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ORIGINAL ARTICLE

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Determinants of platelet count in pediatric patients with congenital cyanotic heart disease: Role of immature platelet fraction

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Abstract

Objectives: Congenital heart defects are common noninfectious causes of mortality in children. Bleeding and thrombosis are both limiting factors in the management of such patients. We assessed the frequency of thrombocytopenia in pediatric patients with congenital cyanotic heart disease (CCHD) and evaluated determinants of platelet count including immature platelet fraction (IPF) and their role in the pathogenesis of thrombocytopenia.

Methods: Forty-six children and adolescents with CCHD during pre-catheter visits were studied; median age was 20.5 months. Complete blood count including IPF as a marker of platelet production and reticulated hemoglobin content (RET-He) as a marker of red cell production and iron status were done on Sysmex XE 2100 (Sysmex, Japan). C-reactive protein, prothrombin time (PT), Activated partial thromboplastin time (APTT) were also assessed.

Results: Thrombocytopenia was found in 6 patients (13%). PT was prolonged ($P = .016$) and IPF was significantly higher in patients with thrombocytopenia compared with patients with normal platelet count ($14.15 \pm 5.2\%$ vs $6.68 \pm 3.39\%$; $P = .003$). Platelet count was negatively correlated with IPF while significant positive correlations were found between IPF and hemoglobin, red blood cells (RBCs) count, hematocrit (Hct), PT, reticulocytes count, and immature reticulocyte fraction.

Conclusions: We suggest that elevated IPF in CCHD patients with thrombocytopenia may denote peripheral platelets destruction as an underlying mechanism. Hemoglobin level, RBCs count, Hct, and RET-He were not significant determinants for platelet count in CCHD.

KEYWORDS
CCHD, immature platelet fraction, RET-H, thrombocytopenia

1 | INTRODUCTION

Congenital heart defects are the most common developmental anomaly and are the commonest noninfectious causes of mortality in newborns; they affect up to 6–8/1000 infants and in most cases the cause is unknown.[1] Erythrocytosis, thrombocytopenia, platelets function defects, coagulation factors deficiencies are the main hematologic disorders in patients with cyanotic congenital heart disease (CCHD). The hemorrhagic tendency in CCHD was initially attributed to an increase in tissue vascularity, but co-existing hemostatic defects were subsequently identified and attributed to thrombocytopenia, shortened platelet survival, and deficient von Willebrand multimers.[2]

In patients with CCHD, platelets are shown to have both qualitative and quantitative abnormalities.[3] However, there are conflicting data as regards the etiology of thrombocytopenia in CCHD.[4] A significant association has been reported between thrombocytopenia and a high hematocrit in cyanotic patients and multiple etiologies has been suggested including chronic compensated disseminated intravascular coagulation (DIC), reduced synthesis of clotting factors and/or deranged platelet aggregation.[5]

Immature reticulated platelets represent the youngest platelets released into the circulation by regenerated marrow megakaryocytes[6] and are the analogue of the red cell reticulocyte. The rate of platelet turnover can be evaluated by the relationship between the percent of reticulated platelets and the platelet count.[7] Measurement of immature platelet fraction (IPF) could reflect platelet production rate. It could be used as a rapid and inexpensive automated marker for the etiology of thrombocytopenia and can be integrated as a standard parameter to evaluate the thrombopoietic state of the bone marrow.[8] IPF is also helpful in predicting the course of thrombocytopenia and identifying patients with a risk for rapid severe drop in platelet count.[9,10]

The measurement of reticulocyte hemoglobin content is a direct assessment of the incorporation of iron into erythrocyte hemoglobin and thus a direct estimate of the recent functional availability of iron into the erythron. The reticulocyte hemoglobin equivalent (RET-He) has been available for use on the Sysmex XE 2100 (Sysmex Corporation, Kobe, Japan), broadening the availability of a tool for assessing reticulocyte hemoglobin content.[11]

This study aimed to assess the frequency of thrombocytopenia in pediatric patients with CCHD as well as evaluating determinants of platelet count including IPF as a marker of platelet production, RET-He as a marker of red cell production, and iron status and their role in the pathogenesis of thrombocytopenia among those patients.

2 | MATERIALS AND METHODS

This cross-sectional study included 46 children and adolescents with CCHD ≤18 years of age) who attended the Pediatric Cardiology Clinic, Ain Shams University during pre-catheter visits. An informed consent was obtained from the guardian of each patient before participation. The procedures applied in this study were approved by the Ethical Committee of Human Experimentation of Ain Shams University, and are in accordance with the Helsinki Declaration of 1975.

Exclusion criteria were evident sepsis, septic shock, high fever, localizing infections, radical operation for a heart defect due to hypoplastic pulmonary arteries, or high pulmonary vascular resistance for the Fontan circulation or due to Eisenmenger syndrome and intake of anti-platelet or anti-inflammatory agents. Patients with congenital noncyanotic heart disease, dysmorphic features/DiGeorge syndrome, down and Noonan syndromes were also excluded. No platelet transfusion was given prior to hematological analysis. Patients were divided into two groups according to the platelet count; CCHD with thrombocytopenia (platelet count $<100 \times 10^9$/L) and CCHD with normal platelet count (platelet count $\geq 100 \times 10^9$/L).

Data collection from hospital records included age, sex, presence of parental consanguinity, age at onset of cyanosis, cyanotic episodes and their frequencies, bleeding manifestations, family history of thrombocytopenia, drug history with assessment of liver, spleen and lymph nodes. Data on height, sitting height and weight were transformed into SD scores (SDS) according to the standards of Tanner et al.[12] Oxygen saturation was measured by pulse-oximetry. Vital data as temperature, heart rate, respiratory rate and blood pressure were recorded.

2.1 | Sample collection and laboratory investigations

Peripheral blood samples were collected on potassium-ethylene diamine tetraacetic acid (K2-EDTA) (1.2 mg/mL) for complete blood count (CBC) and in vacutainer tubes containing 0.2 ml 3.8% trisodium citrate in a ratio of 9 volumes of blood to 1 volume of citrate for coagulation studies. Samples collected in both tubes were properly mixed with the used anticoagulant. For chemical analysis, clotted samples were obtained and serum was separated by centrifugation for 15 minutes at $1000 \times g$.

CBC was performed using Sysmex XE-2100 (Sysmex, Kobe, Japan) with assessment of IPF%, mean platelet volume (MPV), RET-He and immature reticulocyte fraction (IRF). To exclude infections, C-reactive protein was determined by latex agglutination test (Omega, UK). Determination of coagulation profile; prothrombin time and activated partial thromboplastin time (APTT) was done using Stago STA compact (Diagnostica Stago, Parsippany, NJ, USA).

2.2 | Echocardiography

All patients underwent echocardiographic studies using a Philips iE33 machine (Philips Medical Systems, Andover, MA, USA). Standard 2D echocardiogram was done for all patients enrolled in the study using phased array transducers of different frequencies tailored according to each patient's age, body built and weight. Philips S8–3 Sector Array Transducer with a frequency range from 8 to 3 megahertz was generally used for children below 3 years of age and Philips S5–1 Sector Array Transducer with a frequency range from 5 to 1 megahertz was used for older children with few exceptions. The study included 2D, M mode and color flow Doppler from all standard echocardiographic windows (ie, subcostal, apical, parasternal, and suprasternal) applying the sequential analysis to establish the situs, AV and VA connections, great vessel relation and abnormalities, ventricular dimensions and functions, state of cardiac valves, venous connections, and any intracardiac shunts.[13,14]

2.3 | Statistical analysis

Analysis of data was done using Statistical Program for Social Science version 21 (SPSS Inc., Chicago, IL, USA). Quantitative variables were described in the form of mean and standard deviation or median and interquartile range (IQR: difference between 25th and 75th percentiles). Qualitative variables were described as number and percent. In order to compare parametric quantitative variables between two groups, Student *t* test was performed. For comparison of nonparametric quantitative variables between two groups, Mann-Whitney test was applied. Qualitative variables were compared using chi-square (X^2) test or Fisher's exact test when frequencies were below five. Pearson correlation coefficients were used to assess the association between two normally distributed variables. When a variable was not normally distributed, a Spearman correlation test was performed. Multivariable linear regression analysis was employed to determine the relation between platelet count and clinical and laboratory variables. A *P* value $<.05$ was considered significant in all analyses.

TABLE 1 Clinical data among CCHD patients with and without thrombocytopenia

Variables	Patients with CCHD		*P* value
	Thrombocytopenia (*n* = 6)	Normal platelet count (*n* = 40)	
Age (months), median (IQR)	34 (58.3)	18.5 (57)	.62
Weight SDS, median (IQR)	−0.81 (5.3)	−1.7 (2.4)	.25
Height SDS, median (IQR)	−3.1 (4.4)	−2.5 (3.0)	.46
Sex, *n* (%)			
Male	4 (66.7)	26 (65)	.93
Female	2 (33.3)	14 (35)	
Consanguinity, *n* (%)	1 (16.7)	14 (35)	.37
Order of birth, *n* (%)			
First	3 (50)	23 (57.5)	.12
Second	2 (33.3)	14 (35)	
Third	0 (0)	2 (5)	
Fourth	1 (16.7)	0 (0)	
Fifth	0 (0)	1 (2.5)	
Type of CHD, *n* (%)			
TGV	2 (33.3)	7 (17.5)	.63
TOF	4 (66.7)	6 (65)	
DRV	0 (0)	6 (15)	
Single ventricle	0 (0)	1 (2.5)	
Cyanosis, *n* (%)	2 (33.3)	5 (12.5)	.18
Age of start of cyanosis (days), median (IQR)	8.5 (3.0)	10 (1.2)	.13
Cyanotic spells/month, median (IQR)	4.5 (1.25)	4 (1.1)	.18
Duration of cyanotic spells (minutes), mean ± SD	5 ± 0.5	4.7 ± 0.6	.31
Clubbing, *n* (%)	2 (33.3)	5 (12.5)	.18
Systolic BP (mm Hg), mean ± SD	95 ± 13.7	94.5 ± 8.4	.93
Diastolic BP (mm Hg), mean ± SD	60 ± 10	58.5 ± 8.3	.69
Respiratory rate, mean ± SD	28 ± 5.8	29.4 ± 5.9	.58
Heart rate (beat/min), mean ± SD	107.5 ± 11.7	107.3 ± 13.1	.98
Oxygen saturation (%), mean ± SD	81.2 ± 3.18	79.6 ± 10.1	.78

Abbreviations: CCHD, congenital cyanotic heart disease; SDS, standard deviation score; CHD, congenital heart defect; TGV, transposition of great vessels; TOF, tetralogy of Fallot; DORV, double outlet right ventricle; BP, blood pressure; IQR, interquartile range (difference between 75th and 25th percentile). Data were expressed as mean ± SD where Student *t* test was used or as median (IQR) using Mann-Whitney test for comparison unless specified as number (percentages) using chi-square (X^2) test for comparisons.

3 | RESULTS

3.1 | Clinical and laboratory characteristics of the studied patients with CCHD

The 46 studied patients with CCHD included 30 males and 16 females with a male to female ratio of 1.9:1. Their ages ranged from 1–192 months, with a median of 18.5 months (IQR, 55 months). Nine (19.6%) patients had transposition of great vessels (TGV), 30 (65.2%) had tetralogy of Fallot (TOF), 6 (13%) had double outlet right ventricle (DORV) and one (2.2%) patient had single ventricle. Positive parental consanguinity was observed in 31 (67.4%) patients. None had abnormal liver function tests or hepatosplenomegaly. None of the patients complained of overt bleeding manifestations.

3.2 | Thrombocytopenia among patients with CCHD

Thrombocytopenia was present in 6 (13%) of the screened patients. The mean platelet count was $244.7 \pm 88.6 \times 10^9$/L in patients without thrombocytopenia and $63.2 \pm 21.9 \times 10^9$/L in the thrombocytopenic group. No significant difference was found between patients with thrombocytopenia and those with normal platelet count as regards age, sex, weight SDS and height SDS, presence of consanguinity, patients' order of birth, types of congenital heart defects, cyanosis, cyanotic spells, vital signs or oxygen saturation ($P > .05$) (Table 1).

As shown in Table 2, IPF and PT were significantly higher in patients with thrombocytopenia compared with the non-thrombocytopenic group while other variables including white blood

TABLE 2 Hematological and coagulation profile of CCHD patients with thrombocytopenia compared with normal platelet count

Variables	Patients with CCHD		*P* value
	Thrombocytopenia ($n = 6$)	Normal platelet count ($n = 40$)	
WBC count ($\times 10^9$/L), median (IQR)	13.1 (13.5)	8.8 (5.2)	.289
Hemoglobin (g/dL), median (IQR)	13.2 (12.3)	12.1 (4.6)	.757
MCV (FL), mean ± SD	80.9 ± 11.7	75.8 ± 8.9	.275
MCH (pg), mean ± SD	24 ± 4.3	23.8 ± 3.9	.971
Hct (%), median (IQR)	48.5 (38.7)	47.2 (16.7)	.694
Reticulocyte count (%), median (IQR)	0.95 (5.6)	1.2 (0.76)	.909
RET-He (pg), mean ± SD	25.1 ± 6.9	25.8 ± 6.3	.803
LFR, mean ± SD	76.9 ± 11.9	83.3 ± 10.7	.196
MFR, mean ± SD	14.53 ± 5.5	11.94 ± 6.4	.260
HFR, mean ± SD	8.5 ± 9.4	4.8 ± 5.1	.282
IPF (%), median (IQR)	16.3 (9.5)	6.6 (4.5)	.003
MPV (FL), median (IQR)	11.2 (2.4)	11.5 (1.7)	.989
PT (s), mean ± SD	17.08 ± 3.37	13.99 ± 1.41	.016
APTT (s), mean ± SD	34.3 ± 3.61	32.12 ± 3.5	.272

Abbreviations: WBC, white blood cell count; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; Hct, Hematocrit; RET-He, reticulocyte hemoglobin equivalent; LFR, low fluorescence reticulocytes; MFR, medium fluorescence reticulocytes; HFR, high fluorescence reticulocytes IPF, immature platelet fraction; MPV, mean platelet volume; PT, prothrombin time; APTT, activated partial thromboplastin time.
Data were expressed as mean ± SD where Student *t* test was used or as median (IQR) using Mann-Whitney test for comparison unless specified as number (percentages) using chi-square (X^2) test for comparisons.

cells (WBCs) count, hemoglobin, hematocrit (Hct) and RET-He were nonsignificant among both groups (Table 2).

3.3 | Relation between platelet count and the studied laboratory variables among CCHD patients

We found significant negative correlations between platelet count with IPF ($r = -0.659$, $P < .001$) (Figure 1) and PT ($r = -0.427$, $P = .003$). Moreover, IPF was positively correlated with hemoglobin ($r = 0.430$, $P = .003$), red blood cells (RBCs) count ($r = 0.483$, $P = .001$), Hct ($r = 0.501$, $P = .002$), PT ($r = 0.293$, $P = .048$), reticulocytes count ($r = 0.352$, $P = .016$) and IRF ($r = 0.302$, $P = .041$). Multivariable linear regression analysis (Table 3) revealed that IPF is the only significant independent determinant of platelet counts among CCHD patients ($r^2 = 0.712$).

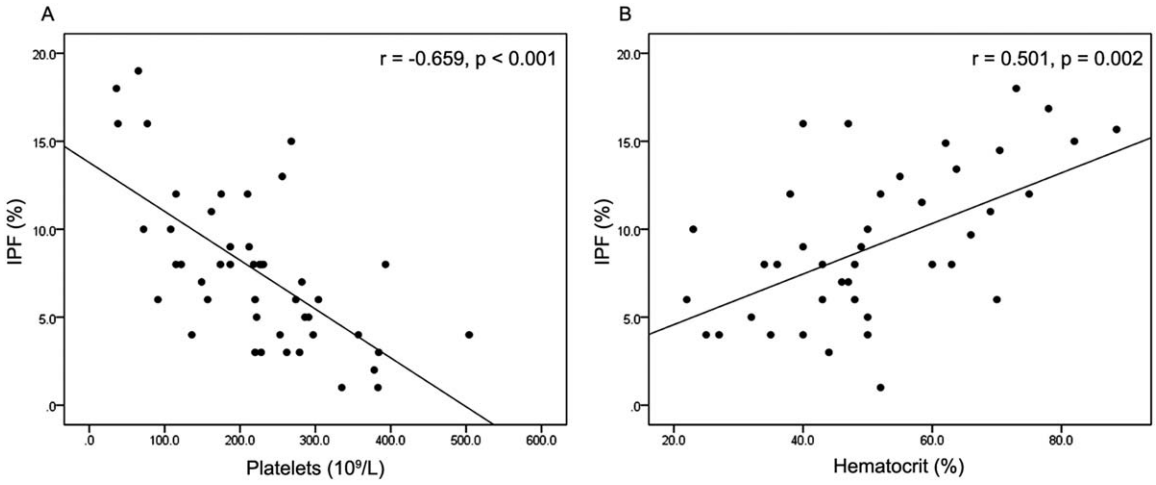

FIGURE 1 Correlations between immature platelet fraction and platelet count (A) and hematocrit level (B) among patients with congenital cyanotic heart disease

TABLE 3 Multivariable linear regression analysis of the relation between platelet count and laboratory variables in CCHD

Independent variables	Unstandardized Coefficients		
	B	Standard Error	*P* value
(Constant)	494.381	95.963	<.001
IPF (%)	−14.340	2.964	<.001
PT (seconds)	−13.523	11.743	.295

Abbreviations: IPF, immature platelet fraction; PT, prothrombin time.
Dependent variable: Platelet count.

4 | DISCUSSION

Platelet count in CCHD appears to represent a continuum beginning with low normal counts and ending with thrombocytopenia. [15] The frequency of thrombocytopenia was 13% among our patients with CCHD. In a previous study for prevalence of thrombocytopenia in CCHD, Lill et al. (2006) found that out of 105 patients with CCHD, 26 (25%) had thrombocytopenia; however, all these patients with thrombocytopenia had Eisenmenger syndrome and their mean platelet count was $155 \pm 12 \times 10^9$/L (range, 125–332 $\times 10^9$/L).[15] Another more recent study found that the mean platelet count of patients with CCHD was $159 \pm 60 \times 10^9$/L.[16]

To determine the pathogenesis of thrombocytopenia, platelet production was determined by assessment of IPF as previously reported.[17] We found higher IPF levels in CCHD patients with thrombocytopenia compared with the nonthrombocytopenic group suggesting increased platelet production among those patients. Elevated IPF levels among our CCHD patients with thrombocytopenia mean the absence of central marrow pathology and the significant negative correlations between the platelet count and each of IPF and PT make the likelihood of peripheral platelet destruction and/or platelet activation a higher possibility. These results were supported by multiple regression analysis which showed that IPF was the only significant independent factor related to platelet count in CCHD. However, the cause of increased destruction whether subclinical DIC or increased platelet activation is not yet settled.

Four pathogenic mechanisms were suggested in CCHD (1) decreased megakaryocyte production, (2) decreased platelet production, (3) increased platelet destruction, and (4) increased platelet activation.[15] Some studies suggested that thrombocytopenia does not originate from the process of platelet production (fragmentation of megakaryocytes)[18] and patients with CCHD had abnormalities of platelet turnover secondary to an increase in their peripheral destruction.[19] While others showed that the thrombocytopenia of CCHD is primarily related to a decrease in platelet production and/or an increase in platelet activation.[15,20,21]

Platelet activation in patients with CCHD has been shown in a recent study[18] where platelet microparticles and p-selectin were increased. Although platelet count was lower in CCHD group compared with acyanotic heart disease, their patients with CCHD did not have thrombocytopenia[18]; Horigome et al.[21] also reported elevated platelet microparticles in patients with CCHD and the patients were not thrombocytopenic. The authors attributed platelet activation to polycythemia.[21]

On the other hand, Lill et al.[15] found low absolute reticulated platelet count denoting decreased platelet production, together with normal thrombopoeitin level, PT, APTT, and D-dimer excluding the possibility of DIC. Nevertheless, all their thrombocytopenic patients had Eisenmenger Syndrome; therefore, they hypothesized that right-to-left shunts deliver whole megakaryocytes into the system arterial circulation, bypassing the lungs where megakaryocytic cytoplasm is fragmented into platelets, thus reducing platelet production.[15] It has also been suggested that polycythemia increases blood viscosity and reduces tissue perfusion. The resultant hypoxia of marrow tissues causes inhibition of platelet production, causing thrombocytopenia.[3]

In our study, PT was prolonged among patients with thrombocytopenia and whether subclinical DIC could be a contributing factor for thrombocytopenia in CCHD is another possibility. Increased D-dimer in CCHD has been reported.[16] However, in a review of hematologic abnormalities among patients with CCHD, it has been suggested that hyperviscosity of the blood and sluggishness of the microcirculation causes hypoxic damage to the liver decreasing the synthesis of vitamin K-dependent clotting factors.[3,21]

Although some studies reported a significant negative correlation between platelet count and the Hct values,[16,18] we found no significant difference in hemoglobin, Hct or RET-He values between patients with CCHD with and without thrombocytopenia. Moreover, platelet count was not correlated with Hct; however, a significant positive correlation was found between Hct and IPF.

One limitation of the present study is that we included a relatively small number of patients. However, our findings were clear and indicative, allowing us to assume that IPF could have a potential clinical value among patients with CCHD. It is possible that the inclusion of more patients would have revealed further correlations, in addition to those derived from the present analysis.

In conclusion, we suggest that CCHD can be complicated with thrombocytopenia which occurred in 13% of the studied patients. IPF as a marker for platelets production was elevated in CCHD patients with thrombocytopenia suggesting peripheral platelets destruction as underlying mechanism. Hemoglobin level, RBCs count, Hct and RET-He as a marker for red cell production and iron status were not significant determinants for platelet count in CCHD.

CONFLICT OF INTEREST

The authors report no declarations of interest.

AUTHOR CONTRIBUTIONS

All the authors equally contributed in this article.
All authors were involved in concept, design, data collection, analysis and drafting of the manuscript.

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