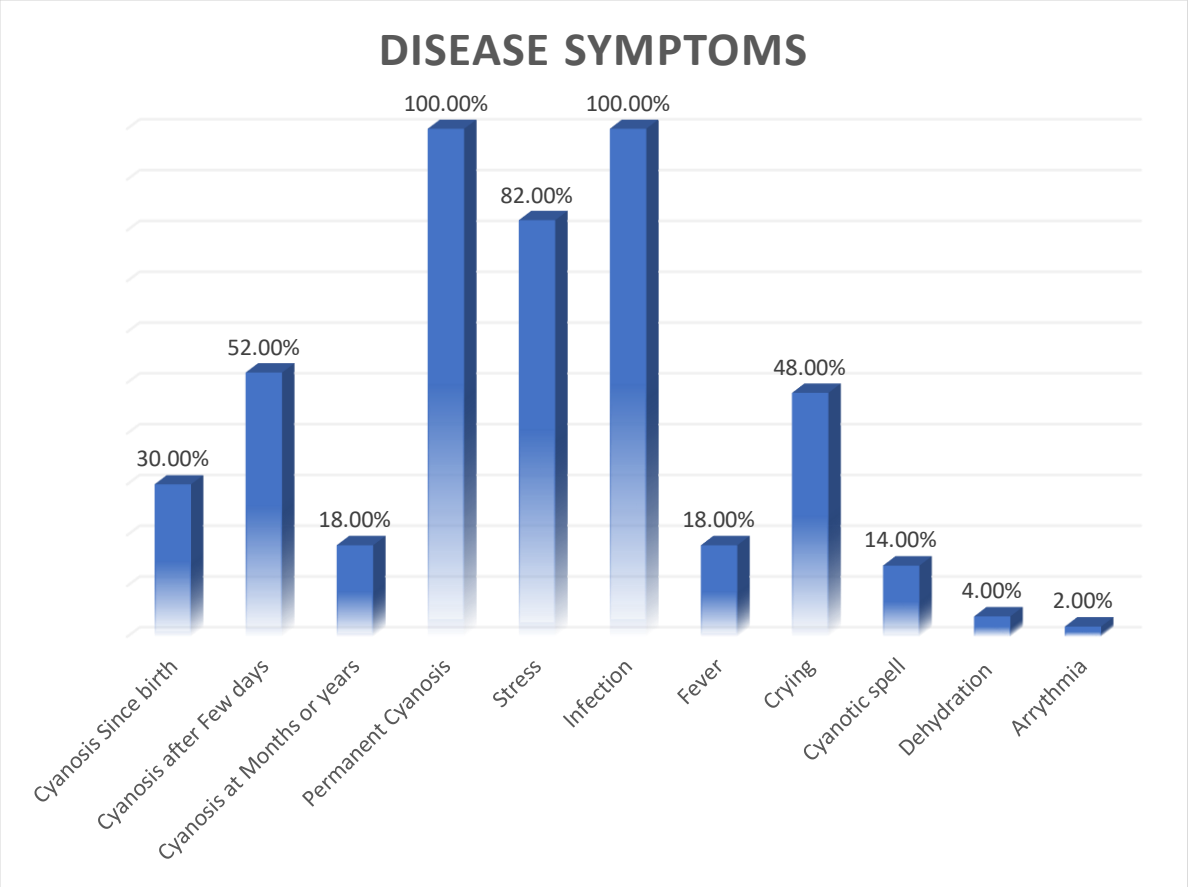
Regarding the demographic and clinical data of the studied cases, as shown in Table [1]:

Table (1): Demographics of 50 children with a cyanotic congenital heart defect at the Pediatric Cardiology Unit of Assiut University Hospitals

Variable	Frequency	Percent%	Mean ±SD
Gender			
Male	27	54.0%	
Female	23	46.0%	
BMI categories			
Normal	33	66.0%	
Underweight	17	34.0%	
Consanguinity status			
Yes	23	46.0%	
No	27	54.0%	
Age (years)			2.29 ±3.31
Weight (kg)			9.51 ±7.83
Height (cm)			75.72 ±23.36
BMI			15.29 ±2.81

Out of the 50 studied cases, 27 cases (54%) were male, and less than half of the studied cases (46 %) had a positive history of consanguinity; when body weight and height were measured, and BMI was calculated, almost 34% were underweight.

Regarding the disease symptoms in the study population, as shown in Figure (1):



Infection was the primary trigger for increased cyanosis in 82% of the cases, while stress was a contributing factor in less than 20%. Fever and cyanotic spells exacerbated symptoms, and dehydration or arrhythmia were responsible in fewer than 5% of cases.

Upon examination, all patients showed a tendency to bleed, along with swelling and tenderness, although joint pain was present in only 6% of the cases. Additionally, 46% of the patients had a fever, with a median temperature of 37.2°C (range: 35.7–38.0°C), and only 8% exhibited thromboembolic manifestations.

Regarding the Signs on physical examination as shown in Table (2):

Variable	Frequency	Percent %
Site of apex		
4th ics lml	9	18.0%
4th ics mcl	30	60.0%
5th ics lml	10	20.0%
5th ics mcl	1	2.0%
Heart sound		
S3	5	10.0%
Decrease s2	26	52.0%
Ns1.louds2	3	6.0%
Ns1.lows2	1	2.0%
Ns1.s2	10	20.0%
S2loud.single	5	10.0%
Type of murmur		
Machinery	2	4.00%
Ejection systolic	46	92.0%
Pansystolic	2	4.0%
Site of murmur		
2right	1	2.0%
Left parasternal	49	98.0%
Cardiomegaly		
Yes	33	66.0%
No	17	34.0%
Vital signs		
Heart rate		
Normal	22	44.0%
High	28	56.0%
Respiratory rate		
Low	1	2.0%
Normal	17	34.0%
High	32	64.0%
O2 saturation		
Low	50	100.0%

A decreased S2 was observed in 52% of the cases, while only 20% had normal S1 and S2 sounds. In 52% of the cases, an ejection systolic murmur was detected, and 44% presented with a pansystolic murmur. In 98% of the cases, the murmur was heard in the left parasternal area. Additionally, more than half of the patients (66%) had cardiomegaly.

Upon examination, 56% of the patients had an elevated heart rate, with a mean of 134 bpm and a range of 90–177 bpm. Respiratory rate was elevated in 64% of the patients, while 34% had a normal rate, with a mean of 42 breaths per minute and a range of 20–68.

Regarding the radiological findings and echocardiography as shown in Table (3):

Variable	Frequency	Percent %
Radiological finding		
Oligemia	36	72.0%
Plethora	14	28.0%
Echocardiography		
Tof.vsd.ps	20	40.0%
Complex.avcanal.pa.pda	1	2.0%
Dor.d.tga	2	4.0%
Dorv.asd.ps	1	2.0%
Dorv.d.tga.phtn	1	2.0%
Dorv.d.tga.ps	3	6.0%
Dorv.pda.vsd	1	2.0%
Dorv.vsd.pda	1	2.0%
Ebstein a2maly	1	2.0%
Hlhs	1	2.0%
Single left ventricle.ta.vsd	1	2.0%
Sv.tga.dorv	1	2.0%
Ta.dorv.tga.ps	1	2.0%
Ta.severe phtn	1	2.0%
Ta.vsd	4	8.0%
Ta.vsd.ps	1	2.0%
Tapvr.vsd.phtn	3	6.0%
Tga.vsd	3	6.0%
Tof.vsd.mildps	2	4.0%
Tof.vsd.pa	1	2.0%

72% of the cases had oligemia, and 28% of the cases had lung plethora.
When echocardiography was done, 40% of the cases had TOF.VSD.PS, and 8% had TA.VSD and 6.0% TGA.VSD or DORV.D.TGA.PS

Regarding the hematological findings and blood picture as shown in Table(4), (5) and Figures [2],[3]:

Table (4): Hematological findings and blood picture:

Variable	Frequency	Percent%
WBCS		
9.23 ±4.81		
Low	3	6.0%
Normal	32	64.0%
High	15	30.0%
Platelet		
285.96 ±131.43		
Low	4	8.0%
Normal	39	78.0%
High	7	14.0%
RBCS		
5.65 ±1.48		
Low	6	12.0%
Normal	10	20.0%

Variable	Frequency	Percent%
High	34	68.0%
Hemoglobin		
13.9 ± 3.10		
Low	14	28.0%
Normal	19	38.0%
High	17	34.0%
Prothrombin		
13.5 ±1.45		
Normal	24	48.0%
High	26	52.0%
INR		
1.1 ±0.13		
Low	1	2.0%
Normal	36	72.0%
High	13	26.0%
Hematological findings		
MCH		
25.04 ±5.24		
Low	27	54.0%
Normal	23	46.0%
MCV		
80.12 ±11.16		
Low	13	26.0%
Normal	36	72.0%
High	1	2.0%
Hematocrit		
45.12 ±10.03		
Low	10	20.0%
Normal	20	40.0%
High	20	40.0%
MCHC		
29.8 ±2.85		
Low	31	67.4%
Normal	15	32.6%

Table (5): The iron profile:

Variable	Serum iron	Serum ferritin	Serum creatinine	Blood urea nitrogen	Serum uric acid
Mean	29.77	81.30	0.35	6.70	6.65
Standard deviation	26.50	32.0	0.30	4.9	7.0
Range	5.4 -112.0	1.4 -582.0	0.1-0.8	1.7 -22.7	2.2 -12.0

Fig. [2], Hematological findings in the study population.

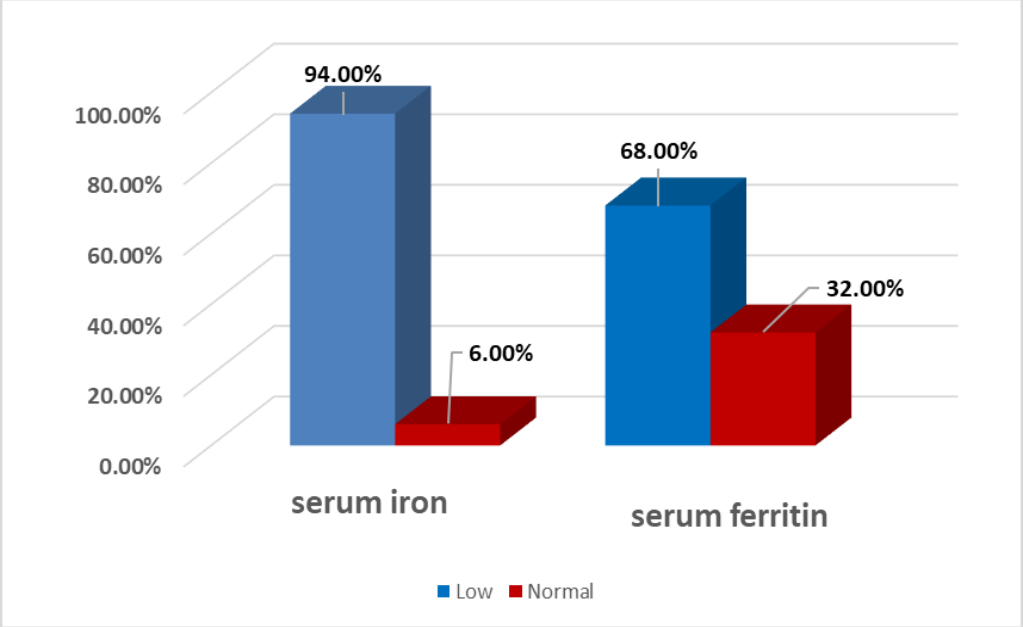
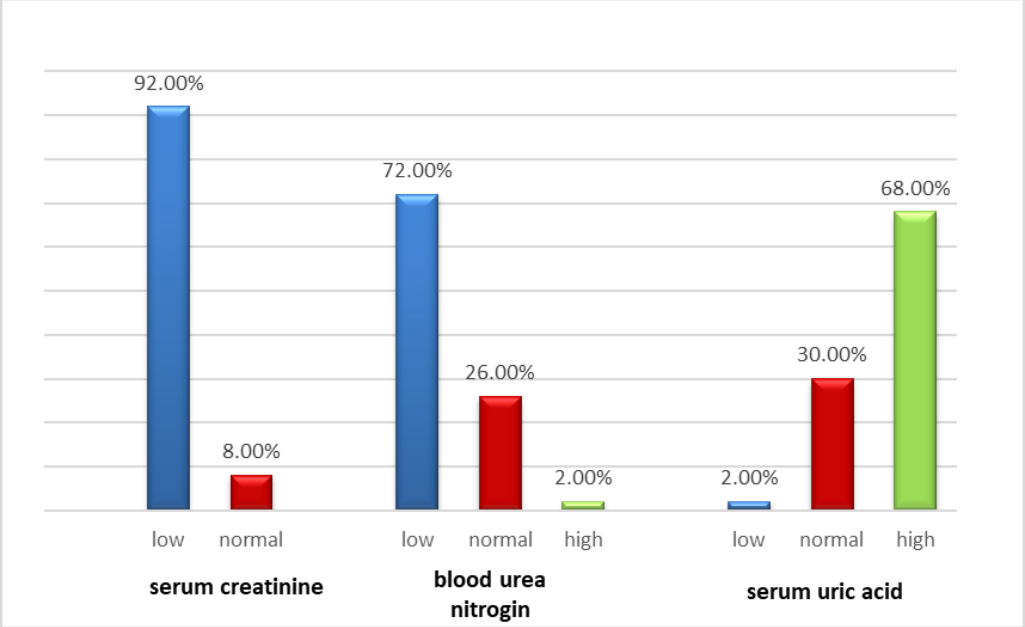


Fig. [3]Hematological findings in the study population.



- For RBCs count (*10^6/ul), Ten cases (20%) have normal RBCs count, (68%) have raised RBCs (erythrocytosis), and (12%) have low RBCs count. With a mean value of 5.65±1.48, (94%) suffered from low iron level, and only (6%) had normal iron level, with a mean value of 29.77± 26.50.
- For serum ferritin level (ng/dl), (68%) suffered from low serum ferritin level, with a mean value of 81.30± 32.0.
- For serum creatinine level (ug/dl); (92%) suffered from low creatinine level, with a mean value of 0.35±0.30
- For serum BUN level (ug/dl); (72%) suffered from low BUN level, with a mean value of 6.70±4.9.
- For serum uric acid level (ug/dl); (68%) suffered from high uric acid level, with a mean value of 6.65±7.0

Discussion:

In our study, we found that RBCs count (68%) has raised RBCs (erythrocytosis), and (12%) has a low RBCs count.

Also, we found that For HCT level (40%) have raised HCT level, and (20%) have low HCT level. Recent studies have indeed found that Hematocrit (HCT) values can be elevated, causing polycythemia in patients with cyanotic heart disease.

Another study found that among forty adults with cyanotic congenital heart disease, there was a subset of eleven patients with especially pronounced erythrocytosis, repeatedly rising haematocrit, recurring symptoms of hyperviscosity, and little or no shift of the haemoglobin/oxygen-dissociation curve. These patients were iron deficient as a result of many therapeutic phlebotomies; nevertheless, their red-cell mass was comparable to that in iron-replete patients with similar but stable haematocrits. Iron repletion in deficient patients resulted in rapidly increasing haematocrit and hyperviscosity. **[5]**

In our study, we found that (94%) suffered from low iron level, (68%) suffered from low serum ferritin level.

Furthermore, we found that (34%) had high hemoglobin level, and (28%) suffered from low hemoglobin level.

A study investigating the Preoperative Hemoglobin Level, Oxygen Saturation, and Post-operative Outcomes in Children with Cyanotic Congenital Heart Disease found that the optimal preoperative hemoglobin (Hb) level is difficult to define in children with cyanotic congenital heart disease (CHD) due to hypoxemia-induced secondary erythrocytosis. **[6]**

Theories on Iron Deficiency Anemia in Congenital Heart Disease (CHD):

Several theories explain the increased prevalence of iron deficiency anemia (IDA) in CHD patients. Here are two key ones with recent references:

1. Inflammatory Response and Iron Sequestration:

Theory: CHD can trigger chronic inflammation in the body. This inflammation may lead to the sequestration (trapping) of iron in tissues, making it unavailable for red blood cell production. This can contribute to IDA even if total body iron stores are seemingly normal. **[7]**

2. Impaired Iron Absorption:

Theory: Some studies suggest that chronic low oxygen levels in CHD, particularly cyanotic types, may impair the body's ability to absorb iron from the digestive tract. This can lead to iron deficiency even with adequate dietary intake. **[8]**

Moreover, we found that, for serum creatinine level (ug/dl), 92% of the subjects suffered from low creatinine level, and only 8% had a normal level.

For serum BUN level (ug/dl), 72% of the subjects suffered from low BUN level.
Some of the main risk factors for developing chronic kidney disease in the adult congenital heart disease population include:

- Chronic hypoxia.
- Neurohormonal derangements.
- Intraglomerular hemodynamic changes.
- Cardiac surgeries, from minimally invasive to open heart surgeries with ischemia and nephrotoxins. **[9]**

We also found that 68% of the subjects suffered from high uric acid level. These findings are consistent with the article on Hematologic Abnormalities in Cyanotic Congenital Heart Disease Patients, which mentions that 23% of the patients had serum levels of uric acid more than or equal to 8 mg/dl. **[10]**

The link between CHD and high uric acid levels (hyperuricemia) is an emerging area of research. Here are three potential explanations:

1- Increased Uric Acid Production. **[11]**
2- 2. Impaired Uric Acid Excretion. **[12]**
3- 3. Oxidative Stress and Inflammation. **[13]**

We also found elevated heart rate and low oxygen levels in our patients, which is similar to the finding of this study that characterizes pulse oxygen saturation (SpO2) trajectories and respiratory interventions after birth for newborns with cyanotic congenital heart disease (CCHD).

Conclusion:

We conclude that the majority of the studied cases have:

- An increased count of red blood cells (RBCs), hematocrit (HCT) levels (polycythemia), and serum uric acid levels.
- A low level of serum iron mean corpuscular hemoglobin concentration (MCHC) levels, serum ferritin levels, low serum creatinine level, and low serum BUN level.
- Upon examination, more than half of the patients show an elevated heart rate, while the majority show an elevated respiratory rate. Oxygen saturation is low in all patients.

Recommendations:

1. Regular Health Check-ups: Given that a significant proportion of the studied cases showed abnormalities in various blood parameters, regular health check-ups could be recommended for early detection and management of potential health issues.
2. Adequate hydration and lifestyle modifications to manage uric acid levels.
3. All patients had low oxygen saturation. These patients should be advised to seek immediate medical consultation.

References:

1. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002 Jun 19;39(12):1890-900.
2. Mohammadi H, Mohammadpour Ahranjani B, Aghaei Moghadam E, et al. Hematological indices in pediatric patients with a cyanotic congenital heart disease: a cross-sectional study of 248 patients. Egypt J Med Hum Genet. 2022;23(1):47. doi: 10.1186/s43042-022-00262-4.
3. Auluck A, Manohar C. Haematological considerations in patients with cyanotic congenital heart disease: a review. Dent Update. 2006 Dec 2;33(10):617-22.
4. Pons I, Monteagudo M, Lucchetti G, et al. Correlation between immature platelet fraction and reticulated platelets. Usefulness in the etiology diagnosis of thrombocytopenia. Eur J Haematol. 2010 Aug;85(2):158-63.
5. Spence L, Brown WJ, Pyne DB, et al. Incidence, etiology, and symptomatology of upper respiratory illness in elite athletes. Med Sci Sports Exerc. 2007 Apr 1;39(4):577-86.
6. Zhou D, Deng LJ, Ling YF, et al. Preoperative hemoglobin level, oxygen saturation and post-operative outcomes in children with cyanotic congenital heart disease: A propensity-score matching analysis. Front Pediatr. 2022 Jan 21;9:762241.
7. Begum S, Latunde-Dada GO. Anemia of inflammation with an emphasis on chronic kidney disease. Nutrients. 2019 Oct 11;11(10):2424. doi: 10.3390/nu11102424.
8. Ossei I, Buabeng KO, Ossei PPS, et al. Iron-deficiency anaemia in children with congenital heart diseases at a teaching hospital in Ghana. Heliyon. 2020 Feb 19;6(2). doi: 10.1016/j.heliyon.2020.e03408.
9. El Sayegh S, Ephrem G, Wish JB, et al. Kidney disease and congenital heart disease: partnership for life. Front Physiol. 2022 Aug 19;13:970389. doi: 10.3389/fphys.2022.970389.
10. Chamanian S, Maleki M, Rohani A, et al. Hematologic abnormalities in cyanotic congenital heart disease patients. J Cardio-Thorac Med. 2015 Jan 1;3(1):270-2.
11. Muiesan ML, Agabiti-Rosei C, Paini A, et al. Uric acid and cardiovascular disease: an update. Eur Cardiol. 2016 Aug;11(1):54-9. doi: 10.15420/ecr.2016:4:2.

12. Tang X, Liu S, Qiu X, et al. High prevalence of hyperuricemia and the association with metabolic syndrome in the rural areas of Southwestern China: a structural equation modeling based on the Zhuang minority cohort. Nutr Metab Cardiovasc Dis. 2024 Feb 1;34(2):497-505.
13. Kim JH, Kwon MJ, Choi HG, et al. The association between hyperuricemia and cardiovascular disease history: a cross-sectional study using KoGES HEXA data. Medicine (Baltimore). 2022 Dec 23;101(51).