

# Evaluation of the usefulness of red blood cell distribution width in critically ill pediatric patients

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## Abstract

Red blood cell distribution width (RDW) is a component of routine complete blood count, which reflects variability in the size of circulating erythrocytes. Recently, there have been many reports about RDW as a strong prognostic marker in various disease conditions in the adult population. However, only a few studies have been performed in children. This study aimed to investigate the association between RDW and pediatric intensive care unit (PICU) mortality in critically ill children. This study includes 960 patients admitted to the PICU from November 2012 to May 2018. We evaluated the associations between RDW and clinical parameters including PICU mortality outcomes. The median age of the study population was 15.5 (interquartile range, 4.8–54.5) months. The mean RDW was  $15.6\% \pm 3.3\%$ . The overall PICU mortality was 8.8%. As we categorized patients into 3 groups with respect to RDW values (Group 1:  $\leq 14.5\%$ ; Group 2: 14.5%–16.5%; and Group 3:  $> 16.5\%$ ) and compared clinical parameters, the higher RDW groups (Groups 2 and 3) showed more use of vasoactive-inotropic drugs, mechanical ventilator support, higher severity scores, including pediatric risk of mortality III, pediatric sequential organ failure assessment, pediatric logistic organ dysfunction-2 (PELOD-2), and pediatric multiple organ dysfunction syndrome scores, and higher PICU mortality than the lower RDW group (Group 1) ( $P < .05$ ). Based on multivariate logistic regression analysis adjusted for age and sex, higher RDW value ( $\geq 14.5\%$ ) was an independent risk factor of PICU mortality. Moreover, adding RDW improved the performance of the PELOD-2 score in predicting PICU mortality (category-free net reclassification index 0.357, 95% confidence interval 0.153–0.562,  $P = .001$ ). In conclusion, higher RDW value was significantly associated with worse clinical parameters including PICU mortality. RDW was an independent risk factor of PICU mortality and the addition of RDW significantly improved the performance of PELOD-2 score in predicting PICU mortality. Thus, RDW could be a promising prognostic factor with advantages of simple and easy measurement in critically ill pediatric patients.

**Abbreviations:** ANOVA = analysis of variance, AUROC = areas under the receiver operating characteristic, BNP = B-type natriuretic protein, CBC = complete blood count, CI = confidence intervals, Cnri = category-free net reclassification index, CRP = C-reactive protein, Hg = hemoglobin, ICU = intensive care unit, IDI = integrated discrimination improvement index, IQR = interquartile range, MV = mechanical ventilator, OR = odds ratios, PELOD = pediatric logistic organ dysfunction, PICU = pediatric intensive care unit, PIM = pediatric index of mortality, plt = platelet, pMODS = pediatric multiple organ dysfunction syndrome, PRISM = pediatric risk of mortality, pSOFA = pediatric sequential organ failure assessment, RBC = red blood cell, RDW = red blood cell distribution width, WHO = world health organization.

**Keywords:** erythrocyte indices, intensive care units, mortality, pediatrics

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## 1. Introduction

Red blood cell (RBC) distribution width (RDW), calculated by dividing the standard deviation of RBC volume by the mean corpuscular volume and multiplied by 100, is routinely reported as part of the complete blood count (CBC) using automated flow cytometry. RDW has been traditionally used as additional information in the differential diagnosis of the cause of anemia.<sup>[1]</sup>

RDW has been recently reported as a strong prognostic factor in several diseases of various organ systems, including the cardiovascular, respiratory, renal, neurologic, and gastrointestinal systems.<sup>[2–15]</sup> It also showed significant associations with ventilator-free days, postoperative outcome, intensive care unit (ICU) discharge outcome, out-of-hospital outcome, and all-cause mortality in critically ill patients.<sup>[16–20]</sup> However, most studies were conducted in adult patients. Only a few studies have investigated RDW in children, especially in the critically ill pediatric population.<sup>[21–23]</sup>

In these critically ill children, it is crucial to promptly and accurately assess the severity of illness and organ dysfunction and predict outcomes for prompt management. For this purpose, many studies have investigated proper prognostic factors including several scoring systems such as the pediatric risk of mortality (PRISM), pediatric sequential organ failure assessment (pSOFA), pediatric logistic organ dysfunction-2 (PELOD-2), and

pediatric multiple organ dysfunction syndrome (pMODS).<sup>[24–27]</sup> However, considering the qualification of a good clinical parameter for predicting outcomes, which should be easily assessable, reproducible, widely accessible, and acceptable, these scoring systems could be slightly complex and inconvenient for use in practice.

Thus, this study aimed to evaluate the association between pediatric intensive care unit (PICU) mortality and RDW, which is easily measured as a component of CBC and investigate if RDW could be useful as a prognostic marker for predicting PICU mortality in critically ill pediatric patients.

## 2. Methods

### 2.1. Patients

The study protocol was approved by the institutional review board of the Asan Medical Center, Seoul, Korea. The requirement of parental consent was waived because of the retrospective nature of the study. All children who were consecutively admitted to the 14-bed multidisciplinary PICU of our tertiary academic children's hospital from November 2012 to May 2018 were eligible for enrollment. We limited our analysis to include patients under 18 years and in whom a CBC including RDW was obtained within 24 hours of PICU admission. Patients older than 18 years and with a history of hematopoietic stem cell transplantation and hemato-oncologic disorders were excluded.

### 2.2. Data collection

We retrospectively reviewed the electronic medical records and available PICU database of all enrolled patients and obtained data on demographics such as sex, age, weight, height, underlying diseases, reasons for PICU admission, duration of PICU stay, length of hospital stay, and PICU mortality. We also collected data on the use of vasoactive-inotropic drugs, mechanical ventilator (MV) support, laboratory tests, including routine CBC with RDW, chemistry, C-reactive protein (CRP) level, serum lactate level, and B-type natriuretic peptide (BNP) level. We evaluated the presence of anemia, which was defined according to the diagnostic cutoff values with respect to age and sex suggested by the World Health Organization (WHO). For evaluation of the severity of illness and organ dysfunction, the PRISM-III, pSOFA, PELOD-2, and pMODS scores were calculated using the worst documented values within the first 24 hours of admission to the PICU.

### 2.3. Primary exposure and outcomes

Our primary exposure of interest was RDW, which was obtained as a component of CBC within 24 hours of PICU admission. According to this RDW value, we apportioned the included patients into 3 groups (Group 1:  $\leq 14.5\%$ ; Group 2:  $14.5\%–16.5\%$ ; and Group 3:  $>16.5\%$ ).

Our primary outcome was PICU mortality, which was defined as death during PICU stay. To evaluate the relationship between RDW and PICU mortality, we first performed a general descriptive analysis by comparing groups, and then, we performed univariate logistic regression analysis for all variables and an adjusted multivariate logistic regression analysis. In addition, we evaluated the performance of predicting PICU mortality using areas under the receiver-operating characteristic (AUROC) curves.

### 2.4. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS version 21.0 for Windows; SPSS Inc, Chicago, IL). Descriptive statistics were performed for patients with each group classified according to RDW values and mortality (survivors and non-survivors). Continuous data are expressed as mean  $\pm$  standard deviation or median and interquartile range (IQR), as appropriate. Categorical variables are expressed as number and percentages.

We used the  $\chi^2$  or 2-tailed Fisher exact test to compare qualitative variables and Student *t* test to compare continuous quantitative categorical variables between 2 groups. We performed trend analysis for the 2 variables using a linear-by-linear association test. For the 3 group comparison, we used 1-way analysis of variance. Risk factors for PICU mortality were evaluated using univariate and multivariate logistic regression analyses. The multivariate logistic regression analysis with backward elimination was conducted using variables yielding *P* values  $<.05$  in the univariate analysis to identify independent variables associated with PICU mortality. Confounding factors were entered into the multivariate logistic regression analysis for adjustment. Model fits were assessed using the Hosmer–Lemeshow goodness-of-fit test. A nonsignificant value ( $P > .05$ ) for the Hosmer–Lemeshow goodness-of-fit test suggested the absence of a biased fit. Results are expressed as the adjusted odds ratios (OR) and respective 95% confidence intervals (CIs).

Given the rarity of data on the relationship between RDW and PICU mortality, a realistic a priori sample size calculation was not feasible. Instead, we performed a post hoc power analysis to assess the likelihood of type II error and explored a range of OR that can be detectable with our study sample size.

The usefulness and discrimination capacity of the models for predicting PICU mortality were evaluated by determining the AUROC curves with a 95% CI. To evaluate whether RDW provided additional prognostic information to improve the performance for predicting PICU mortality or not, the integrated discrimination improvement index (IDI) and category-free net reclassification index (cNRI) were calculated using the method proposed by Pencina et al,<sup>[28]</sup> which was implemented in the R package PredictABEL (Suman Kundu, Yurii S. Aulchenko, A. Cecile J.W. Janssens). For all analyses, variables with a 2-sided *P* value  $<.05$  were considered statistically significant.

## 3. Results

### 3.1. Study population

A total of 960 critically ill pediatric patients were included (Fig. 1). There were 495 boys and 465 girls; the median age and body weight of 15.5 (IQR, 4.8–54.5) months and 8.5 (IQR, 5.0–16.0) kg, respectively. The mean RDW was  $15.6\% \pm 3.3\%$ . The overall PICU mortality was 8.8% (Table 1).

On comparison of the 3 groups categorized based on RDW, the highest RDW group (Group 3) showed a lower hemoglobin (Hgb) and platelet (plt) count and higher total bilirubin, BNP, and severity of illness and organ failure scores, including PRISM-III, pSOFA, PELOD-2, and pMODS scores. The proportions of patients requiring vasoactive-inotropic drugs and MV support and nonsurvivors was higher in Group 3 than in the other 2 groups, which showed a statistically significant increasing tendency in the linear-by-linear association test ( $P < .001$ ,  $P = .009$ , and  $P < .001$ , respectively).

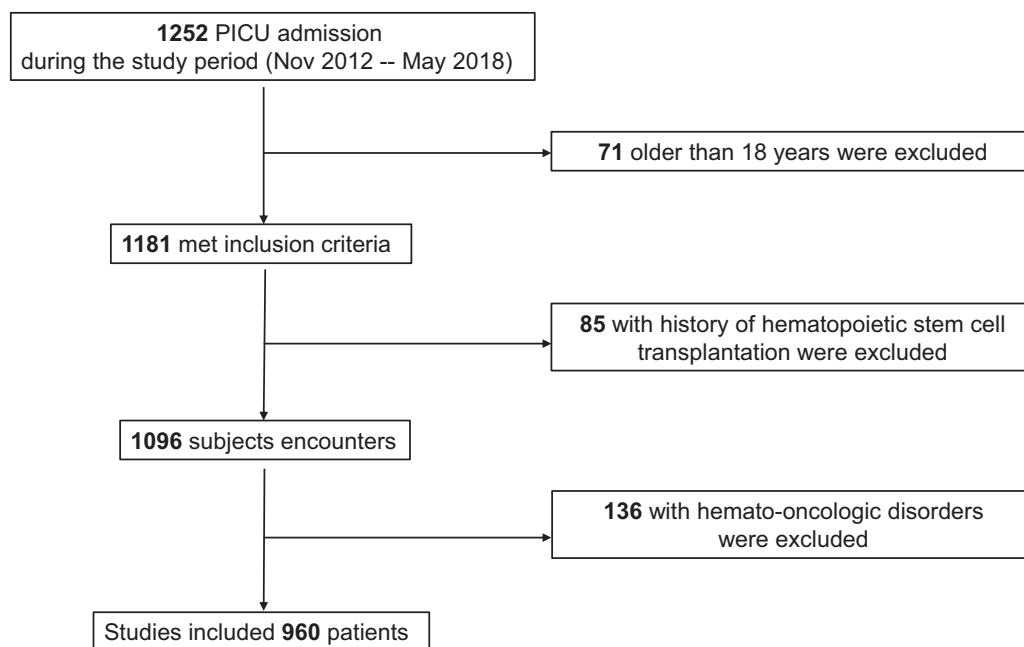


Figure 1. Flow diagram for patient inclusion and exclusion.

### 3.2. Comparison between survivors and non-survivors

There were significant differences between survivors and non-survivors. Nonsurvivors required more vasoactive-inotropic drugs and MV support. They showed a lower plt count, higher Hg, RDW, and severity of illness and organ failure scores (PRISM-III, pSOFA, PELOD-2, and pMODS scores) than survivors ( $P < .05$ ) (Table 2).

### 3.3. Evaluation of the association between RDW and PICU mortality

The univariate logistic regression analysis revealed that the requirement for MV support, use of vasoactive-inotropic drugs, Hg, white blood cell count, plt count, RDW, and severity of illness and organ failure scores, including PRISM-III, pSOFA, PELOD-2, pMODS scores, were significantly associated with PICU mortality. The multivariate analysis adjusted for age, sex, and CRP revealed that the PELOD-2 score, Hg, and elevated RDW ( $>14.5\%$ ) were independent risk factors for PICU mortality (Table 3).

Power analysis was conducted based on the previous study in which the estimated PICU mortality was 11% and 20% in the lower and higher RDW groups (RDW:  $\leq 15.7$  vs  $>15.7\%$  OR = 2.0), respectively.<sup>[29]</sup> Considering that the considered cutoff value is 14.5%, we investigated a minimum detectable OR. The sample size used in our analysis ( $n=960$ ) can detect a minimum of OR = 1.34 with at least 80% power.

### 3.4. Evaluation of the usefulness of RDW as a prognostic factor

Discrimination capacity of PELOD-2 for predicting PICU mortality, which was assessed and determined using AUROC, was 0.803 (95% CI 0.751–0.855). Adding the RDW slightly improved the performance (AUROC 0.821, 95% CI 0.773–0.868). In terms of cNRI, the performance of RDW added model

was significantly better (cNRI 0.357, 95% CI 0.153–0.562,  $P = .001$ ). However, IDI failed to show a significant improvement in discrimination (IDI: 0.008 [95% CI 0.004–0.021],  $P = .196$ ) (Fig. 2).

## 4. Discussion

This study showed that compared with the other 2 groups categorized based on RDW, the higher RDW group was associated with higher PICU mortality and other worse clinical outcomes, such as more requirements of vasoactive-inotropic drugs, MV support, and higher severity of illness and organ failure scores. Furthermore, adding RDW to the PELOD-2 score significantly improved the performance for PICU mortality prediction.

Although several previous studies reported an association of RDW with various clinical parameters in adults, there have only been a few studies that included children. Recently, it was shown that a higher RDW at admission was associated with a higher pediatric index of mortality (PIM) 2 score, higher need for MV support, lower 28-day ventilator-free days, and higher hospital mortality.<sup>[23,30]</sup> However, to the best of our knowledge, this is the first study to extensively evaluate the associations between RDW and various clinical parameters and outcomes, including the use of vasoactive-inotropic drugs, MV support, and several severity scores, in critically ill pediatric patients. As RDW is a simple and routinely reported measurement without additional effort or costs, it is advantageous as a prognostic factor. Furthermore, although it has been controversial whether or not adding RDW improves the discrimination and performance for outcome prediction of some previously used scores or models, this study showed a significant improvement in the performance of prediction of PICU mortality assessed using the cNRI test,<sup>[7,13,30,31]</sup> which could prove its validity.

However, despite several reports on the associations between RDW and various clinical conditions, the exact pathophysiologic

**Table 1**  
**Comparison of variables between three groups in the study cohort.**

Variables	Total (n=960)	RDW (%)			P
		Group 1 (≤14.5) (n=434)	Group 2 (14.5–16.5) (n=230)	Group 3 (> 16.5) (n=296)	
Sex (M:F)	495: 465	222: 212	124: 106	149: 147	.699
Age, mo, median (IQR)	15.52 (4.8–54.5)	22.22 (6.09–77.72)	10.37 (2.69–29.50)	13.27 (4.44–40.73)	<.001
Weight, kg, median (IQR)	8.5 (5.0–16.0)	10.25 (5.7–20.20)	7.02 (4.15–11)	7.75 (4.5–13.23)	<.001
Height, cm, median (IQR)	72.25 (59.0–101.8)	81.25 (62–116)	66.75 (55.5–87)	68 (58–94.9)	<.001
Duration of PICU stay, days, median (IQR)	8 (4–18)	7 (4–17)	8 (4–20)	9.5 (5–20)	.172
Length of hospital day, days, median (IQR)	29 (15–57)	23 (12–47.75)	31 (16–55)	39 (20.5–80.5)	<.001
Mortality, n (%)	84 (8.8)	24 (5.5)	21 (9.1)	39 (13.2)	.002
Underlying disease, n (%)					<.001
Cardiac	323 (33.6)	109 (25.1)	93 (40.4)	121 (40.9)	
Respiratory	137 (14.3)	75 (17.3)	28 (12.2)	34 (11.5)	
Neurological	154 (16)	109 (25.1)	23 (10)	22 (7.4)	
Gastrointestinal	162 (16.9)	48 (11.1)	40 (17.4)	74 (25)	
Endocrinology	72 (7.5)	37 (8.5)	20 (8.7)	15 (5.1)	
Nephrology	57 (5.9)	27 (6.2)	16 (7)	14 (4.7)	
None	55 (5.7)	29 (6.7)	10 (4.3)	16 (5.4)	
Reason for PICU admission, n (%)					<.001
Cardiac	172 (17.9)	68 (15.7)	46 (20)	58 (19.6)	
Respiratory	409 (42.6)	201 (46.3)	90 (39.1)	118 (39.9)	
Neurological	77 (8)	50 (11.5)	14 (6.1)	13 (4.4)	
Gastrointestinal	150 (15.6)	46 (10.6)	39 (17)	65 (22)	
Endocrinology	21 (2.2)	7 (1.6)	9 (3.9)	(1.7)	
Nephrology	51 (5.3)	28 (6.5)	12 (5.2)	11 (3.7)	
Shock	75 (7.8)	31 (7.1)	18 (7.8)	26 (8.8)	
Others	5 (0.5)	3 (0.7)	2 (0.9)	0	
Use of mechanical ventilation, n (%)	554 (57.7)	235 (54.1)	129 (56.1)	190 (64.2)	.022
Use of vasoactive drugs, n (%)	478 (49.8)	174 (40.1)	118 (51.3)	186 (62.8)	<.001
Diagnosis of anemia, n (%)	673 (70.1)	269 (62.0)	173 (75.2)	231 (78.0)	<.001
WBC ( $\times 10^3$ cells/ $\mu$ L)	13,743.30 $\pm$ 17,065.97	13,668.89 $\pm$ 9696.61	12,247.00 $\pm$ 7758.73	15,015.07 $\pm$ 27,544.25	.181
Hg, g/dL	10.66 $\pm$ 2.48	11.08 $\pm$ 2.26	10.44 $\pm$ 2.58	10.19 $\pm$ 2.62	<.001
Platelet ( $\times 10^3$ cells/ $\mu$ L)	278.60 $\pm$ 156.31	288.04 $\pm$ 151.16	287.58 $\pm$ 157.65	257.77 $\pm$ 161.15	.022
RDW (%)	15.60 $\pm$ 3.26	13.26 $\pm$ 0.97	15.29 $\pm$ 0.42	19.27 $\pm$ 3.39	<.001
CRP, mg/dL	2.98 $\pm$ 5.30	3.33 $\pm$ 5.97	2.35 $\pm$ 3.90	2.95 $\pm$ 5.16	.075
Lactate, mmol/L	3.26 $\pm$ 8.08	2.90 $\pm$ 7.07	3.38 $\pm$ 8.55	3.70 $\pm$ 9.07	.426
BNP, pg/mL	950.74 $\pm$ 2311.62	668.27 $\pm$ 1787.46	1099.95 $\pm$ 2307.67	1262.32 $\pm$ 2894.97	.002
AST, IU/L	299.11 $\pm$ 953.25	309.34 $\pm$ 1114.22	219.39 $\pm$ 620.98	345.87 $\pm$ 908.64	.307
ALT, IU/L	200.39 $\pm$ 692.81	217.85 $\pm$ 857.88	170.36 $\pm$ 507.41	198.23 $\pm$ 529.28	.702
Total bilirubin, mg/dL	2.13 $\pm$ 4.63	1.04 $\pm$ 2.61	1.90 $\pm$ 3.12	3.89 $\pm$ 6.87	<.001
PRISM III score	9.04 $\pm$ 7.60	8.37 $\pm$ 7.10	8.40 $\pm$ 8.22	10.53 $\pm$ 7.63	<.001
pSOFA score	5.75 $\pm$ 3.84	5.05 $\pm$ 3.72	5.54 $\pm$ 3.54	6.95 $\pm$ 3.96	<.001
PELOD-II score	10.42 $\pm$ 10.92	10.04 $\pm$ 10.20	9.28 $\pm$ 10.84	11.86 $\pm$ 11.84	.017
pMODS score	4.27 $\pm$ 3.45	3.44 $\pm$ 3.09	4.22 $\pm$ 3.33	5.52 $\pm$ 3.66	<.001

Quantitative clinical characteristics are presented as mean and standard deviation (SD). ALT = alanine aminotransferase, AST = aspartate aminotransferase, BNP = B-type natriuretic peptide, CRP = C-reactive peptide, F = female, Hg = hemoglobin, IQR = interquartile ranges, M = male, n = number, PELOD = pediatric logistic organ dysfunction, PICU = pediatric intensive care unit, p-MODS = pediatric multiple organ dysfunction syndrome, PRISM = pediatric risk of mortality, pSOFA = pediatric sequential organ failure assessment, RDW = red blood cell distribution width, WBC = white blood cell.

mechanisms have not been elucidated. High RDW can result from any disease process that causes ineffective RBC production and releasing more premature RBCs into the blood circulation. This could be attributable to inflammatory and related process. There are growing evidences of the understanding of crosstalk between the inflammatory and hematologic systems. It was well established that inflammatory cytokines interfere with the maturation of RBCs in the bone marrow through multiple mechanisms, such as the inhibition of the production of or response to erythropoietin, which impairs iron metabolism and shortens RBC survival, in turn contributing to high RDW.<sup>[1,11,32,33]</sup> A high RDW has been shown to be associated with elevated inflammatory markers, such as the CRP level, erythrocyte sedimentation rate, and interleukin-6. RDW was

reported to have a strong, graded association with inflammatory biomarkers.<sup>[2]</sup> A proinflammatory cytokine, tumor necrosis factor- $\alpha$ , promotes hypoferrremia and enhances erythrophagocytosis. Other cytokines, such as interleukin-6 and interleukin-1 $\beta$ , have been shown to directly and negatively affect the survival of RBCs in the circulation, promote deformity of the RBC membrane, and suppress erythrocyte maturation. These inflammatory mediators can thus lead to newer and larger reticulocytes entering the peripheral circulation and increasing RDW, indicating that RDW also reflects the severity of inflammation.<sup>[2,13,23,33–35]</sup> Therefore, RDW has been suggested as the final result of multiple pathologic processes associated with inflammation.

Another explanation was oxidative stress. Although the erythrocytes usually have an excellent antioxidant capacity

**Table 2****Comparison of variables between survivors and non-survivor in the study cohort.**

Variables	Nonsurvivor (n = 84)	Survivor (n = 876)	P
Sex (M:F)	46: 38	449: 427	.539
Age, mo, median (IQR)	6.47 (1.4–28.5)	16.67 (5.1–55.2)	.145
Weight, kg, median (IQR)	5.39 (3.4–14.0)	8.64 (5.2–16.3)	.015
Height, cm, median (IQR)	61 (51.0–92.8)	73.35 (60–102)	.009
Duration of PICU stay, days, median (IQR)	15 (5–68)	8 (4–17)	.001
Length of hospital day, days, median (IQR)	28.5 (7.0–89.3)	29 (15–56)	.098
Use of mechanical ventilation, n (%)	74 (88.1)	480 (54.8)	<.001
Use of vasoactive drugs, n (%)	76 (90.5)	402 (45.9)	<.001
Underlying disease, n (%)			<.001
Cardiac	30 (35.7)	293 (33.4)	
Respiratory	9 (10.7)	128 (14.6)	
Neurological	11 (13.1)	143 (16.3)	
Gastrointestinal	6 (7.1)	156 (17.8)	
Endocrinology	7 (8.3)	65 (7.4)	
Nephrology	5 (6.0)	52 (5.9)	
None	16 (19)	39 (4.5)	
Underlying cause, n (%)			<.001
Cardiac	11 (13.1)	161 (18.4)	
Respiratory	34 (40.5)	375 (42.8)	
Neurological	8 (9.5)	69 (7.9)	
Gastrointestinal	5 (6)	145 (16.6)	
Endocrinology	3 (3.6)	18 (2.1)	
Nephrology	3 (3.6)	48 (5.5)	
Shock	20 (23.8)	55 (6.3)	
Others	0	5 (0.6)	
Diagnosis of anemia, n (%)	622 (71.0)	51 (60.7)	.049
WBC ( $\times 10^3$ cells/ $\mu$ L)	20,839.29 $\pm$ 49,303.69	13,062.87 $\pm$ 9128.30	.153
Hg, g/dL	11.29 $\pm$ 3.08	10.60 $\pm$ 2.41	.049
Platelet ( $\times 10^3$ cells/ $\mu$ L)	212.81 $\pm$ 137.95	284.90 $\pm$ 156.59	<.001
RDW (%)	16.53 $\pm$ 3.71	15.51 $\pm$ 3.20	.006
CRP, mg/dL	2.27 $\pm$ 3.79	3.05 $\pm$ 5.42	.198
Lactate, mmol/L	4.55 $\pm$ 4.12	3.15 $\pm$ 8.31	.173
BNP, pg/mL	1296.12 $\pm$ 3145.13	916.62 $\pm$ 2211.98	.159
AST, IU/L	420.78 $\pm$ 984.71	287.56 $\pm$ 949.98	.224
ALT, IU/L	294.00 $\pm$ 797.44	191.38 $\pm$ 681.74	.195
Total bilirubin, mg/dL	2.84 $\pm$ 6.51	2.06 $\pm$ 4.40	.137
PRISM III score	17.71 $\pm$ 11.01	8.21 $\pm$ 6.62	<.001
pSOFA score	9.59 $\pm$ 4.64	5.39 $\pm$ 3.55	<.001
PELOD-II score	23.93 $\pm$ 15.15	9.12 $\pm$ 9.46	<.001
pMODS score	6.92 $\pm$ 4.00	4.01 $\pm$ 3.28	<.001

Quantitative clinical characteristics are presented as mean and standard deviation (SD). ALT = alanine aminotransferase, AST = aspartate aminotransferase, BNP = B-type natriuretic peptide, CRP = C-reactive peptide, F = female, Hg = hemoglobin, IQR = interquartile ranges, M = male, n = number, n = number, PELOD = pediatric logistic organ dysfunction, PICU = pediatric intensive care unit, p-MODS = pediatric multiple organ dysfunction syndrome, PRISM = pediatric risk of mortality, pSOFA = pediatric sequential organ failure assessment, RDW = red blood cell distribution width, WBC = white blood cell.

and serve as the primary “oxidative sink,” they could be prone to oxidative damage.<sup>[36]</sup> Oxidative stress plays a role in RBC homeostasis such as fragility, maturation, and lifespan that reduces RBC survival. It also affects many biological processes, including apoptosis and inflammatory reactions, which could change the size of RBC, consequently, increasing RDW.<sup>[37–40]</sup>

In addition, there were several other suggestions for possible pathophysiology for high RDW, such as poor nutritional status, activation of renin-angiotensin system, and impaired renal function.<sup>[34,41,42]</sup>

As this study included critically ill pediatric patients, all the aforementioned explanations could be applied. However, the exact pathophysiology still largely remains unknown, which requires further large-scale multicenter clinical studies with a specified subgroup analysis.

This study had several strengths. The study included a relatively significant number of critically ill pediatric patients.

Post hoc power analysis demonstrated that the sample size used in our analysis (n = 960) can detect a minimum of OR = 1.34 with at least 80% power. We excluded patients with hemato-oncologic disorders that could affect RDW and reduced potential confounding factors. We extensively evaluated and showed significant associations between RDW and several clinical parameters including the use of vasoactive-inotropic drugs, MV support, and severity scores of illness and organ failure scores (PRISM-III, pSOFA, PELOD-2, and pMODS scores) as well as PICU mortality. These are important parameters in critically ill pediatric patients, which could be helpful in managing these patients. Therefore, we suggested RDW as a promising prognostic marker with advantages of simple measurement, good cost-effectiveness, and being well-correlated with other risk factors for worse clinical outcomes in these patients.

However, this study had several limitations. First, it was a retrospective observational study conducted at a single tertiary

**Table 3**  
**Univariate and Multivariate logistic regression analysis of the pediatric intensive care unit mortality.**

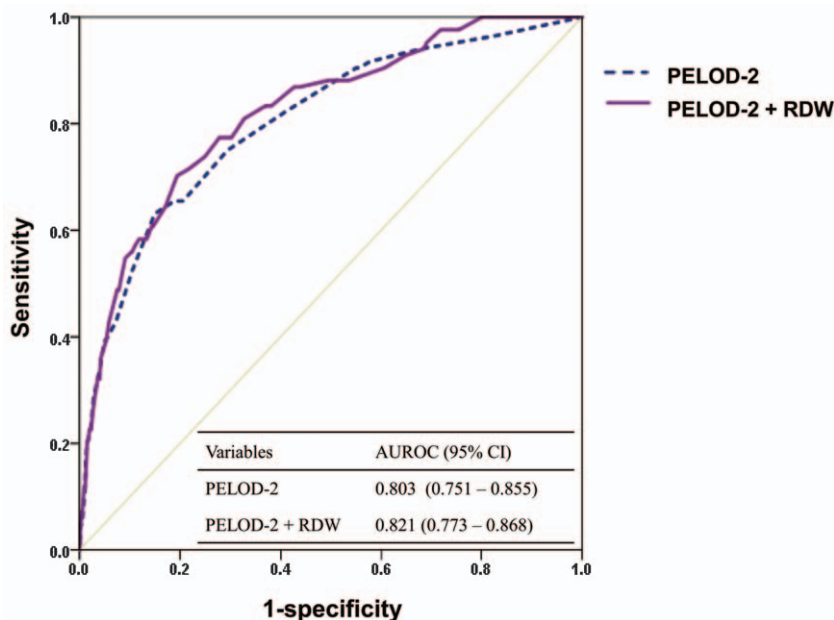
	<i>P</i>	Univariate OR (95% CI)	<i>P</i>	Multivariate* OR (95% CI)
Age, mo	.147	0.997 (0.992–1.001)		
Sex	.539	0.869 (0.554–1.362)		
Use of mechanical ventilation	<.001	6.105 (3.113–11.974)		
Use of vasoactive-inotropic drugs	<.001	11.036 (5.262–23.145)		
Hg (g/dL)	.015	1.114 (1.021–1.216)	.039	1.103 (1.008–1.207)
Elevated RDW (≥14.5%)	.002	2.200 (1.345–3.596)	.002	2.316 (1.348–3.977)
WBC (×10 <sup>3</sup> cells/μL)	.026	1.000 (1.000–1.000)		
Platelet (×10 <sup>3</sup> cells/μL)	<.001	0.996 (0.995–0.998)		
CRP	.202	0.965 (0.914–1.019)		
PRISM III score	<.001	1.134 (1.103–1.165)		
PELOD-2 score	<.001	1.099 (1.078–1.120)	<.001	1.098 (1.077–1.120)
pSOFA score	<.001	1.291 (1.217–1.369)		
pMODS score	<.001	1.239 (1.166–1.317)		

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BNP = B-type natriuretic peptide, CI = confidence incidence, Hg = hemoglobin, OR = odd ratio, PELOD = pediatric logistic organ dysfunction, pMODS = pediatric multiple organ dysfunction, PRISM = pediatric risk of mortality, pSOFA = pediatric sequential organ failure assessment, RDW = red blood cell distribution width, WBC = white blood cell.  
 \* Multivariate model; adjusted for age, sex, and CRP.

academic hospital and only included critically ill pediatric patients who were admitted to the PICU. Thus, there could be some limitations in generalizability of the results to other patients in different settings. Second, there could be other confounders to be adjusted for several potential confounding parameters. Third, we analyzed the RDW measurement only at the time of admission to PICU, which could be insufficient to obtain information of these patients' conditions associated with worse clinical outcomes. Fourth, by considering the effect of anemia and inflammation on RDW, we included Hg and CRP as clinical markers in the multivariate logistic regression analysis. However, we did not collect data on patients' iron status, erythropoietin levels, or other precise inflammatory cytokines, which could provide more helpful information.

**5. Conclusions**

RDW in critically ill children is strongly associated with PICU mortality and poor clinical parameters, including higher severity scores, use of vasoactive-inotropic drugs, and MV support. It was an independent risk factor for PICU mortality with additional effect to improve the performance of PELOD-2 for predicting PICU mortality. Its measurement is simple, inexpensive, and convenient as included in routine CBC; thus, it could be a promising additional prognostic factor in these patients. Further large-scale studies, including clinical, epidemiologic, and molecular biologic studies, are required to identify the exact causative pathophysiologic mechanisms of the association between RDW and worse clinical outcomes.



**Figure 2.** Area under the receiver-operating characteristic curves of the pediatric logistic organ dysfunction-2 (PELOD-2) score and addition of red blood cell distribution width (RDW) to the PELOD-2 score for predicting pediatric intensive care unit (PICU) mortality.

## Author contributions

**Da Hyun Kim:** Investigation, Formal analysis, Writing – Original Draft. **Eun Ju Ha:** Investigation, Formal analysis. **Seong Jong Park:** Conceptualization, Methodology. **Won Kyoung Jhang:** Conceptualization, Methodology, Formal analysis, Writing – Original Draft, Writing – Review & Editing, Supervision.

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