Changes in Red Blood Cell Distribution Width in Very Low Birth Weight Infants for Predicting Bronchopulmonary Dysplasia

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Abstract

It is unknown whether RDW can be used to predict the severity and prognosis of various diseases in children, especially newborns. This study aimed to investigate the RDW values of preterm infants born at < 30 weeks' gestation with a birth weight < 1500 g and evaluate whether the RDW values in the early days of life can predict bronchopulmonary dysplasia (BPD) development. The mean RDW values on day 1 (D1), day 7 (D7), and day 28 (D28) after birth were 16.2 ± 1.4%, 17.5 ± 2.4%, and 17.6 ± 1.7%, respectively. The RDW at birth was lower in the infants born at < 28 weeks' gestational age than in those born at ≥ 28 weeks' gestational age (15.7 ± 0.8 vs 16.4 ± 1.5, P = 0.003). The RDW values of both groups increased during the first week after birth and did not differ significantly. The levels remained similar levels at 1 month of life. The RDW values examined at D1, D7, D28 and the changes of RDW from D1 to D7 were not correlated with the development of BPD independent of severity. The usefulness of RDW as a predictor of BPD development remains questionable and requires further study.

Introduction

Red blood cell distribution width (RDW) as part of complete blood count (CBC) has traditionally been used with mean corpuscular volume (MCV) to determine the cause of anemia. RDW values increase in circumstances of ineffective erythropoiesis in the bone marrow such as iron deficiency anemia, folate and vitamin B12 deficiency or shortening of the red blood cell (RBC) life span by destruction such as in sickle cell anemia.[1]

Many recent studies reported that RDW is related to inflammation[2–4] and hypoxemia[5], and an easily available parameter that can predict the severity[4, 6, 7] and prognosis of various diseases in adults[3, 7–17]. However, studies of the same in children are limited[18–21]. Additional blood sampling is not required to determine the RDW values, as CBC is performed relatively frequently and requires only a small amount of blood. Therefore, RDW might be a useful tool for assessing the medical conditions of newborns, especially preterm infants. Nevertheless, this remains unknown and the normal range of RDW values in preterm infants has yet to be determined.[22–25]

Bronchopulmonary dysplasia (BPD) occurs when premature lung tissue and vessels are injured and their development and differentiation are disrupted by the factors causing perinatal inflammation, such as chorioamnionitis, hyperoxia, mechanical ventilation, and infection. The authors investigated the changes in RDW values in very low birth weight infants born before 30 weeks' gestation and whether the RDW values measured in the early days of life can predict BPD development.

Results

Clinical characteristics

Of the 171 infants eligible for this study, 63 were excluded. The mean gestational age (GA) and birth weight of the remaining 108 patients were 28.4 ± 1.4 weeks' gestation and 1165.6 ± 212.9 g. Eleven infants (10.2%) were small for gestation. Four infants died in the first month of life.

RDW values in preterm infants

The mean RDW values checked at day 1 (D1), day 7 (D7), and day 28 (D28) after birth were 16.2 ± 1.4%, 17.5 ± 2.4%, and 17.6 ± 1.7%, respectively. The RDW increased during the first week after birth (P < 0.001) and did not change significantly from D7 to D28 (P = 0.658) (Table 1).

Table 1. Changes in RDW levels during the first month of life and the differences in RDW changes between infants born at < 28 weeks' GA and those born at ≥ 28 weeks' GA.

	D1	D7	D28	P value					
				Interaction effect	Time effect			Group effect		
					Overall	D1 vs D7	D7 vs D28	D1	D7	D28
All	16.2 ± 0.1	17.5 ± 0.2	17.6 ± 0.2		<0.001	<0.001	0.658			
GA <28	15.7 ± 0.3	17.6 ± 0.5	17.8 ± 0.3	0.012	<0.001	<0.001	0.639	0.024	0.832	0.501
GA ≥28	16.4 ± 0.2	17.5 ± 0.3	17.6 ± 0.2		<0.001	<0.001	0.772			

D1, first day of life; D7, seventh day of life; D28, twenty-eighth day of life; GA, gestational age; RDW, red blood cell distribution

Data are presented as mean ± standard deviation.

The mean RDW value at D1 was lower in the infants born at < 28 weeks' GA (n = 27) than in those born at 28–29 weeks' GA (n = 81) (15.7 ± 0.8 vs 16.4 ± 1.5, P = 0.003). On the other hand, the mean RDW values checked at D7 and D28 did not differ between the groups (Table 2). The RDW of both groups increased in the first week of life (P < 0.001 both) and then stayed at the similar levels for a month after birth (P = 0.639, P = 0.772, respectively) (Table 1, Fig. 1). White blood cell count (WBC) and C-reactive protein measured at birth were higher in the lower gestational group (P < 0.001 and P = 0.003, respectively)

Table 2
Demographic characteristics and laboratory data by GA

	GA < 28 weeks (n = 27)	GA 28–29 weeks (n = 81)	P value
GA (weeks)	26.5 ± 1.3	29.0 ± 0.7	< 0.001
Birth weight (g)	976.9 ± 213.2	1228.5 ± 172.8	< 0.001
SGA (n, %)	3 (11.1)	9 (11.1)	1.000
Male (n, %)	14 (51.9)	54 (66.7)	0.167
C-sec (n, %)	16 (59.3)	62 (76.5)	0.135
WBC (10^3/μL)	11.1 (5.9–15.9)	5.7 (4.1–8.2)	< 0.001
Hemoglobin (g/dL)	15.5 ± 1.04	16.0 ± 1.6	0.059
MCV (fL)	115.6 ± 6.4	115.4 ± 6.0	0.855
RDW at D1 (%)	15.7 ± 0.8	16.4 ± 1.5	0.003
RDW at D7 (%)	17.6 ± 2.5	17.5 ± 2.4	0.832
RDW at D28 (%)*	17.9 ± 1.3	17.6 ± 1.7	0.398
Platelet (10^3/μL)	256.1 ± 69.1	232.2 ± 67.8	0.118
CRP (mg/L)	0.3 (0.2–0.4)	0.2 (0.1–0.2)	0.003

CRP, C-reactive protein; C-sec, cesarean section; D1, first day of life; D7, seventh day of life; D28, twenty-eighth day of life; GA, gestational age; MCV, mean corpuscular volume; RDW, red blood cell distribution width; SGA, small for gestational age; WBC, white blood cell count

Data are presented as mean ± standard deviation or median (interquartile range), and number (%).

Relationship between RDW and BPD

After four patients who died in the first month of life were excluded, the remaining 104 patients were evaluated the relationship between RDW and BPD development. In multivariable logistic regression, the RDW values examined at D1, D7, D28 and the changes in RDW from D1 to D7 did not differ between the infants with BPD and those without BPD independent of severity (Table 3).

Table 3
Multivariable association between RDW and BPD

	BPD				Moderate/severe BPD			
	Crude OR	P value	Adjusted OR*	P value	Crude OR	P value	Adjusted OR*	P value
RDW at D1	1.145	0.37	0.964	0.831	1.093	0.595	0.868	0.518
RDW at D7	1.165	0.113	1.054	0.658	1.188	0.065	0.88	0.323
RDW at D28	1.153	0.248	1.031	0.822	1.059	0.702	0.937	0.747
RDW D1-D7	1.187	0.167	1.119	0.462	1.261	0.048	0.854	0.402

BPD, bronchopulmonary dysplasia; D1, first day of life; D7, seventh day of life; D28, twenty-eighth day of life; OR, odds ratio; RDW, red blood cell distribution width

*Adjusted by birth weight, small for gestational age, and white blood cell count.

Discussion

The present study aimed to determine the changes of RDW values in preterm infants born at < 30 weeks' gestation and the relationship of RDW with BPD. The mean RDW value at birth were 16.2 ± 1.4 % and increased in a week of life. Thereafter, no significant change occurred until a month of life. The RDW values of infants born at < 28 weeks' GA were lower than those of infants born at 28–29 weeks' GA. However, the RDW values increased in both groups, did not differ significantly after 1 weeks of life, and remained similar levels for a month. The RDW values did not differ significantly between the BPD groups.

Although it is known that the RDW levels of newborns are higher than those of children or adults due to active erythropoiesis and physiologic reticulocytosis,[26, 27] Determining the normal range of RDW in newborns is challenging because they are changing physiologically during perinatal period and are easily influenced by various conditions including GA. Therefore, the normal range of RDW values of preterm infants have not yet been established. Garofoli et al. reported that RDW and GA were negatively correlated.[28] A study of a multihospital dataset showed similar results that the upper reference was higher in preterm infants than in term and late preterm infants (23% vs 20%), although the authors mentioned of a selection bias in which more sick babies might be included in the preterm group.[26] Tonbul et al. and Desai et al. reported that mean RDW was the highest at 32–34 weeks' gestation in the both studies and suggested that it was secondary to active erythropoiesis in the third trimester.[27, 29] In the present study of preterm infants with a lower GA than in previous studies, the RDW levels at birth were higher in the infants at 28–29 weeks' gestation than the infants born at < 28 weeks' GA. On the other hand, Alur et al. reported no significant difference in the RDW values among preterm infants born at 23–

25 weeks, 26–28 weeks, 29–31 weeks' GA.[30] Looking into the data, we noticed that the RDW in 26–28 weeks' GA and 29–31 weeks' GA groups were higher than that in the 23–25 weeks' GA group, although these were no significant differences. It appears that erythropoiesis increased in the fetal period and peaked at 32–34 weeks' gestation.

The RDW values in the < 28 weeks' and ≥ 28 weeks' GA groups increased during the first week of life, while the gap of RDW level between the groups disappeared. Christensen et al.[26] explained that the increase of RDW in the early days of life in preterm infants was secondary to that induced by a previous RBC transfusion. However, the RDW showed similar trends in the present study, although the infants who received RBC transfusions in the first week of life were excluded. The increase in RDW seems to be partially due to physiologic anemia of preterm accompanied by reticulocytosis. White blood cell counts and C-reactive protein levels were higher in the < 28 weeks' GA than in the ≥ 28 weeks' GA group. It seems relevant that early preterm labor was induced by perinatal inflammation/infection.[31]

In adult studies, a number of studies were reported in terms of the role of RDW as indicators of severity or predictors of outcome for various diseases including sepsis, respiratory disease, cardiovascular disease and critical illness.[3, 6, 8, 9, 12–17, 32–35] Even though the mechanism of RDW increase was not fully determined, it was suggested that chronic hypoxia, malnutrition and inflammation cause an increase in RDW values.[4, 5, 36] Hypoxia induces erythropoietin release, which leads to release immature reticulocyte into circulation.[5] Injured RBC by inflammation aggravates the progress of disease through decrease of oxygen transfer to organs and tissues.[4]

RDW values were higher in patients with COPD than healthy people[33] and associated with its severity and outcomes including mortality and readmission rates.[8, 32–34] The pathophysiology of BPD and COPD are similar.[37] Both are resulted of the impairment of alveolarization/vascularization after inflammation and oxidative stress that can present as chronic hypoxia. However, in this study, the RDW values measured in the first month of life were not related to development of BPD. It appeared that other clinical conditions affected the relationship during the period from RDW measurement to BPD presentation. Garofoli et al. reported that the RDW at 1 month of life was higher in the BPD group than in non-BPD group, whereas the RDW within the first 3 days of life did not differ between groups.[28] However, the GA range was too broad and other contributing factors were not considered in the previous study.

There were some limitations in this study. First, it could not evaluate whether the infants with an evaluated RDW were likely to develop BPD because the normal RDW range has not yet been established in preterm infants yet. Second, chorioamnionitis was not evaluated as a perinatal factor because pathologic exam data of placenta were not available.

In conclusion, the RDW values at birth were higher in infants born at 28–29 weeks' GA than in those born at < 28 weeks' GA. The RDW values of both groups increased in the first week of life and remained similar for the first month of life. Studies about the RDW values for preterm infants are rare and the present study, to our knowledge, is the first to evaluate changes in RDW within the first month of life for preterm

infants. The RDW values in the first month of life were not associated with BPD development independent on severity. Thus, the usefulness of RDW as a predictor of BPD remains unknown and requires further studies.

Methods

This study was a retrospective review of the medical records of patients hospitalized in the two level lll neonatal intensive care units in Gyeongsang National University Hospital and Changwon Gyeongsang National University Hospital in South Korea between January 2009 and August 2019. This study was approved by the institutional review boards of the Changwon Gyeongsang National University Hospital (IRB no. 2020-02-017) and Gyeongsang National University Hospital (IRB no. 2020-02-014), which waived the need for informed consent. All methods were performed in accordance with the relevant guidelines and regulations.

The patients who were born at GA < 30 weeks and birth weight < 1500 g were included in this study. Patients with 1) a chromosomal abnormality or major congenital anomaly; 2) culture-proven early onset sepsis; 3) a recent RBC transfusion (within 1 week after birth); or 4) maternal anemia (Hemoglobin < 8g/dL) were excluded.

RDW values measured at D1, D7 and D28 were reviewed. The RDW levels according to GA and the associations between RDW and BPD development were analyzed. RDW were determined as part of a CBC, which was checked within 1 h after birth (D1), at D7, D28, and per the local routine protocol as necessary. The 0.3–0.5 mL of blood sample was taken from radial or umbilical artery and placed in ethylenediaminetetraacetic acid-containing tube. CBC was measured by automated hematology analyzer (Sysmex, Kobe, Japan) and their quality controls and calibrations were performed regularly following standard rules. WBC, hemoglobin, MCV, platelet count were also collected with the RDW from the CBC.

BPD was diagnosed if the patient required artificial respiratory support providing positive airway pressure or oxygen for more than 28 days but was discontinued before 36 weeks' postmenstrual age or discharge, whichever comes first. Moderate or severe BPD was diagnosed if the patient needed artificial respiratory support or oxygen at 36 weeks' postmenstrual age or at discharge.

The statistically analysis was performed using SAS software version 9.4 (SAS Institute, Inc, Cary, NC). The normality of continuous values was assessed by Kolmogorov-Smirnov test. Categorical and continuous variables were presented as number (percentage) and mean ± standard deviation or median (interquartile range [IQR]), respectively. Categorical variables were analyzed using the Chi-square test or Fisher's exact test. Continuous variables were analyzed through the Student's t-test or Mann-Whitney's U-test. A linear mixed-effects model was performed to analyze the trends of RDW levels during the first month of life and compare them between the infants born at < 28 weeks' GA and those born at ≥ 28 weeks' GA. Multivariable logistic regression was used to analyze the association of RDW with BPD. P-values < 0.05 were considered statistically significant.

Abbreviations

BPD, bronchopulmonary dysplasia; CBC, complete blood cell count
COPD, chronic obstructive pulmonary disease; D1, first day of life; D7, seventh day of life; D28, twenty-eighth day of life; GA, gestational age; RBC, red blood cell; RDW, red blood cell distribution width; WBC, white blood cell

Declarations

Author contribution

S.H. Oh and C.H. Park designed the study and S.H. Oh wrote the main manuscript text. H.J. Do and J.Y. Cho collected and analyzed the data. S.H. Oh and J.S. Park interpreted the data and prepared figures. All authors reviewed the manuscript.

Additional information

Competing interests statement

The author(s) declare no competing financial and non-financial interest.

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Figures

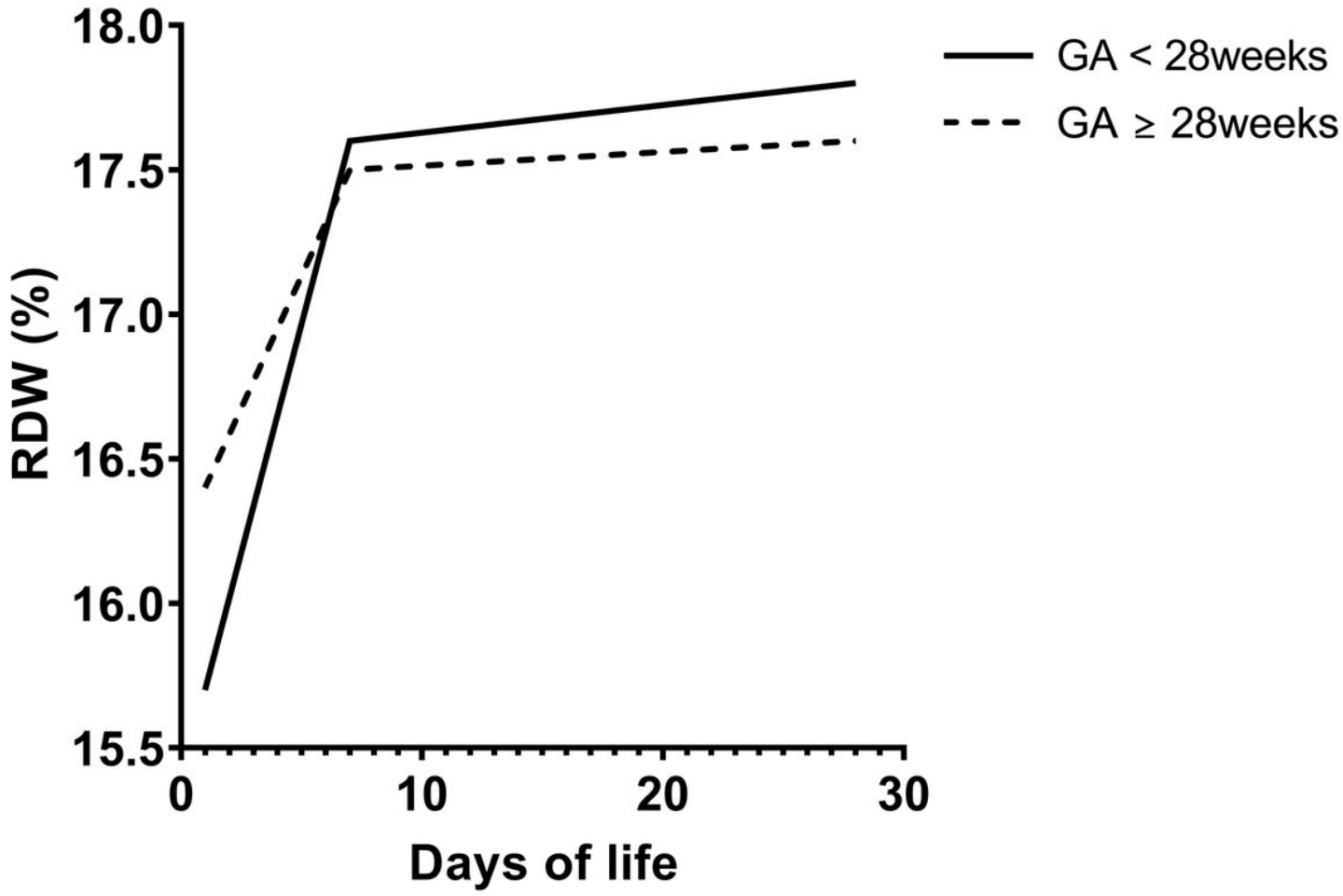

Figure 1

The trends of RDW in preterm infants born at < 28 weeks' GA versus those born at ≥ 28 weeks' GA. The RDW increased during the first week after birth and remained similar for the first month independent of GA. GA, gestational age; RDW, red blood cell distribution width