Cardiology in the Young

cambridge.org/cty

Predictive value of red cell distribution width in children with pulmonary arterial hypertension associated with CHD

Doaa El Amrousy[1], Mona Hashem[1], Hassnaa Hassan[1], Hossam Hodeib[2] and Rehab Elmeazawy[1]

[1]Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta, Egypt and [2]Department of Clinical Pathology, Faculty of Medicine, Tanta University, Tanta, Egypt

Original Article

Cite this article: El Amrousy D, Hashem M, Hassan H, Hodeib H, and Elmeazawy R (2024). Predictive value of red cell distribution width in children with pulmonary arterial hypertension associated with CHD. *Cardiology in the Young*, page 1 of 5. doi: 10.1017/S1047951124000817

Received: 5 January 2024
Revised: 3 February 2024
Accepted: 26 February 2024

Keywords:
CHD; pulmonary hypertension; red cell distribution width

Corresponding author:
Doaa El Amrousy;
Email: doaamoha@yahoo.com

Abstract

Background: Pulmonary arterial hypertension, a common consequence of untreated CHD, is associated with a significant morbidity and mortality. Recent researches have demonstrated that patients with clinically severe cardiovascular illnesses, including pulmonary hypertension, have a greater mortality risk when their red cell distribution width is high. This work aimed to assess the predictive value of red cell distribution width in children with pulmonary arterial hypertension-CHD and to correlate red cell distribution width with various clinical and echocardiographic data. *Subjects and methods:* Sixty patients with CHD associated with pulmonary arterial hypertension were enrolled as the patient group. Another 60 patients with CHD and no pulmonary arterial hypertension, matched for age and sex, were enrolled as the control group. Electrocardiography and echocardiographic evaluation were performed for all included children. Red cell distribution width as part of the complete blood count was also performed using a Coulter® LH 700 series haematology analyzer. *Results:* The red cell distribution width was significantly higher in the pulmonary arterial hypertension-CHD group than in the CHD-only group ($P < 0.05$). There was a significant positive correlation between the red cell distribution width and mean pulmonary artery pressure. Red cell distribution width was an independent predictor of mortality in children with pulmonary arterial hypertension-CHD. The best red cell distribution width cut-off for predicting mortality in children with pulmonary arterial hypertension-CHD was $\geq 17.6\%$. *Conclusion:* Red cell distribution width was significantly higher in children with pulmonary arterial hypertension–CHD than in those without pulmonary arterial hypertension. Moreover, red cell distribution width could be a cheap easy predictive marker for mortality in children with pulmonary arterial hypertension-CHD.

Introduction

Pulmonary arterial hypertension is a serious chronic illness of the pulmonary vasculature that causes elevated pulmonary vascular resistance, right ventricular failure, and mortality. In paediatric patients, CHD-related pulmonary arterial hypertension is the most prevalent form of pulmonary arterial hypertension.[1]

Because of the diversity in pulmonary haemodynamics during the postnatal transition, paediatric pulmonary hypertension has been defined as mean pulmonary artery pressure ≥ 25 mmHg after 3 months of age.[2] The current definition of pulmonary hypertension is mean pulmonary artery pressure > 20 mmHg, as determined by cardiac catheterisation at rest.[3] Unlike hereditary and idiopathic pulmonary arterial hypertension, pulmonary arterial hypertension linked with CHD is more common in children.[4]

One of the parameters in a complete blood count that assesses variation in red blood cell size or volume (anisocytosis) is the red cell distribution width. Anaemia is the most common cause of increased red cell distribution width. High red cell distribution width has also been defined as a risk factor for negative clinical outcomes in various paediatric illnesses.[5]

High red cell distribution width can be a sign of inflammation, dietary deficiency, pulmonary dysfunction, and other pathological processes that affect erythropoiesis.[6] In adults with pulmonary hypertension, red cell distribution width is a well-known prognostic indicator.[7] The value of this test in paediatric pulmonary arterial hypertension has not yet been established.

This work aimed to assess the predictive value of red cell distribution width in children with pulmonary arterial hypertension-CHD and to correlate red cell distribution width with various clinical and echocardiographic data.

Methods

This prospective cohort study was conducted at the Cardiology Unit, Paediatric Department, Tanta University Hospital between April 2022 and December 2023. Sixty children with pulmonary arterial hypertension-CHD were enrolled as the patient group. Another 60 patients with CHD and no pulmonary hypertension, matched for age and sex, were enrolled as the control group. Written informed consent was obtained from all subjects of the study or their parents or guardians. The Ethics Committee of the Faculty of Medicine, Tanta University approved the study.

Inclusion criteria were children aged more than 1 month with CHD and pulmonary arterial hypertension.

Children with pulmonary hypertension secondary to other causes rather than CHD such as persistent pulmonary hypertension of neonate, chronic lung diseases, or thromboembolism, children with Eisenmenger syndrome, sepsis, malignancy, chronic inflammation, or autoimmune diseases, and children with blood transfusion within 1 month of laboratory testing were excluded from the study.

All children were subjected to full history taking, a thorough clinical examination including heart rate, respiratory rate, oxygen saturation, signs of CHD, signs of pulmonary hypertension, plain chest and heart X-ray, and electrocardiography.

Laboratory tests including complete blood count were performed using two ml of venous blood on 20 µL EDTA solution using a Coulter® LH 700 series haematology analyser to assess haemoglobin level, haematocrit, mean corpuscular volume, red cell distribution width. Quantitative C-reactive protein was also measured by latex agglutination test. Positive results were obtained at concentrations of > 6 mg/L.

Echocardiography: A Vivid 7 ultrasound machine (GE Medical System, Horten, Norway) with 7 and 4s MHz multi-frequency transducers was used. Doppler, two-dimensional (2-D), and M mode were used to assess the followings:

- Type of CHD
- Mean pulmonary artery pressure was measured from the peak pulmonary regurge Doppler signal. The pulmonary regurge signal was obtained in the parasternal short-axis view using colour Doppler. A continuous wave Doppler at a sweep speed of 100 mm/s was used to measure the peak pulmonary regurge velocity. The peak pressure difference (measured by the Bernoulli equation) was then added to the right atrial pressure. The mean pulmonary artery pressure can be approximated from the peak pulmonary regurge Doppler signal using the following formula: mean pulmonary artery pressure $= 4$ (pulmonary regurge peak velocity)^2 + right atrial pressure.
- Right ventricular diameter
- Right ventricular systolic function: right ventricular fractional area change was measured using 2-D echocardiography from the apical four-chamber view. Right ventricular fractional area change can be calculated using the following equation:

Right ventricular fractional area change = right ventricular end-diastolic area – right ventricular end-systolic area/right ventricular end-diastolic area × 100.

- Right ventricular diastolic function was measured using pulsed trans-tricuspid Doppler in the form of tricuspid E/A ratio, where the E wave is the peak early filling velocity, and the A wave is the peak late filling velocity.
- Left ventricle systolic function was also measured using left ventricular end-systolic diameter and left ventricular end-diastolic diameter to calculate left ventricular ejection fraction (LV EF%) where: (LV EF%) = (left ventricular end-diastolic diameter)^3 - (left ventricular end-systolic diameter)^3 / (left ventricular end-diastolic diameter)^3 × 100%

All investigations were performed at the same time on all included patients at admission and the patients were followed up for 6 months for mortality. A good prognosis was defined as no mortality during the follow-up period, whereas a poor prognosis was defined as the occurrence of death during the follow-up period.

Statistical analysis

Statistical analysis of the present study was conducted using the SPSS V20 program (IBM, Chicago, IL, USA). The Shapiro–Wilk test was used to assess data normality. Quantitative data were presented using the mean and standard deviation if normally distributed, while skewed quantitative data were presented using the median and interquartile range. Qualitative data were presented as numbers and percentages. The Student's *t*-test was used to compare means between the two studied groups, while the Mann–Whitney test was used to compare the median between the two studied groups. Chi-square was used to compare qualitative data in both groups. Pearson correlation coefficient was used to detect the correlation between red cell distribution width and various clinical, echocardiographic, and laboratory data in the studied groups. Logistic regression analysis was performed to assess the prognostic value of red cell distribution width in predicting mortality in children with pulmonary arterial hypertension-CHD. Receiver operating characteristic curves were constructed to assess the predictive value of red cell distribution width in children with pulmonary arterial hypertension-CHD. Statistical significance was set at $p \leq 0.05$.

Results

Of the 120 children, 60 patients had pulmonary arterial hypertension-CHD (53.3% male) with a median age of 5 m (interquartile range: 3–12) and 60 patients with CHD and no pulmonary hypertension (60.0% male) with a median age of 5 m (interquartile range: 3.7–12). Age, sex, and weight are comparable in both groups. The baseline characteristics of the studied groups are summarised in (Table 1). Heart rate, respiratory rate, red cell distribution width, and C-reactive protein were significantly higher in pulmonary arterial hypertension-CHD compared to the CHD-only group, while O_2 saturation was significantly lower in children with pulmonary arterial hypertension-CHD compared to the CHD only group. Haemoglobin, haematocrit, mean corpuscular volume, and MCH were comparable in both groups. Types of CHD in both groups are presented in Table 1.

Table 2 shows that mean pulmonary artery pressure and right ventricular diameter were significantly higher in group I than in group II, whereas right ventricular fractional area change was significantly lower in group I than in group II. Right ventricular diastolic function and LV EF were comparable in both groups.

The overall mortality among all patients was 10 patients: 8 patients in the CHD-pulmonary hypertension group and 2 patients in the CHD-only group. Red cell distribution width was significantly higher in non-survivors (19.1 ± 2) than in

https://doi.org/10.1017/S1047951124000817 Published online by Cambridge University Press

Table 1. Demographic, clinical, and laboratory data among the studied groups

Parameters	PAH-CHD group ($n = 60$)	CHD only group ($n = 60$)	p value
Age (month) Median (IQR)	5.0 (3.0–12.0)	5.0 (3.4–12.0)	0.847
Sex (Male:Female)	32:28	36:24	0.602
Weight (kg.)	6.4 ± 2	7 ± 2.3	0.239
HR (beat/min)	149.3 ± 14.8	128.5 ± 19.7	<0.001
RR (cycle/min)	58 ± 6.5	45.4 ± 10.7	<0.001
O_2 saturation %	95.1 ± 2.4	92.1 ± 5.4	0.10
Haemoglobin level (g/dl)	10.7 ± 1.6	11.3 ± 1.3	0.121
Haematocrit %	32.9 ± 3.9	34.6 ± 3.7	0.096
MCV (fl)	77.7 ± 7.4	78.5 ± 5.9	0.645
MCH (pg)	26.9 ± 3.9	26.5 ± 2.1	0.587
RDW %	17 ± 2.3	15.5 ± 1.8	0.005*
CRP (mg/L)	48 (10.5–96)	12 (6–37.5)	0.005*
Types of CHD (N)	• VSD (18) • ASD + PDA (14) • PDA (10) • PDA + VSD (4) • ASD (4) • ASD + VSD + PDA (4) • CAVC (4) • ASD + VSD (2)	• ASD (30) • VSD (8) • TOF (8) • PDA (6) • VSD + ASD (6) • VSD + PDA (2)	

* means significant. PAH-CHD = pulmonary arterial hypertension-CHDs; IQR = interquartile range; HR = heart rate; RR = respiratory rate; O_2 = oxygen; MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin; RDW = red cell distribution width; CRP = C-reactive protein; VSD = ventricular septal defect; ASD = atrial septal defect; PDA = patent ductus arteriosus; CAVC = complete atrioventricular canal; TOF = tetralogy of Fallot.

Table 2. Echocardiographic findings among the studied groups

Parameters	PAH-CHD ($n = 60$)	CHD ($n = 60$)	p value
mPAP (mmHg)	48.8 ± 13.9	18.3 ± 3.8	<0.001
RVD (mm)	18.4 ± 4.8	16.3 ± 6.1	0.049
RV systolic function (FAC)	33.9 ± 3.5	37.6 ± 5.4	0.003
RV (E/A ratio)	1.0 ± 0.10	1.1 ± 0.25	0.251
LVEF%	68.6 ± 8.9	71.7 ± 7.4	0.135

PAH-CHD = pulmonary arterial hypertension-CHDs; mPAP = mean pulmonary artery pressure; RVD = right ventricular diameter; FAC = functional area change; E/A = early/late filling phase; LVEF = left ventricular ejection fraction.

survivors (15.8 ± 0.8) among children with pulmonary arterial hypertension-CHD (Table 3).

There was a significant positive correlation between red cell distribution width and heart rate, respiratory rate, and mean pulmonary artery pressure, but a significant negative correlation between red cell distribution width and Hb, mean corpuscular volume, and MCH in the studied groups (Table 4).

Binary logistic regression analysis showed that red cell distribution width was a good predictor of mortality in patients with pulmonary arterial hypertension-CHD (OR = 1.437, 95% CI: 1.098–1.880, $P = 008$). Moreover, receiver operating characteristic curve analysis for the predictive value of red cell distribution width

Table 3. RDW in survivors and non-survivors among patients with PAH-CHD

Parameters	Survivors ($n = 52$)	Non-survivors ($n = 8$)	p value
RDW %	15.8 ± 0.8	19.1 ± 2	0.001

PAH = pulmonary arterial hypertension; RDW = red cell distribution width.

Table 4. Correlation between RDW and different parameters in the studied groups

	RDW	
Parameters	*R*	*P*
HR (beat/min)	0.272	0.036*
RR (cycle/min)	0.373	0.003*
O_2 saturation %	−0.030	0.818
Hb (gm/dl)	−0.332	0.010*
Haematocrit %	−0.141	0.283
MCV (fl)	−0.359	0.005*
MCH (pg)	−0.422	0.001*
CRP (mg/L)	0.028	0.832
mPAP (mmHg)	0.331	0.010*
RVD (mm)	0.079	0.550
RV FAC	−0.075	0.571
RV E/A ratio	−0.065	0.624
LV EF%	−0.043	0.743

* means significant. HR = heart rate; RR = respiratory rate; O2 = oxygen; Hb = haemoglobin; MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin; RDW = red cell distribution width; TLC = total leucocytic count; CRP = C-reactive protein; CTR = cardiothoracic ratio; mPAP = mean pulmonary artery pressure; RVD = right ventricular diameter; RV FAC = right ventricular functional area change; E/A = early/ late; LVEF = left ventricular ejection fraction.

in children with pulmonary arterial hypertension-CHD showed that the best cut-off point of red cell distribution width to predict mortality in the pulmonary arterial hypertension-CHD group was ≥17.6% with a sensitivity of 80% and a specificity of 66.7% (Fig. 1).

Discussion

Pulmonary arterial hypertension is a common complication of CHD with a significant morbidity and mortality. Many biomarkers that may be useful, particularly in the follow-up of patients with pulmonary hypertension, have recently been identified. The discovery of novel prognostic markers may allow for the early identification of susceptible patients and provide therapeutic alternatives for pulmonary arterial hypertension patients.[8,9]

In the current study, patients with pulmonary arterial hypertension-CHD had significantly higher red cell distribution width values than those with CHD alone. This is consistent with the research conducted by Thayer et al.[10] who showed that individuals with pulmonary hypertension from various causes, including CHD, typically had greater red cell distribution width values than that of patients without pulmonary hypertension.

The results of the current study showed that red cell distribution width was a reliable predictor of mortality in patients with pulmonary hypertension-CHD which coincides with the results of

https://doi.org/10.1017/S1047951124000817 Published online by Cambridge University Press

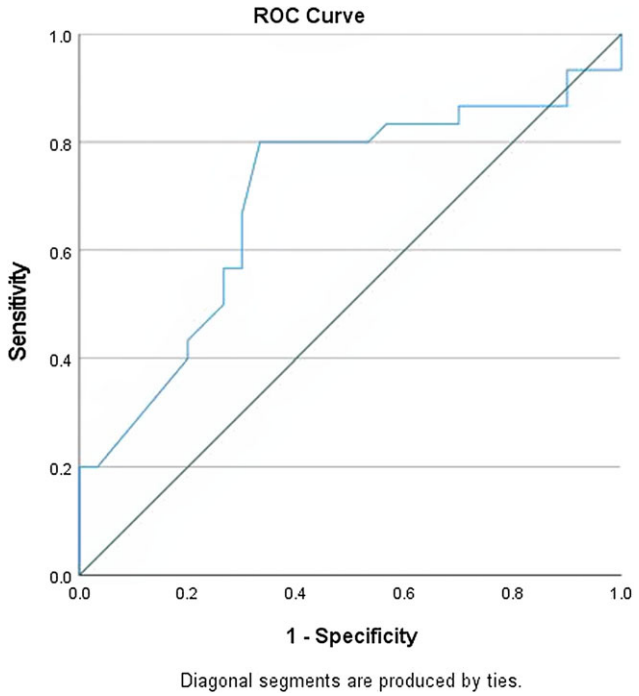

Figure 1. Receiver operating characteristic (ROC) curve of red cell distribution width for prediction of mortality in children with pulmonary arterial hypertension-CHD.

other studies[11–13] which reported that red cell distribution width was independently associated with higher mortality in patients with pulmonary hypertension. On the other hand, Baltazares-Lipp et al.[14] found that increased red cell distribution width was a severity-associated feature but was unable to predict death. This difference may be related to the different studied populations.

The results of the current study showed that the best cut-off point of red cell distribution width to predict mortality in the pulmonary arterial hypertension-CHD group was ≥ 17.6%. This is consistent with a study by Smukowska-Gorynia et al.[11] who found that red cell distribution width at a cut-off value of 17.7% had a good sensitivity and specificity for predicting death in adult patients with pulmonary arterial hypertension.

In the current study, patients with pulmonary arterial hypertension-CHD showed a significant positive relationship between red cell distribution width and mean pulmonary artery pressure, which is in line with the results of Thayer et al.[10] However, this contradicts the findings of Petrauskas et al.[15] who observed that red cell distribution width and mean pulmonary artery pressure were not significantly correlated in adult pulmonary hypertension patients. This discrepancy could be explained by older participants with different diagnoses.

In our study, there was a significant positive correlation between red cell distribution width, heart rate, and respiratory rate. This concurs with Safar's study,[16] who found a statistically significant positive association between red cell distribution width levels and Ross classification of heart failure (which includes tachypnoea and tachycardia).

Our study suggests that red cell distribution width might serve as an indicator of mortality in children with pulmonary arterial hypertension-CHD; however, the exact mechanism remains unclear. There are several possible explanations for this observation. First, inflammation may bridge the association between elevated red cell distribution width and worse pulmonary hypertension prognosis. Elevated red cell distribution width may be due to inflammatory markers, and inflammation may play a positive role in pulmonary arterial hypertension linked to underlying diseases. Another possible mechanism might be associated with iron deficiency, whereby elevated red cell distribution width may be due to iron deficiency and ineffective erythropoiesis. It is well documented that iron status in the human body plays an important role in regulating pulmonary vascular tension, and iron deficiency is common in patients with pulmonary arterial hypertension-CHD. Third, pulmonary hypertension can lead to systemic haemodynamic disorders and tissue hypoxia. Hypoxia promotes the synthesis and release of erythropoietin, which leads to elevated red cell distribution width. Therefore, red cell distribution width may play an important role in the long-term prognosis of cardiopulmonary vascular disease. Nonetheless, the role of red cell distribution width in the pathogenesis of pulmonary hypertension and its influence on pulmonary hypertension development and prognosis are worthy of further discussion.[5]

Limitations of the study are small sample size, short duration of follow-up, and inability to assess the prognostic value of red cell distribution width to predict response to treatment in children with pulmonary arterial hypertension-CHD.

Conclusion

Red cell distribution width was significantly elevated in children with pulmonary arterial hypertension-CHD compared to children with CHD and no pulmonary arterial hypertension. Moreover, red cell distribution width could be used as a predictive marker for mortality in children with pulmonary arterial hypertension-CHD.

Financial support. This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Competing interests. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the institutional committees of Faculty of medicine, Tanta University.

References

1. Ploegstra M-J, Zijlstra WMH, Douwes JM, Hillege HL, Berger RMF. Prognostic factors in pediatric pulmonary arterial hypertension: a systematic review and meta-analysis. Int J Cardiol 2015; 184: 198–207.
2. Rosenzweig EB, Abman SH, Adatia I, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J 2019; 53: 1801916.
3. Simonneau G, Montani D, Celermajer DS, et al. Hemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019; 53: 1801913.
4. Meinel K, Koestenberger M, Sallmon H, Hansmann G, Pieles GE. Echocardiography for the assessment of pulmonary hypertension and congenital heart disease in the young. Diagnostics 2021; 11: 49.
5. Liu J, Yang J, Xu S, et al. Prognostic impact of red blood cell distribution width in pulmonary hypertension patients: a systematic review and meta-analysis. Medicine 2020; 99: e19089.
6. Zhao J, Mo H, Guo X, et al. Red blood cell distribution width as a related factor of pulmonary arterial hypertension in patients with systemic sclerosis. Clin Rheumatol 2018; 37: 979–985.
7. Geenen LW, Baggen VJ, Koudstaal T, et al. The prognostic value of various biomarkers in adults with pulmonary hypertension; a multi-biomarker approach. American Heat J 2019; 208: 91–99.

https://doi.org/10.1017/S1047951124000817 Published online by Cambridge University Press

8. Awad A, Elnemr S, Hodeib H, El Amrousy D. Platelet activation markers in children with pulmonary arterial hypertension associated with congenital heart disease. Pediatr Cardiol 2022; 43: 1264–1270.
9. Gaheen R, El Amrousy D, Hodeib H, Elnemr S. Plasma copeptin levels in children with pulmonary arterial hypertension associated with congenital heart disease. Eur J Pediatr 2021; 180: 2889–2895.
10. Thayer TE, Huang S, Levinson RT, et al. Unbiased phenome-wide association studies of red cell distribution width identifies key associations with pulmonary hypertension. Ann Am Thorac Soc 2019; 16: 589–598.
11. Smukowska-Gorynia A, Tomaszewska I, Malaczynska-Rajpold K, et al. Red blood cells distribution width as a potential prognostic biomarker in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Hear, Lun Circ 2018; 27: 842–848.
12. Hampole CV, Mehrotra AK, Thenappan T, Gomberg-Maitland M, Shah SJ. Usefulness of red cell distribution width as a prognostic marker in pulmonary hypertension. Am J Cardiol 2009; 104: 868–872.
13. Xiaohua SH, Jiangjun YO, Lin LI. Study of ventricular end-diastolic diameter ratio in Han, Tibetan and Hui adults patients with congenital heart disease associated with pulmonary hypertension at high altitude area. J Clin Cardiol. 2022; 38: 323–327.
14. Baltazares-Lipp ME, Aguilera-Velasco A, Aquino-Gálvez A, et al. Evaluating of red blood cell distribution width, comorbidities and electrocardiographic ratios as predictors of prognosis in patients with pulmonary hypertension. Diagnostics 2021; 11: 1297.
15. Petrauskas LA, Saketkoo LA, Kazecki T, et al. Use of red cell distribution width in a population at high risk for pulmonary hypertension. Respir Med 2019; 150: 131–135.
16. Safar H. Clinical grading of pediatric heart failure in Egypt: a single-center study. Alex J Pediatr 2022; 35: 208.

https://doi.org/10.1017/S1047951124000817 Published online by Cambridge University Press