CHILD HEALTH

Relationship between the Value of Red Cell Distribution Width and Parameters of Left Ventricular Function in Children with Heart Failure

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ABSTRACT

Background: **Early identification of left ventricular dysfunction is important in children with heart failure (HF). Echocardiography is no widely available, thus other simple marker, namely red cell distribution width (RDW) can be alternative. It has been shown as a good predictor in adults with HF, but research in peadiatric population is still limited.**

Objective: **To analyze the relationship between RDW values and left ventricular function (ejection fraction (EF), fractional shortening (FS) and E/A ratio) in children with HF.**

Methods: **A cross-sectional, observational analytic study was conducted in 53 children with HF in Haji Adam Malik Hospital Medan. The relationship between RDW values and parameters of left ventricular function was analyzed using *Chi-squre* test.**

Result: **Of all 53 children, congenital heart defect (CHD) dominated 48.9% the underlying cause of HF with rheumatic heart disease (RDH) represented 43.3% dan dilated cardiomyopathy (DCM) 1.9%. From the multivariate anaylsis, EF, FS, E/A, and hemoglobin level were independent variables significantly affecting the value of RDW in children with HF (*P* value 0.002, 0.002, 0.044, 0.012, respectively).**

Conclussion: **The value of RDW can be used as an initial assessment of the severity of HF in children before performing echocardiography.**

KEY WORDS

red cell distribution width, left ventricular function, children with heart failure

INTRODUCTION

Heart failure (HF) in children is a clinical and pathophysiological syndrome that results from ventricular dysfunction, volume or pressure overload, either alone or in combination[1]. The pathogenesis of HF in children can be divided into two groups namely over circulation failure and pump failure[2]. Heart failure result in a disease cycle, decreased cardiac output causes tissue hypoxia, activates a renin-angiotensin-aldosterone system, sympathetic nervous system, and inflammatory cytokine production[3]. Several pro-inflammatory cytokines implicated in the progression of HF are tumor necrosis factor (TNF-α), interleukin (IL) -1, and IL-6[4].

Red cell distribution width (RDW) is a relatively simple asessment for assessing the heterogenecity of erythrocyte morphology (such as anisocytosis)[5]. The value of RDW was studied previously only in problems of hematological disorders, such as anemia or thalassemia. However, over time, the result of recent studies indicated RDW was associated with several other diseases and HF is one of them[6].

The persistent increase of RDW in cardiovascular diseases has been attributed to the effective stimulation of erythropoiesis by erythropoietin (EPO), a hormone secreted during hypoxic events, which promotes the release of enlarged RBCs from bone marrow[7]. Another hypothesis is that elevated RDW may be due to a slight reduction of RBC turnover[8]. One study in Hungary, 2009, reported that pro-inflammatory cytokines (TNF-α, IL-1, IL-6) had been shown to be predictors in HF and could impact bone marrow function and iron metabolism. Furthermore, the inflammatory reaction inhibited the maturation of red blood cells which was reflected by an increase in RDW values[9].

From our knowledge, research conducted on evaluating the relationship between RDW values and left ventricular function in children is still limited. Early identification of left ventricular dysfunction is needed to determine initial therapy and prognosis. However, in Indonesia, facility such as echocardiography, is not always available in peripheral hospitals[10]. Therefore, this study aims to evaluate the relationship between RDW values and left ventricular function.

METHODS

This was a cross sectional, observational analytic study to evaluate relationship between RDW values and left ventricular function (ejection fraction (EF), fractional shortening (FS) and E/A ratio) in children with heart failure. This study was done at Pediatric Out-Patient Department and In-Patient Department H. Adam Malik Hospital, Medan, from November 2018 to May 2019.

Inclusion criterias were children from 1 month to 18 years old with heart failure. Informed consent was obtained from all participants. Exclusion criterias were iron deficiency anemia, thalassemia, sepsis, renal and liver disfunction.

The sample size in this study was calculated based on the sample size formula for testing hypotheses in one population with categorical variables

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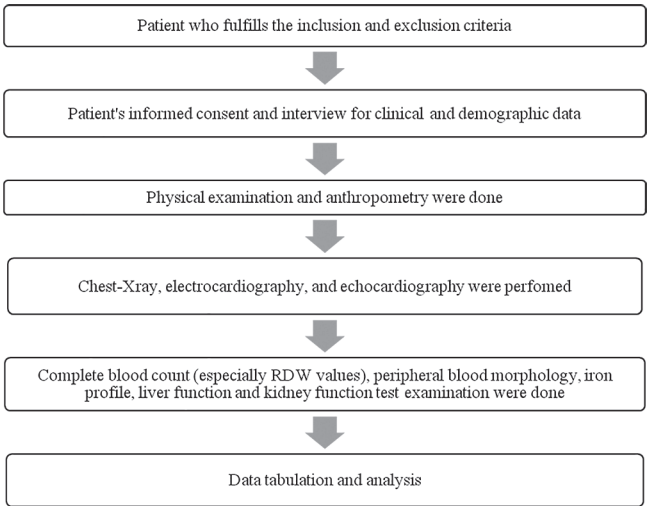

Figure 1: Research Flow Diagram

Table 2: Relationship between RDW value and parameters of left ventricular in children with heart failure

Parameters	RDW		*P*	PR (CI95%)
	Abnormal	Normal		
EF n(%)				
Abnormal, (*n* = 16)	14 (87.5)	2 (12.5)	< 0.001[a]	2.698 (1.635- 4.451)
Normal, (*n* = 37)	12 (32.4)	25 (67.6)		
FS, *n*(%)				
Abnormal, (*n* = 16)	14 (87.5)	2 (12.5)	< 0.001[a]	2.698 (1.635- 4.451)
Normal, (*n* = 37)	12 (32.4)	25 (67.6)		
E/A, *n*(%)				
Abnormal, (*n* = 31)	20 (64.5)	11 (35.5)	0.012[a]	2.366 (1.139- 4.912)
Normal, (*n* = 22)	6 (27.3)	16 (72.7)		

[a] *Chi-Square* test, PR: Prevalence ratio, CI: Confidence interval

Table 3: Factors affect RDW value in children with heart failure

Factors	RDW		*P*	PR (CI95%)
	Abnormal	Normal		
Functional class Ross, *n*(%)				
III&IV, (*n* = 32)	21 (65.6)	11 (34.4)	0.012[a]	2.366 (1.139-4.912)
I&II, (*n* = 21)	5 (23.8)	16 (76.7)		
Nutritional status, *n*(%)				
Moderate. severe, (*n* = 21)	19 (65.5)	10 (34.5)	0.013[a]	2.246 (1.141- 4.421)
Baik, (*n* = 32)	7 (29.2)	17 (70.8)		

[a] Chi-Square test, PR: Prevalence ratio, CI: Confidence interval

Tabel 1: Subject characteristics

Characteristics	n = 53
Gender, n(%)	
• Male	24 (45.3)
• Female	29 (54.7)
Age (years), median (min-max)	10 (1-17)
Weight (kg), median (min-max)	
Height (cm), median (min-max)	24 (3-50)
131 (49-168)	
Nutritional status, n(%)	
• Normal	24 (45.3)
• Moderate malnutrition	14 (26.4)
• Severe malnutrition	15 (28.3)
RDW (%), median (min-max)	14.4 (11.6-23.2)
Etiology of heart failure, n(%)	
1. RHD	23 (43.4)
2. VSD	10 (18.9)
3. ASD	6 (11.3)
4. PDA	9 (17)
5. DCM	4 (7.5)
6. VSD + PDA	1 (1.9)
Functional classification of Ross, n(%)	
Ross II	21 (39.6)
Ross III	18 (34)
Ross IV	14 (26.4)
Creatinine (mg/dL), median (min-max)	0.6 (0.3-0.9)
SGOT (U/L), median (min-max)	26 (18-31)
SGPT (U/L), median (min-max)	25 (6-40)
Serum iron (µg/dL), median (min-max)	95 (61-165)
TIBC (µg/dL), median (min-max)	206 (140-302)
Ferritin (ng/mL), median (min-max)	62.05 (21.08 -224.01)

Table 4: Relationship between hemoglobin levels and RDW values

Factor	Median	*P*
	Minimun-maximun	
RDW n(%)		
Anemia, (*n* = 18)	15.85 (12-21)	0.142 [a]
Normal, (*n* = 35)	14.2 (12-23)	

[a] *Mann-Whitney* test

$$n = [\frac{(Z\alpha + Z\beta) \text{ x } s}{(X1\text{-}X0)}]^2$$

The calculation was done using a 95% confidence level with minimal sample size was 46 patients. Subject in this study was recruited consecutively.

History taking, physical examination, and anthropometry data were carried out and informed consent was obtained from the parents. Echocardiography was performed to assess left ventricular function. The examination was carried out by pediatric cardiologist in Haji Adam Malik General Hospital Medan. The instrument used was the Philips echocardiograph type Affiniti 50 C made in the United States. Left ventricular function is determined based on the ejection fraction (EF), the fractional shortening (FS), and the E/A ratio. In addition, subject also underwent chest X-ray examination in the radiology department and electrocardiography examination at the integrated diagnostic installation of Haji Adam Malik General Hospital.

Subjects underwent blood tests in the Clinical Pathology laboratory of Haji Adam Malik Hospital. Data needed is complete blood count (especially RDW values), peripheral blood morphology, iron profile, liver function and kidney function test. The specimen used was venous blood. Specimens were taken by laboratory personnel and examined with a Sysmex XN-1000 machine.

Table 5: Multivariate analysis of all factors affect RDW value in children with heart failure

		Coefficient	S.E.	*P*	OR	CI95%	
						Min	Max
Step 3	EF	2.840	0.912	0.002	17.115	2.867	102.159
	FS	2.840	0.912	0.002	17.115	2.867	102.159
	E/A	1.500	0.745	0.044	4.481	1.041	19.289
	Hemoglobin	1.599	0.736	0.035	4.946	1.123	21.775
	Constant	-2.263					

OR: *Odd ratio*

Research Flow Diagram

Research flow of this study shown in Figure 1.

Data Processing and Data Analysis

Univariate analysis was performed to study the distribution of demographic characteristics and clinical samples in the study. Numeric data is presented in mean ± standard deviation (SD) if normally distributed or median (maximum and minimum) if not normally distributed. Categorical data are in frequency and percentage. To find out the relationship between RDW values with EF, FS E/A, functional classification of Ross and nutrional status, bivariate analysis was done, namely the Chi-square test with an alternative Fisher test. To find out the relationship between hemoglobin values and RDW values, a paired t-test or *Mann-Whitney* test was performed. Data processing was performed using Statistical Package for Social Sciences for Windows (SPSS) version 24.0, 2016 with $P < 0.05$ was significance, and 95% confidence interval.

The health research ethical committee number 395/TGL/KEPK FK USU-RSUP HAM/2019 was obtained from medical faculty of Universitas Sumatera Utara and number LB.02.03/II.4/154/2019 was obtained from the clinical research unit of H. Adam Malik Hospital.

RESULTS

During study period, 53 children with heart failure who met the study's inclusion and exclusion criteria were collected. 53 subjects included male 45.3% and female 54.7% with the median of RDW value was 14.4% (11.6-23.2). 43.4% of our patients were diagnosed with RDH, while CHD with left to right shunt represented 48.9%. All characteristic data from the research sample was listed in Table 1.

Table 2 showed that there is a significant relationship between the increase of RDW value and parameters of left ventricular function such as EF, FS, E/A ($P < 0.001$, $P < 0.001$, $P = 0.012$, respectively). We also found that there was a significant relationship between factors (functional classification of Ross and nutritional status) and the change of RDW values ($P = 0.012$, $P = 0.013$, respectively) (listed in table 3).

In our bivariate analysis, the Mann-whitney test's result found no significant differences between hemoglobin level and RDW value (listed in table 4). Due to the P values of all analysis were below $P < 0.25$, therefore we continued to analyze all variables in multivariate analysis. We found, EF, FS, E/A, and hemoglobin level were independent variables that significantly affect the value of RDW in children with heart failure ($P = 0.002$, $P = 0.002$, $P = 0.044$, $P = 0.035$, respectively) (listed in table 5).

DISCUSSION

Our study found that the proportion of causes of heart failure in children is still dominated by congenital heart diseases (CHDs) (48.9%) consisting of ventricular septal defect (VSD) (18.9%), atrial septal defect (ASD) (11.3%), patent ductus arteriosus (PDA) (17%), and combination VSD and PDA (1.9%) and the rests were caused by rheumatic heart disease (RHD) (43.4%) and dilated cardiomyopathy (DCM) (7.5%). As what had been reported, the causes of heart failure differed between developed countries and developing countries. In developed countries, the causes are cardiomyopathy and CHD that has undergone surgery, whereas in developing countries, unoperated CHD and acquired heart disease are more prevalent[11].

The role of pro-inflammatory cytokines are to desensitize bone marrow erythroid progenitors to EPO, blocking its antiapoptotic and promaturation effects. By this evidence, it can be concluded that the value of RDW itself does not entirely depend on the hemoglobin level[12]. Most studies had even been conducted were assessing the value of RDW as a prognostic factor in adult patients with heart failure[13-15]. In contrast to previous studies, our study assessed the relationship of RDW values to the parameters of left ventricular function in pediatric patients with heart failure. Our study found that the RDW value was significantly related to each of the ventricular function parameters assessed, namely EF, FS, and E/A.

These results are in line with research conducted in Egypt, 2014, with a group of patients suffering from a left to right shunt of 58.1% (with VSD of 26.7%) and DCM of 41.9%, reported with RDW value of 16.4% closely related to hemoglobin values, FS, and E/A ratio. The difference is that the study did not examine the relationship between EF values and RDW values[16].

Another study conducted in Indonesia, 2017, examined the relationship between RDW values and left ventricular function in acyanotic CHD children. The study found RDW values to be significantly correlated with EF in ASD patients (r -0.491; $P = 0.032$) and E/A ratio in PDA patients (r 0.342; $P = 0.026$)[10]. These results are in line with our study both the function systolic and diastolic, but the difference is the sample population. In our study, subjects were all children with heart failure who met the inclusion and exclusion criterias by considering the changes in RDW values related to the process of heart failure.

Besides, study conducted in Turkey, 2018, reported that RDW values were negatively correlated to EF (r -0.27; $P = 0.004$) and hemoglobin (r -0.54; $P = 0.0001$). The study concluded that an increase in RDW values associated with poor left ventricular function and the degree of anisocytosis could be a marker in identifying high-risk patients and treatment strategies[17]. Another study in India, 2016, also reported in adult heart failure patients, RDW values have a negative correlation towards EF (r -0.432; $P < 0.01$)[18]. In our study, no subject with RDW below normal range was found. Therefore, we concluded that any dysfunction of left ventricular parameters could increase the value of RDW.

In addition to systolic function, RDW values are also associated with diastolic dysfunction in patients with heart failure. There is a positive correlation of RDW values with left ventricular end diastolic pressure (LVEDP), systolic pulmonary arterial pressure (sPAP), and left atrial dimension (LAD). Patients with asymptomatic left ventricular dysfunction and increase in RDW value > 14.5% was assosiated with lower survival rates than patients with RDW values < 14.5%[19].

Systemic inflammation in heart failure mediated by TNF-α can cause loss of appetite that ends in malnutrition-inflammation-cachexia (MIC) and hypoalbumin condition[20]. Our study showed that the RDW was significantly associated with malnutrition in children with heart failure. However, after making adjustments in the multivariate test, it was found that the result was insignificant which meant the role of underlying problems might take an important role in changing the RDW value of heart failure patients.

Another study in Japan, 2015, assessed the relationship between RDW, anemia, and IL-6 levels in patients with congenital heart disease and found that an increase in RDW values > 15% was associated with increased levels of IL-6 and anemia[21]. In our study, we have excluded samples with iron deficiency anemia. After performing adjustment, the value of hemoglobin as an independent variable significantly affected the value of RDW in children with heart failure.

From the bivariate test, we found a significant relationship between RDW values and functional classification of Ross. This was in line with previous study in adult population conducted in the United States, 2007, reported an increase in RDW values > 15.2% was a good predictor of all

morbidity and mortality in patients with heart failure, especially in functional class NYHA III/IV and low EF[22]. Another study in adult population conducted in Japan, 2014, reported the increase in RDW was significantly related to the functional class NYHA III/IV in heart failure patients[23].

Some limitations in this study includes: 1. the variation of the course of the disease and the severity of the disease when the patients were diagnosed with heart failure was very broad, 2. We did not assess the parameters of left ventricular function other than EF, FS, E/A such as left ventricular end-systolic dimension (LVESD), left ventricular end-diastolic dimension (LVEDD), peak velocity of early diastolic filling (É), early mitral inflow velocity to early diastolic mitral annular velocity ratio (E/É), which might improve the accuracy of the assessment of systolic and diastolic dysfunction. 3. In our study, we did not assess the correlation between independent and dependent variables and other inflammatory markers such as interleukin levels and also erythropoetin levels were not included in the study.

The strengths of this study were the sample population taken by all children with heart failure, unlike previous study in Indonesia that took samples only in children with congenital heart disease. In addition, the subjects from our study are excluded heart failure children with iron deficiency anemia, sepsis, liver abnormalities, and kidney disorders which could affect the value of RDW.

CONCLUSION

Parameters of left ventricular function, such as EF, FS, E/A, play an independent factor that significantly affect RDW values in children with heart failure. The value of RDW can be used as an initial assessment of the severity of heart failure in children before echocardiography can be available.

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