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Investigation of Platelet-Related Parameters and BMI in Children with Cyanotic and Non-Cyanotic Congenital Heart Disease

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Abstract

Background: Considering the role platelets play in hemostasis and coagulation, in the present study, we have examined platelet-related parameters and BMI in children with cyanotic and non-cyanotic CHD.

Methods: Fifty children with cyanotic and non-cyanotic CHD were investigated in this case-control study. Platelet-related parameters and other hematologic factors, weight, and BMI were evaluated.

Results: The findings indicated a notable disparity in hemoglobin levels between cyanotic and non-cyanotic cases, with respective mean values of 14.44 ± 2.64 and 12.66 ± 0.77 (P = 0.002). Also, the HCT was significantly higher in cyanotic CHD cases than in non-cyanotic cases (P = 0.002). The regression analysis revealed that cyanotic children had 0.41 times lower odds of having higher weights compared to non-cyanotic children. The mean Hb and HCT in cyanotic children were 1.77 and 7.48 units higher than in non-cyanotic children, and the difference was statistically significant (P = 0.002). The mean PDW in cyanotic children was 0.44 units lower than in non-cyanotic children, and the difference was statistically significant (P = 0.009), and the mean PLT in cyanotic children was 117.687 units lower than in non-cyanotic children, which was not statistically significant (P = 0.165).

Conclusion: Based on the present findings, the platelet indices, specifically PDW and PLT, showed a strong inverse correlation with hematocrit levels, indicating that elevated hematocrit directly affects blood clotting in CCHD. Also, the results showed that the likelihood of elevated weight was lower in cyanotic children compared to non-cyanotic children.

Keywords: Platelet count, Platelet function, CHD, Cyanotic, Non-cyanotic, Weight, BMI

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Introduction

Platelet-related parameters are considered important indicators in evaluating hematological function in patients. These parameters include mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT). Under physiological conditions, mean platelet volume (MPV) is inversely associated with platelet count, maintaining homeostasis and preserving platelet mass. In various pathological conditions, this physiological relationship is disrupted. Therefore, the potential utility of these parameters in diagnosing certain diseases has been suggested (1).

PCT, also known as the platelet aggregometer, combines MPV and platelet count (PLT) and serves as an important and predictive criterion in homeostasis (2). PDW is also a significant factor in homeostasis and can be an important criterion for assessing platelets (3).

Congenital heart disease (CHD) is recognized as the most common and clinically significant congenital anomaly, with an incidence of approximately nine cases per 1000 live births (4). CHD is associated with impaired platelet function and decreased fibrinogen levels, which may increase the likelihood of bleeding and (5).

Multiple recent studies have indicated a potential correlation between platelet count and function and CHD. This correlation may contribute to the hematological abnormalities observed in individuals with CHD (6). PLT, PDW, and MPV are commonly used hematological parameters for evaluating platelet activation and functionality (7). MPV increases during

platelet activation and serves as an indicator of platelet production. On the other hand, PDW is a parameter that measures the variability in platelet size and is considered a marker for platelet activation (8). In addition, plateletcrit and PDW provide data on total platelet mass (8, 9). Body mass index (BMI) can also be considered one of the important factors in evaluating patients with congenital heart disease. Individuals with congenital heart disease may experience weight loss and have a lower BMI (10). In the current study, we conducted an examination of the correlation between platelet count and BMI in children with congenital cyanotic and non-cyanotic heart disease.

Methods

The present study is a case-control study conducted on 50 children with congenital heart disease recruited at Amirkabir Hospital of Arak University of Medical Science, Arak, Iran. The cases included 25 children with cyanotic congenital heart disease (Group I) and 25 children with non-cyanotic congenital heart disease (Group II). The assessed parameters of this study include weight, height, heart rate (HR), systolic and diastolic blood pressure, oxygen saturation (O2sat), respiratory rate (RR), systolic and diastolic blood pressure, PDW, MPV, HCT, hemoglobin (Hb) and PCT.

Children less than 18 years of age with cyanotic or non-cyanotic CHD were included in the study.

Individuals with acute heart failure, chronic respiratory disease, platelet disorders, chronic renal or liver disorder, and those receiving anticoagulant or antiplatelet agents were excluded from the study. A comprehensive medical history was obtained, and a thorough clinical assessment encompassing anthropometric measurements, heart rate (HR), respiratory rate (RR), and hematologic findings were documented. The sample size in this study was determined to be 25 individuals in each group, with a confidence level of 95%, using the Stata software and based on similar study results (According to the following formula by using the STATA software) (Figure 1) (11).

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Estimated sample size for two-sample comparison of means

Test Ho: m1 = m2, where m1 is the mean in population 1
                  and m2 is the mean in population 2
Assumptions:

         alpha =   0.0500  (two-sided)
         power =   0.9000
            m1 =     15.6
            m2 =     16.4
           sd1 =        1
           sd2 =      .72
         n2/n1 =     1.00

Estimated required sample sizes:

            n1 =       25
            n2 =       25
```

Figure 1. Sample size formula

Evaluation of weight and BMI in children:

To interpret the growth status of children up to 5 years old, standard *z*-score curves were used based on the assessment of weight for height available in the *Integrated Care for Healthy Children* booklet. To interpret the growth status of children aged 5 to 18 years, standard *z*-score curves based on the BMI for age were used according to the Integrated Health Care Team for Providing Services for Children Aged 5 to 18 Years booklet.

Statistical Analysis

The data were analyzed using IBM SPSS software version 26.0. Qualitative data were presented using frequency and percentage. The comparison of qualitative data between the two groups was conducted using the $\chi 2$ test. Quantitative data were described using mean and standard deviation (SD). The comparison of quantitative data was performed using an independent samples *t*-test. Linear regression models were employed to explore the relationship between platelet markers and clinical data. Ordinal logistic regression models were utilized to examine the association between children's weight percentiles and clinical data. The receiver operating characteristics (ROC) curve was employed to evaluate the predictive value of PLT and PCT in predicting children's condition at various cutoff levels. The significance level was set at 0.05.

Results

Fifty cases were evaluated: 25 cases with cyanotic and 25 cases with non-cyanotic heart diseases.

Age, gender, and anthropometric information of participants

The mean and SD of age were 6.16 ± 4.02 in the cyanotic group and 6.04 ± 4.89 in the non-cyanotic group, with male/female ratios of 7/18 vs. 10/15 in the cyanotic and non-cyanotic groups, respectively. Anthropometric data, including height ($P = 0.899$) and weight ($P = 0.911$), did not show a statistically significant difference between the two groups. SBP ($P = 0.726$), RR ($P = 0.744$), and HR ($P = 0.747$) were not significantly different; however, there was a significant difference in DBP ($P = 0.031$) and O_2sat ($P = 0.0001$), with significantly lower O2sat in cyanotic cases compared to noncyanotic cases (Table 1).

Distribution types of cyanotic and non-cyanotic heart disease

In the cohort of cyanotic cases ($n = 25$), the predominant conditions identified were atrioventricular septal defect with pulmonary hypertension (AVSD-PH) and single ventricle (SV), each occurring in six cases (12%). Additionally, among the non-cyanotic cases, the most frequently observed condition was atrial septal defect (ASD), documented in nine cases (18%), followed closely

Table 1. Age, gender, anthropometric, and clinical data of participants

Variables	CHD		*P*-value
	Cyanotic	Non-cyanotic	
Age (year)	6.16±4.02	6.04±4.89	0.925
Gender (male/female)	7/18	10/15	0.680
Height (cm)	103.88±25.77	104.68±17.83	0.899
Weight (kg)	20.94±13.07	21.33±11.70	0.911
SBP	87.20±18.21	88.88±15.33	0.726
DBP	55.56±13.81	62.80±8.65	0.031
RR	18.12±1.90	17.96±1.56	0.744
HR	103.76±12.13	102.60±12.81	0.747
O2sat	77.0±15.39	94.52±1.32	0.0001

HR: heart rate, RR: respiratory rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, O2sat: O_2 saturation

Table 2. Distribution types of cyanotic and non-cyanotic heart disease

Types	*n* (%)
Cyanotic	
TGA	1 (2.0)
EBA	2 (4.0)
TOF	5 (10.0)
SV	6 (12.0)
Tr.A	4 (8.0)
AVSD with PH	6 (12.0)
DORV	1 (2.0)
Non-cyanotic	*n* (%)
ASD	9 (18.0)
COA	1 (2.0)
PDA	8 (16.0)
VSD	5 (10.0)
AS	1 (2.0)
PS	1 (2.0)

by patent ductus arteriosus (PDA), which was present in eight cases (16%) (Table 2).

The relationship between CCHD and levels of Hb, HCT, PDW, and PLT

On average, the mean Hb and HCT in cyanotic children were 1.77 and 7.48 units higher than in non-cyanotic children, respectively, which was significantly different ($P=0.002$). Also, the mean PDW in cyanotic children was 0.44 units lower than in non-cyanotic children, which was significantly different ($P=0.009$). The mean PLT in cyanotic children was 117.687 units lower than in non-cyanotic children, which was not significant ($P=0.165$). The mean MPV in cyanotic children was 0.19 units higher than in non-cyanotic children, which was not significant ($P=0.412$). The mean PCT in cyanotic children was 2.92 units lower than in non-cyanotic children, which was not significant ($P=0.302$) (Table 3).

The correlation coefficient between hematocrit (HCT) and hemoglobin (Hb) was 0.53 in the cyanotic group and 0.66 in the non-cyanotic group, with both correlations being statistically significant ($P<0.05$). The correlation of HCT with MPV and PDW was 0.35 and 0.14 in the cyanotic group, respectively, while it was 0 and 0.11 in the non-cyanotic group, respectively. However, the association between HCT and MPV and PDW was not statistically significant ($P>0.05$). The ratios of HCT/Hb, HCT/PCT, HCT/MPV, HCT/PDW, and HCT/PLT were higher in the cyanotic group compared to the non-cyanotic group. The MPV/PCT ratio was 0.19, with a 95% confidence interval of 0.17 to 0.20 (Table 4).

Table 5 illustrates the prevalence of obesity (BMI) among participating children based on the type of disease (cyanotic/non-cyanotic). According to the obtained results, 72% of cyanotic children had normal weight, and only 8% were obese. On the other hand, 64% of non-cyanotic children had normal weight, and 20% were obese. Regression analysis results indicated that the odds of having higher weight were 0.41 lower in cyanotic children than in non-cyanotic children (OR=0.59, 95% CI=0.18, 1.92; $P=0.387$).

Hemoglobin levels demonstrated an area under the curve of 89.9%, with a cutoff value of 12.09 mg/dl, yielding a sensitivity of 96% and specificity of 60% in predicting a cyanotic type in children with CHD. Meanwhile, HCT exhibited an area under the curve of 69%, with a cutoff value of 37.5%, resulting in a sensitivity of 80% and specificity of 44% for predicting the cyanotic type in children with CHD. MPV displayed an area under the curve of 53.1%, with a cutoff value of 8.05%, and demonstrated a sensitivity of 68% and specificity of 46% in predicting the cyanotic type in children with CHD (Table 6 and Figure 2).

Discussion

The platelet counts in CCHD cases ranged from slightly below normal levels to thrombocytopenia. In a prior investigation on the frequency of thrombocytopenia in CCHD, Lill et al (12) (2006) reported that 26 out of 105 CCHD patients (25%) exhibited thrombocytopenia.

Platelet activation was observed in a recent study of patients with CCHD, as evidenced by an increase in platelet microparticles and p-selectin levels. Although the CCHD group had a lower platelet count than those with cyanotic heart disease, the patients with CCHD did not show signs of thrombocytopenia (13). We observed no significant reduction in platelet count in the cyanotic group. However, the data indicated that the cyanotic group had a lower platelet count compared to the non-cyanotic group.

It has been proposed that polycythemia leads to elevated blood viscosity and decreased tissue perfusion. This can result in hypoxia in the bone marrow, leading to the suppression of platelet production and, subsequently,

Table 3. Association between congenital cyanotic heart disease and Hb, HCT, PDW, PLT, MPV, and PCT

Congenital heart disease	Hb			HCT			PDW			PLT			MPV			PCT		
	Mean (SD)	Mean difference (cyanotic/ non-cyanotic)	*P* value*	Mean (SD)	Mean difference (cyanotic /non-cyanotic)	*P* value*	Mean (SD)	Mean difference (cyanotic /non-cyanotic)	*P* value*	Mean (SD)	Mean difference (cyanotic /non-cyanotic)	*P* value*	Mean (SD)	Mean difference (cyanotic/ non-cyanotic)	*P* value*	Mean (SD)	Mean difference (cyanotic /non-cyanotic)	*P* value*
Cyanotic	14.44 (2.64)	1.77	0.002	45.32 (10.86)	7.48	0.002	8.01 (0.55)	-0.44	0.009	310.72 (260.37)	-117.68	0.165	8.68 (0.96)	0.19	0.412	43.52 (9.31)	-2.92	0.302
Non-cyanotic	12.66 (0.77)			37.84 (2.57)			8.45 (0.57)			428.40 (326.39)			8.49 (0.64)			46.44 (10.45)		

* Linear regression model

Abbreviation: Hb: hemoglobin, HCT: hematocrit, MPV: mean platelet volume, PDW: platelet distribution width, PCT: plateletcrit

Table 4. Association between HCT and other hematological indices

Index	Congenital heart disease	HCT					
		Correlation		Ratio			
		Coefficient	p-value	Ratio		95% confidence interval	
						Lower bound	Upper bound
HB	Non-cyanotic	0.66	<0.001	HCT/HB	2.98	2.92	3.05
	Cyanotic	0.53	0.006	HCT/HB	3.13	2.87	3.40
PCT	Non-cyanotic	0.16	0.430	HCT/ PCT	0.81	0.74	0.88
	Cyanotic	0.10	0.633	HCT/ PCT	1.04	0.91	1.16
MPV	Non-cyanotic	0.11	0.602	HCT/ MPV	4.45	4.28	4.62
	Cyanotic	0.35	0.079	HCT/ MPV	5.21	4.74	5.68
PDW	Non-cyanotic	0.00	0.98	HCT/ PDW	4.47	4.30	4.64
	Cyanotic	0.14	0.481	HCT/ PDW	5.65	5.10	6.19
PLT	Non-cyanotic	0.21	0.308	HCT/ PLT	0.08	0.06	0.11
	Cyanotic	-0.11	0.589	HCT/ PLT	0.14	0.09	0.19

Table 5. Association between children's obesity status in cyanotic and non-cyanotic congenital heart disease

Congenital heart disease	Normal number (%)	At Risk over-weight number (%)	Over-weight number (%)	Obesity number (%)	Cumulative OR	95% CI		*P*-value*
						Lower	Upper	
Cyanotic	18 (72%)	4 (16%)	1 (4%)	2 (8%)	0.59	0.18	1.92	0.387
Non-cyanotic	16 (64%)	2 (8%)	2 (8%)	5 (20%)				

* Ordinal logistic regression

Table 6. Sensitivity and specificity of PDW, MPV, PCT, PLT, Hb, and HCT in CHD diagnosis in differentiating cyanotic and non-cyanotic individuals with CHD

Variable	AUC	Cutoff value	Sensitivity	Specificity
HB	89.9%	12.9	96%	60%
HCT	69%	37.5	80%	44%
MPV	53.1%	8.05	68%	46%
PCT	34.2%	43	52%	20%
PLT	34%	274.5	52%	38%
PDW	29.4%	7.85	60%	16%

thrombocytopenia (14). However, we did not observe a significant difference in hematocrit levels between patients with cyanotic and non-cyanotic conditions. Additionally, platelet count and other indicators were not found to be associated with hematocrit levels. Also, we did find a notable positive correlation between hematocrit levels and platelet count. Overall, in patients with congenital heart disease, there is a positive correlation between hematocrit levels and impaired blood clotting. We did not observe a significant difference in the HCT/MPV ratio between the cyanotic and non-cyanotic groups. Furthermore, the average MPV in cyanotic children was 0.19 units higher than in non-cyanotic children but, overall, did not demonstrate a significant difference. In the study of Hussein et al (15), MPV levels increased in individuals with congenital heart disease who had not undergone treatment, which is somewhat consistent with our study findings.

We found that the cyanotic group had lower PDW levels and higher MPV levels compared to the non-cyanotic group. Majumdar et al(16) also reported elevated PDW and MPV levels in children with sepsis.

The result of our study did not indicate a significant difference in PCT levels in the cyanotic and non-

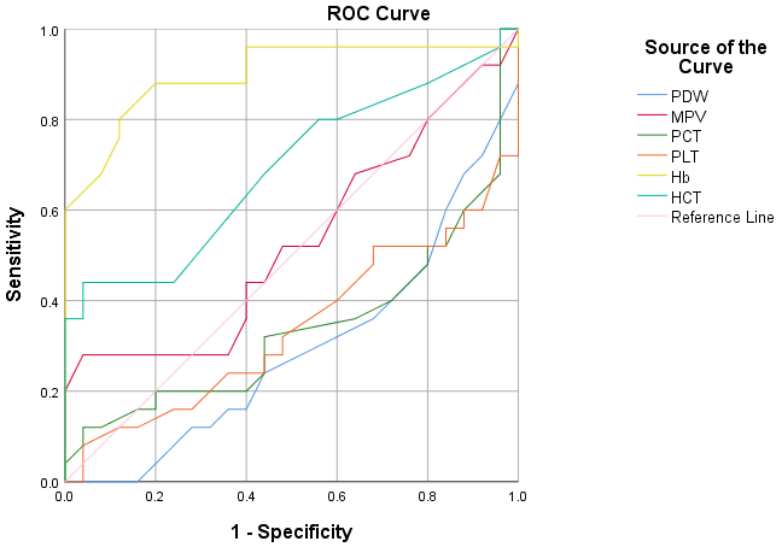

Figure 2. Roc curve of PDW, MPV, PCT, PLT, Hb, and HCT in CHD diagnosis

cyanotic groups. This finding is consistent with the study conducted by Eswaran et al (17), which also found no significant difference in PCT levels in individuals with congenital heart disease.

In our study, the hemoglobin levels in cyanotic individuals were found to be higher than in non-cyanotic individuals. This increase in hemoglobin levels occurs as compensation in individuals with cyanotic disease when the oxygen saturation falls below normal levels. This finding is consistent with the study conducted by Broberg et al(18), which aimed to investigate the optimal relationship between oxygen saturation and hemoglobin concentration in adults with cyanosis due to congenital heart disease. The study revealed that individuals with lower arterial oxygen saturation had higher hemoglobin levels, aligning with our findings.

The majority of cyanotic and non-cyanotic children in the present study had normal weight, and the risk of weight gain was lower in cyanotic children than in non-cyanotic children. This may be attributed to the effects of oxygen saturation on lipid profiles, which requires further investigation. Therefore, no significant statistical difference in weight was observed between these two groups. The findings of Khatab et al (19), who reported that children with congenital cyanotic heart disease had statistically lower height, weight, and BMI. However, overall, the levels of leptin in the cyanotic and non-cyanotic groups did not show a significant difference, which is in line with our study.

In another study conducted by Al-Asy et al (20), height, weight, and BMI in children with cyanotic and non-cyanotic heart disease were lower compared to the control group, which was not consistent with our study. This may be attributed to the consideration of heart failure as an influential variable in that study.

A study conducted by Andriana Anagnostopoulou (21) et al found that body mass index (BMI) exhibited the highest median value in children with non-cyanotic heart disease. Conversely, children with other forms of heart disease demonstrated a lower average BMI. Although the differences observed were not significant, they align with the results of our research.

Sato et al (22) reported that PDW was a significant predictor of hospitalizations related to heart failure and blood clot formation. Patients with lower PDW values had better survival rates without heart failure or thrombosis. In our study, we compared PDW levels between cyanotic and non-cyanotic patients, finding that PDW was 0.44 units lower in cyanotic children.

In another study, Martínez-Quintana et al (23) observed that patients with CHD exhibited a notable decrease in both platelet count and MPV levels compared to individuals in the control group; however, in the present study, cyanotic and non-cyanotic cases were compared.

The findings of the study conducted by Majiyagbe et al (24) (2022) indicated that the platelet count in children with CCHD was lower compared to children with non-cyanotic congenital heart disease. In another study conducted by Lill et al, it was demonstrated that thrombocytopenia was evident in patients with CCHD (12), which is consistent with the findings of our study.

Based on the results of our research, it is apparent that hemoglobin levels, with a sensitivity of 96% and a specificity of 60%, can function as an indicator for the development of CCHD. These results are in line with the investigation carried out by Houghton et al (25), which demonstrated that the Hb level is an autonomous determinant for CHD in both Caucasian and African American demographics, albeit with differing hemoglobin concentrations resulting in distinct levels of risk.

In the present study, hematocrit levels, with a sensitivity of 80% and a specificity of 44%, were found to serve as

a potential diagnostic indicator for CCHD. This finding is corroborated by Sorlie et al's (26) investigation, which demonstrated a correlation between elevated HCT levels and heightened susceptibility to myocardial infarction, coronary artery disease, or mortality related to CHD in urban settings. Also, according to a study conducted by Jin et al(27), elevated levels of HCT may be positively associated with cardiovascular risk factors. On the other hand, the sensitivity and specificity of MPV were 68% and 34%, respectively, for predicting cyanotic heart disease in children with CHD. According to the study conducted by Sansanayudh et al (28), higher MPV levels may be associated with cardiac disorders.

Conclusion

Patients with CCHD and elevated hematocrit exhibited reduced blood clotting. Interventions that alter hematocrit levels have been observed to impact the hemostatic profile, with hematocrit reduction showing potential to improve the hemostatic profile and potentially halt bleeding. However, these findings necessitate further investigation. In CCHD patients, there was an increased risk of both bleeding and thrombosis, particularly in those with elevated hematocrit levels. Platelet indices such as PDW and PLT were strongly inversely correlated with hematocrit levels, indicating that elevated hematocrit itself disrupts hemostasis in CCHD patients. Also, the results showed that the likelihood of elevated weight in cyanotic children was lower compared to non-cyanotic children.

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Authors' Contribution

Conceptualization: Mehran Akbari, Reza Beiranvand, Masoud Bahrami, Yazdan Ghandi.
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Investigation: Mehran Akbari, Yazdan Ghandi.
Methodology: Mehran Akbari, Reza Beiranvand, Masoud Bahrami, Yazdan Ghandi.
Project administration: Yazdan Ghandi.
Supervision: Yazdan Ghandi.
Validation: Mehran Akbari, Reza Beiranvand, Masoud Bahrami, Yazdan Ghandi.
Visualization: Mehran Akbari, Reza Beiranvand, Masoud Bahrami, Yazdan Ghandi.
Writing–original draft: Mehran Akbari, Reza Beiranvand, Masoud Bahrami, Yazdan Ghandi.
Writing–review & editing: Mehran Akbari, Reza Beiranvand, Masoud Bahrami, Yazdan Ghandi.

Competing Interests

The authors declare that they do not have any conflict of interest.

Ethical Approval

The Ethics Committee of Arak University of Medical Sciences approved this study, and the study was performed following the approved guidelines (ethical number: IR.ARAKMU.REC.1399.074). Written informed consent was acquired from the parents of all participants in the initial data collection.

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