

Balancing the Scales: Understanding Hemostatic Abnormalities in Children with Uncorrected Cyanotic Congenital Heart Disease

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ABSTRACT

Background: Children with uncorrected cyanotic congenital heart disease often develop hemostatic abnormalities due to chronic hypoxia, increasing bleeding and thrombotic risks.

Objective: This study aimed to evaluate hemostatic abnormalities in children with uncorrected cyanotic congenital heart disease (CCHD), focusing on thrombocytopenia, coagulation factor deficiencies, bleeding and thrombotic manifestations, and the relationship between hematocrit and coagulation derangements.

Methodology: This study was a cross-sectional study carried out between April and December of 2023 in the Department of Pediatric Cardiology and Hematology, the Children Hospital and Institute of Child Health, Multan, Pakistan. Seventy-eight children who had a confirmed CCHD but were aged 1 to 15 years were recruited through consecutive sampling. Clinical analysis and laboratory tests, such as Complete Blood Count (CBC), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), International Normalized Ratio (INR) and coagulation factor tests (to rule out abnormal screening) were conducted. In patients with recent stroke, Thrombophilia (Protein C, Protein S, Antithrombin III) tests were done. The analysis was made in SPSS v25; p 0.05 was regarded as significant.

Results: In 78 patients, the average age of the patients was 1–5 years (n=30, 38.5) at a male-to-female ratio of 1.4:1. The most common lesion was Tetralogy of Fallot (TOF) (n=53, 68%). Hemostatic abnormalities were thrombocytopenia (47%), increased PT (44%), increased INR (41%), and increased APTT (34%). Hematocrit (>55) was raised in 29% and was significantly related to deranged APTT (p=0.02). The level of bleeding manifestations was 7 patients (9%), and 4 (5.1) had a stroke history. Five percent of the patients were found to be deficient in coagulation factors.

Conclusion: Children with uncorrected CCHD exhibit significant hemostatic abnormalities, including thrombocytopenia and coagulation factor deficiencies, which may remain subclinical but carry risk for bleeding or thrombotic events. Awareness and early evaluation of these abnormalities are essential for optimized perioperative care and improved outcomes in resource-limited settings.

Keywords: Cyanotic Congenital Heart Disease, Hemostasis, Thrombocytopenia, Coagulation Factors, Pediatric Cardiology

INTRODUCTION

Cyanotic congenital heart disease (CCHD) is a category of structural heart defects, manifested by right to left shunting or grossly impaired blood circulation to the lungs, resulting in chronically low systemic hypoxaemia and adaptive physiological changes.^{1,2} The long-term hypoxia saturation in children with CCHD triggers secondary erythrocytosis and hyperviscosity to precondition convoluted hematologic and hemostatic anomalies.^{3,4} The emphasis in such patients has traditionally been on the cardiopulmonary and surgical care, but the hemostatic derangements such as thrombocytopenia, deficiencies in coagulation factors, and disturbed fibrinogen/platelet activity have long gotten relatively lesser consideration.^{5,6}

Pathophysiologically, the chronic hypoxaemia that occurs in CCHD facilitates elevated erythropoietin secretion, raised red cell mass, and resultant rise in blood viscosity. This hyperviscous condition negatively affects the microcirculatory flow and can result in the impairment of hepatic coagulation factor synthesis because of slow flow and hypoxic stress.⁷⁻⁹ Moreover, the decreased plasma volume, which commonly follows erythrocytosis, proportionately decreases the concentration of coagulation factors or disrupts the functional environment of coagulation factors, contributing to an increased risk of bleeding and thrombotic outcomes.^{10,11}

Hemostatic abnormalities in CCHD are heterogeneous, and may include thrombocytopenia, platelet aggregation defect, prothrombin time (PT) and activated partial thromboplastin time (APTT) prolongation, deficiency of vitamin K-dependent clotting

factors (II, VII, IX, X), and low levels of fibrinogen.^{12,13} Wedemeyer et al. in their classic article reported that thrombocytopenia is the commonest hemostatic abnormality in patients with cyanotic heart disease and that the abnormalities of coagulation factors were increasingly pronounced at the hematocrit values above 60%. These deficiencies have significant practical implications: CCHD children are at double risk of hemorrhage (e.g., mucocutaneous bleeding, postoperative bleeding) and thrombosis (e.g., cerebral stroke, paradoxical embolism), especially in the perioperative or interventional cardiology setting.

The hemostatic complications burden can be still higher in the resource-strained environment of Pakistan where CCHD is more frequently diagnosed and treated.¹⁴ Nevertheless, the amount of data is sparse and institution specific.¹⁵ There is an interesting necessity to define the range of hemostatic dysfunction in children with uncorrected CCHD, to measure the rate of the abnormalities in platelet count, coagulation screens, clotting factor levels and clinical bleeding or thrombotic events and correlate these results with patient factors including hematocrit and type of heart lesion.¹⁶ With improved knowledge on these haemostatic profiles, clinicians will be better able to anticipate the risks of peri-interventional risks and to customise monitoring plans and improve the management of these vulnerable children.¹⁷

In this cross sectional study, we, therefore, sought to assess children aged 1–15 years with uncorrected CCHD to ascertain the prevalence of thrombocytopenia, protracted PT/INR and APTT, deficiencies of the clotting factors, and the incidence of bleeding and thrombotic events. We also aimed at investigating the correlation between increased hematocrit and disordered coagulation indices. Through this inquiry in a tertiary paediatric hospital in Pakistan, we expected to create context-specific information regarding hemostatic deviations in CCHD and guide clinical practice in low resource environments.

METHODOLOGY

The study, a cross-sectional one, took place between April and December 2023 in Children Hospital and Institute of Child Health, Department of Pediatric Cardiology and Hematology, Multan,

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Pakistan. A consecutive sampling was used, and 78 children aged between 1 and 15 years with a known resistant diagnosis of uncorrected cyanotic congenital heart disease (CCHD) were enrolled.

Inclusion and Exclusion Criteria: Children aged both males and females diagnosed with CCHD by echocardiography, CT angiography, or cardiac catheterization were included. Children who have a positive screening of Hepatitis B, Hepatitis C or HIV, chronic kidney or liver disease, known bleeding disorders or positive family history of bleeding were excluded. Moreover, patients who had acyanotic congenital heart disease, other causes of central cyanosis, persistent pulmonary hypertension, and a neonate were excluded.

Ethical Considerations: The study protocol was approved by the institutional Ethical Review Committee [IRB#1622/315/CH.MUL; Dated: March 15, 2023]. Informed consent was obtained from parents or legal guardians of all enrolled children.

Method: A thorough history and physical examination were done after consent. Clotting factor assay, Activated Partial Thromboplastin Time (APTT), Prothrombin Time (PT), Complete Blood Count (CBC) and International Normalized Ratio (INR) were examined using laboratory studies to investigate patients with abnormal primary coagulation screen. In children with a hematocrit value above 56, the blood volume was standardized depending on CLSI standards. Thrombophilia studies (Protein C, Protein S and Antithrombin III (AT)) were done among children who had a stroke at least six months prior.

Coagulation testing was done on blood samples collected in 3.2% sodium citrate tubes and CBC, platelet count and morphology were done using EDTA tubes. The CBCs were assessed on a Sysmex XN/2000 analyzer and coagulation tests, such as PT, APTT, fibrinogen, clotting factor assays, and thrombophilia tests, were done on a STA Compact analyzer (Diagnostica Stago, France).

Statistical Analysis: SPSS version 25 was utilized to analyze the data. Categorical variables (sex, type of CCHD, and deficiencies of coagulation factors) were provided in frequencies and percentages. The continuous variables (age, hemoglobin, PT, APTT, INR, platelet counts) were presented in the mean with standard deviation (SD). ANOVA and independent-sample t-tests were used to compare the means between groups and the p-value of the t-test 0.05 was taken as statistically significant.

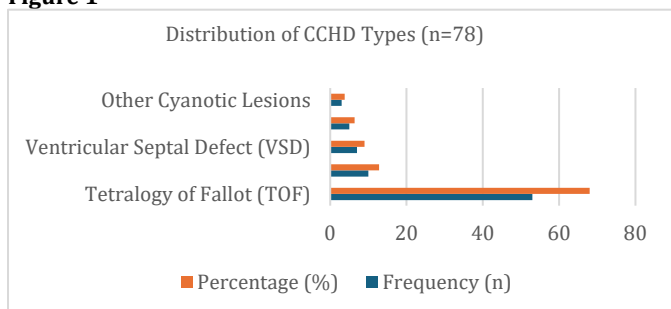
RESULTS

There was a total number of 78 children who had uncorrected cyanotic congenital heart disease (CCHD). The median age of the subjects was 6.2 ± 3.8 years and most of them were aged between 1-5 years ($n=30$, 38.5%). The male-to-female ratio was 1.4:1. Tetralogy of Fallot (TOF) ($n=53$, 68%), Transposition of the Great Arteries (TGA) ($n=10$, 12.8%), and other cyanotic lesions were the most frequently diagnosed (Table 1).

Table 1: Distribution of CCHD Types ($n=78$)

Type of CCHD	Frequency (n)	Percentage (%)
Tetralogy of Fallot (TOF)	53	68
Transposition of Great Arteries (TGA)	10	12.8
Ventricular Septal Defect (VSD)	7	9
Pulmonary Stenosis (PS)	5	6.4
Other Cyanotic Lesions	3	3.8

Figure 1



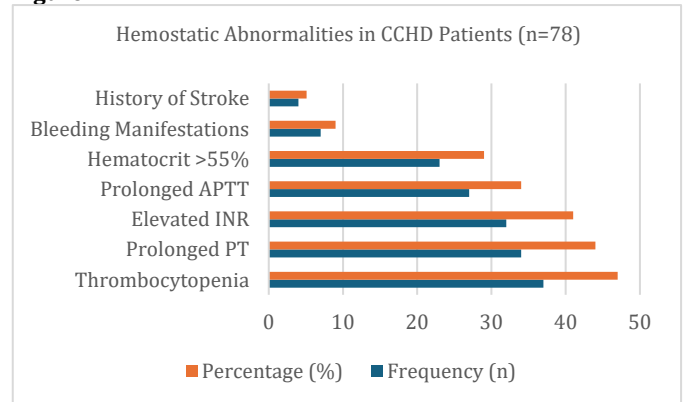
Hemostatic Abnormalities

The laboratory testing showed that in 37 (47) children, thrombocytopenia was detected. PT was prolonged in 44% and INR above 1.2 in 41% and APTT in 34%. Hematocrit elevation (raised to more than 55%) was detected in 29% of the patients and correlated with deranged APTT ($p=0.02$).

Table 2: Hemostatic Abnormalities in CCHD Patients ($n=78$)

Parameter	Frequency (n)	Percentage (%)
Thrombocytopenia	37	47
Prolonged PT	34	44
Elevated INR	32	41
Prolonged APTT	27	34
Hematocrit >55%	23	29
Bleeding Manifestations	7	9
History of Stroke	4	5.1

Figure 2



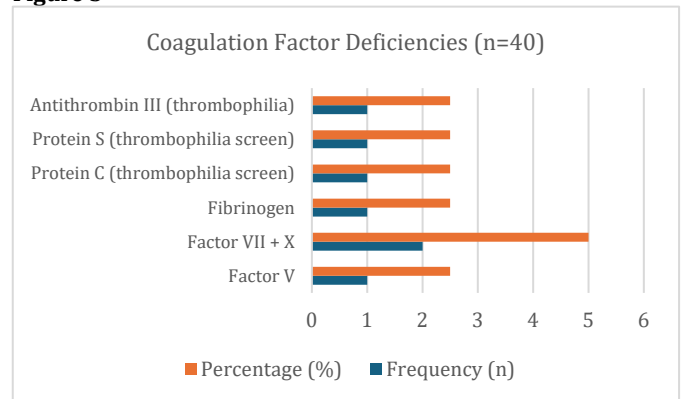
Coagulation Factor Deficiencies

In abnormally screened primary screening ($n=40$), coagulation factor assays were carried out. There were noticed shortages of Factor deficiencies in 4 patients (5%), such as Factor V deficiency ($n=1$), Factor VII plus X deficiency ($n=2$), and low fibrinogen ($n=1$). Protein C deficiency in 1 patient, Protein S deficiency in 1 patient and Antithrombin III deficiency in 1 patient were found in screening of thrombophilia in children with recent history of stroke ($n=40$).

Table 3: Coagulation Factor Deficiencies ($n=40$)

Factor Deficiency	Frequency (n)	Percentage (%)
Factor V	1	2.5
Factor VII + X	2	5
Fibrinogen	1	2.5
Protein C (thrombophilia screen)	1	2.5
Protein S (thrombophilia screen)	1	2.5
Antithrombin III (thrombophilia)	1	2.5

Figure 3



Clinical Manifestations

Epistaxis, easy bruising, and bleeding of the gums were seen in 7 (9%) children and are considered bleeding manifestations. Stroke

occurred in 4 (5.1%) patients. Abnormal APTT was also significantly related to raised hematocrit and demonstrates the effect of secondary polycythemia on coagulation in non-corrective CCHD patients.

DISCUSSION

We discover that the magnitude of hemostatic derangements in children with uncorrected cyanotic congenital heart disease (CCHD) is similar to and enhances previous studies in the area. Thrombocytopenia was observed in close to half of the patients in this cohort, and a high percentage of patients had a prolonged coagulation (PT, APTT, INR). Echoing Wedemeyer et al. who noted that thrombocytopenia was the most common abnormality, and directly proportional to the extent of polycythemia. Additionally, the correlation between high hematocrit and deranged APTT in our study validates the mechanistic relationship between secondary erythrocytosis (hyperviscosity) and hemostatic perturbation, as proposed in the review of hypoxemia induced alterations in CCHD.¹⁸⁻²⁰

The deficiencies of clotting factors found (e.g., Factor V, combined VII/X, low fibrinogen) resemble previous literature (such as Henriksson et al.) that reported the deficiencies of the vitamin K dependent factors and Factor V in cyanotic children, and the deficits were attributed to impairment. The existence of these factor deficiencies in some patients in our context underlines the idea that hemostatic dysfunction in CCHD is not only multifactorial, but was not simply offered by thrombocytopenia or hyperviscosity.

The low rate of overt bleeding (<human>The low rate of overt bleeding (~9%) and stroke history (~5) in our cohort is evidence that a large proportion of the children are storing subclinical hemostatic abnormalities that might not be apparent until surgery, intercurrent illness or other stressors occur. This is reminiscent of literature that warns that in a given concentration of citrate solution, the volume should be reduced to compensate the lower plasma volume of the persons with high hematocrits since otherwise standard methods of analysis can lead to underestimation of risk.

The findings have important implications on clinical management in resource constrained environments. To begin with, it is important to note that children with uncorrected CCHD are susceptible to two issues: bleeding caused by deficiencies of clotting factors/platelets and thrombosis caused by hyperviscosity and endothelial dysfunction. Therapeutic approaches should be sensitive to this paradox as it is discussed in the literature. Secondly, our data justify a reason of more detailed hemostatic screening in CCHD children, especially before interventions (cardiac catheterisation, surgery) or with hematocrit significantly high (>55 60%). Finally, the correlation of increased hematocrit and deranged APTT in our study points to

the result that hematocrit can be an easy surrogate marker to indicate patients who are at greater risk of hemostatic disruption. There are however limitations that must be considered. Because we are a cross sectional study, our design does not allow us to make definitive causal inferences, and even our sample size is insufficient to conduct subgroup analyses (e.g. particular factor deficiencies by diagnosis type). Additionally, like many CCHD studies, there is variability in the results of hemostasis due to variability in underlying cardiac lesion, and the period of cyanosis. Future studies must strive to conduct longitudinal follow up (pre and post correction) and investigate viscoelastic testing modalities (e.g., TEG/ROTEM) as may be suggested in recent reviews.

CONCLUSION

We have established that children left untreated with CCHD present a high rate of hemostatic disorder, the most notable of which are thrombocytopenia, prolonged PT, INR and APTT, and deficiency of clotting factors. Despite the fact that relatively few of them had overt bleeding or thrombotic events, it is important to note that subclinical abnormalities were present, which implies that severe complications might develop during interventions or at the times of physiological stress. The important correlation between increased hematocrit and deranged APTT highlights the impact of secondary polycythemia in interrupting the normal coagulation processes. The results support the use of holistic hemostatic screening of all children with uncorrected CCHD, especially before undergoing surgical or catheter-based interventions. It can be alleviated by proactive follow-up, anticipation of coagulation deficits, and individualized perioperative care to reduce the risk of bleeding or thrombosis, eventually leading to better clinical outcomes in this at-risk pediatric population, particularly where health care resources are limited.

Authors' Contribution

ME, AM: Concept & study design, data collection and drafting of the manuscript.

SK: Data entry, statistical analysis, interpretation of the results.

MS: Manuscript editing and critical revision of the manuscript.

All authors approved the final version of the manuscript to be published.

Conflict of Interest

The authors declared no conflict of interest.

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Data Availability

Data is available with authors and can be provided on request.

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