Original Article

Red Cell Distribution Width as a Predictor of Outcome in Cyanotic Congenital Cardiac Surgery

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Abstract

Background: Red blood cell distribution width (RDW) is a vital marker associated with various clinical states. In the present study, we aimed to determine the associations between RDW changes and adverse effects caused by pediatric cardiac surgery.

Materials and Methods: In the present research, we retrospectively analyzed 100 pediatric patients enrolled in this study who were candidates for cardiac surgery. RDW was determined pre-and postoperatively and at the time of discharge from the hospital. Intubation time, duration of intensive care unit (ICU) stay and hospital stay, cardiopulmonary bypass (CPB) time, aortic cross-clamp (ACC) time, vasoactive inotropic score (VIS), and mortality rate were determined as well.

Results: Intubation time, duration of hospital stay, CPB time, ACC time, VIS, and mortality rate were significantly higher in the patients with higher RDW rates.

Conclusion: This study demonstrated that RDW could be used as an essential indicator in predicting both morbidity and mortality caused by pediatric congenital heart surgery.

Keywords: Red Cell Distribution Width, Pediatric Cardiac Surgery

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Please cite this article as:
Baghaei R, Omidi Farziz A, Murodov M, Fani K, Heidarpour A, Hajikarimloo B. Red Cell Distribution Width as a Predictor of Outcome in Cyanotic Congenital Cardiac Surgery. J Cell Mol Anesth. 2022;7(4):229-36. DOI: https://doi.org/10.22037/jcma.v7i4.37386

Introduction

Congenital heart diseases (CHD) are one of the most important causes of mortality and morbidity in children. In patients with this disease, inflammatory markers increase, especially heart failure symptoms. As Interleukins and Tissue necrosis factor (TNF) are released during chronic diseases, bone marrow function and red blood cell formation are consequently impaired, resulting in the elevated Red blood cell distribution width (RDW). Accordingly, this can be used as an indicator of the severity of heart disease (1).

RDW is a quantitative parameter that demonstrates variations in the size of red blood cells and indicates the inflammatory phase in many chronic diseases. Recent studies reported that elevated RDW is associated with an increase in both mortality and morbidity in those who have undergone pediatric cardiac surgery, although the underlying mechanism is unknown (1-3, 6).

During pediatric heart surgery, inflammatory

responses will be induced due to cardiopulmonary bypass (CPB), and its related markers such as RDW will be increased sharply after surgery. This increase is associated with early side effects of surgery (4, 5). In time to establish CPB, the circulating pro-inflammatory mediators bind to receptors of the cerebral vascular-associated cells, increasing the permeability of the blood-brain barrier and brain edema. Also, damage to the alveolar-endothelial barrier leads to pulmonary edema and decreased lung compliance. Inflammatory mediators impair systolic function by exerting a direct inhibitory effect on cardiomyocyte shortening, vasogenic and cytogenic edema decreased ventricular compliance. Finally, the inflammatory response to CPB may affect vascular function. Histamine and bradykinin directly vasodilate venous capacitance and systemic arterial resistance vessels. That leads to compromised systemic venous return and systemic arterial hypotension. Neurohormonal systems and endothelial function regulate systemic vascular tone, which may be adversely affected by the inflammatory response (21).

This study aimed to evaluate the effect of RDW amounts on intensive care unit (ICU) stay, hospital stay, intubation time, aortic cross-clamp (ACC) time, CPB time, and cardiac function in pediatric cardiovascular patients' surgery.

Methods

The children between 6 and 60 months who were scheduled for open-heart surgery with CPB were recruited from Modarres Hospital, a tertiary referral center (May 2017 - June 2020).

Ethics considerations: the written informed consent was obtained from the parents and the Research Ethics Committees, School of Medicine, Shahid Beheshti University of Medical Sciences approved the project (IR.SBMU.MSP.REC1399.371).

One hundred cyanotic children were enrolled in this study. Of them, 54 cases had tetralogy of Fallot, 27 tricuspid atresia, 11 tetralogies of Fallot combined with pulmonary atresia (TF+PA), and eight subjects had double outlet right ventricle (DORV).

Exclusion criteria were a history of infectious disease, fever, thyroid, and other endocrine diseases, as well as preoperative use of inotropic drugs for circulatory support.

For patients enrolled in the study, preoperative blood samples containing hematologic variables such as hemoglobin (Hb), white blood cell (WBC), and RDW were obtained 24 hours before cardiac surgery. Postoperative blood tests were performed once passing 24 hours of the surgery and once at the time of the patient's discharge from the hospital. All these tests were evaluated in one laboratory; the normal range for RDW in that laboratory is between 12 and 14.5%.

After premedication and transfer of the patient to the operating room, complete monitoring and routine preoxygenation were performed. Anesthesia was induced with sevoflurane, fentanyl, and cisatracurium. After the intubation, the lungs were ventilated using intermittent positive pressure ventilation, with a tidal volume of 8 to 10 ml/kg, a respiratory rate of 18-25 breaths/min, and 3-5 cm water of positive end-expiratory pressure (PEEP).

All the children received standardized surgical and CPB management. Surgical procedures were performed under mild hypothermia (30–34 °C). During CPB, hematocrit was maintained at 24% to 28%, and a mixture of oxygen and air was also applied with atrial blood gasometry guidance. The cold blood cardioplegia solution (4°C) was also perfused to provide cardioprotection. The durations of ACC and CPB were recorded. After the completion of surgery and systemic re-warming, the children were transferred to the ICU, where they received standardized postoperative management in terms of the institutional guidelines.

Next, the perioperative RDW levels and hemodynamic variables were determined. The intubation time, duration of ICU stay and hospital stay, CPB time, ACC time, use of inotropic drugs in the ICU based on VIS, and mortality cases were recorded. Vasoactive inotropic score (VIS) is a conventional scale used to evaluate children's inotropic need for cardiovascular support after cardiovascular surgery (8). VIS was measured using the following formula:

VIS = dopamine (mcg/kg/min) + dobutamine (mcg/kg/min) + 100 x epinephrine (mcg/kg/min) + 100 x norepinephrine (mcg/kg/min) + 10 x milrinone (mcg/kg/min) +10,000 x vasopressin (mUnits/kg/min).

All the patients were continuously monitored and managed in ICU. Afterward, they were weaned

from mechanical ventilation when they were alert and hemodynamically stable. They were discharged from ICU after extubation and the discontinuation of all vasoactive-drug infusions.

We compared intubation time, the length of ICU stays, hospital stay, VIS in the first 24h, CPB time, ACC time, ejection fraction (EF), and mortality rate with RDW levels. Descriptive statistics were calculated for continuous variables, including means, medians, standard deviations, and ranges. The correlation between quantitative data was tested using a T-test. A P-value of < .05 was considered statistically significant. Ethical approval was also obtained for this study from Shahid Beheshti University of Medical Sciences.

Results

One hundred cyanotic patients were evaluated during this study period. The patients consisted of 55 men and 45 women. In this study, 11 patients died. The demographic characteristics and clinical data of the cases are shown in table 1. Amounts of RDW1 (preoperative), RDW2 (postoperative), and RDW3 (at hospital discharge time) were 13.2 ± 0.69, 14.6 ± 0.58 and 13.9 ± 0.5 respectively.

Based on this study, regardless of the RDW changes from before the operation until the time of discharge from the hospital, it was found that higher rates of RDW before surgery in cyanotic patients are associated with longer intubation time (P=0.001) and hospitalization stay (P-value=0.01). As shown in Table 2, there was a significant relationship between RDW before surgery and VIS, CPB time, and ACC time in cyanotic patients (P=0.01, 0.004, and 0.029, respectively). No significant relationships were found between the RDW before surgery and ICU stay (P=0.76). There was also a significant relationship between RDW 24 hours after surgery and intubation time (P=0.01), VIS, CPB time, and ACC time (Fig. 1), and RDW at the hospital discharge time was only related to VIS (P=0.03). There is no relationship with other variables.

Overall, in this study, ICU stay time was not correlated with RDW values before surgery, 24 hours after surgery, or at the time of discharge. (P=0.76, 0.09, and 0.97 respectively). Also, Hospital stays time is not meaningfully related to RDW on the day after surgery and hospital discharge time. Still, only RDW before surgery (P=0.06, 0.6, and 0.01, respectively) (Fig. 2). Finally, mortality and arrhythmia were significantly associated with RDW before and 24 hours after surgery.

Discussion

RDW is a quantitive measurement of variations in the size of red blood cells called anisocytosis. Recent studies on RDW have reported its relationship with mortality and morbidity caused by cardiovascular surgery. RDW has a more substantial predictability potential compared to other laboratory parameters (1-3, 11).

This study evaluated RDW as a prognostic factor in pediatric heart surgery. Our study selected 100 cyanotic patients (median age of 21.45 months), all having undergone congenital heart surgery.

Extensive studies have shown that the level of RDW and differentiating the cause of anemia can be used as a predictor parameter of cardiac dysfunction, mortality, and complications in patients with cardiovascular diseases, including heart failure, peripheral vasculopathy, myocardial infarction, and angina pectoris. The underlying mechanism of this correlation is still unclear, but some hypotheses exist, such as increased inflammatory and oxidative stress (11, 18, 19).

Yousefi et al. demonstrated that RDW increases during hospitalization after myocardial infarction, which is associated with a poor prognosis. Therefore, patients with increased RDW amounts should be monitored more closely to achieve a better outcome (9).

According to the study by Mawlana et al., although the interaction between heart failure and the hematological system is not well understood, RDW is related to left ventricular function. Their results showed that the higher the rate of RDW, the more significant the decline in heart function (2).

People with higher RDW levels were at higher risk for peripheral artery disease (PAD). The association between RDW and PAD is independent of sex, diabetes, hypertension, and other factors. So RDW

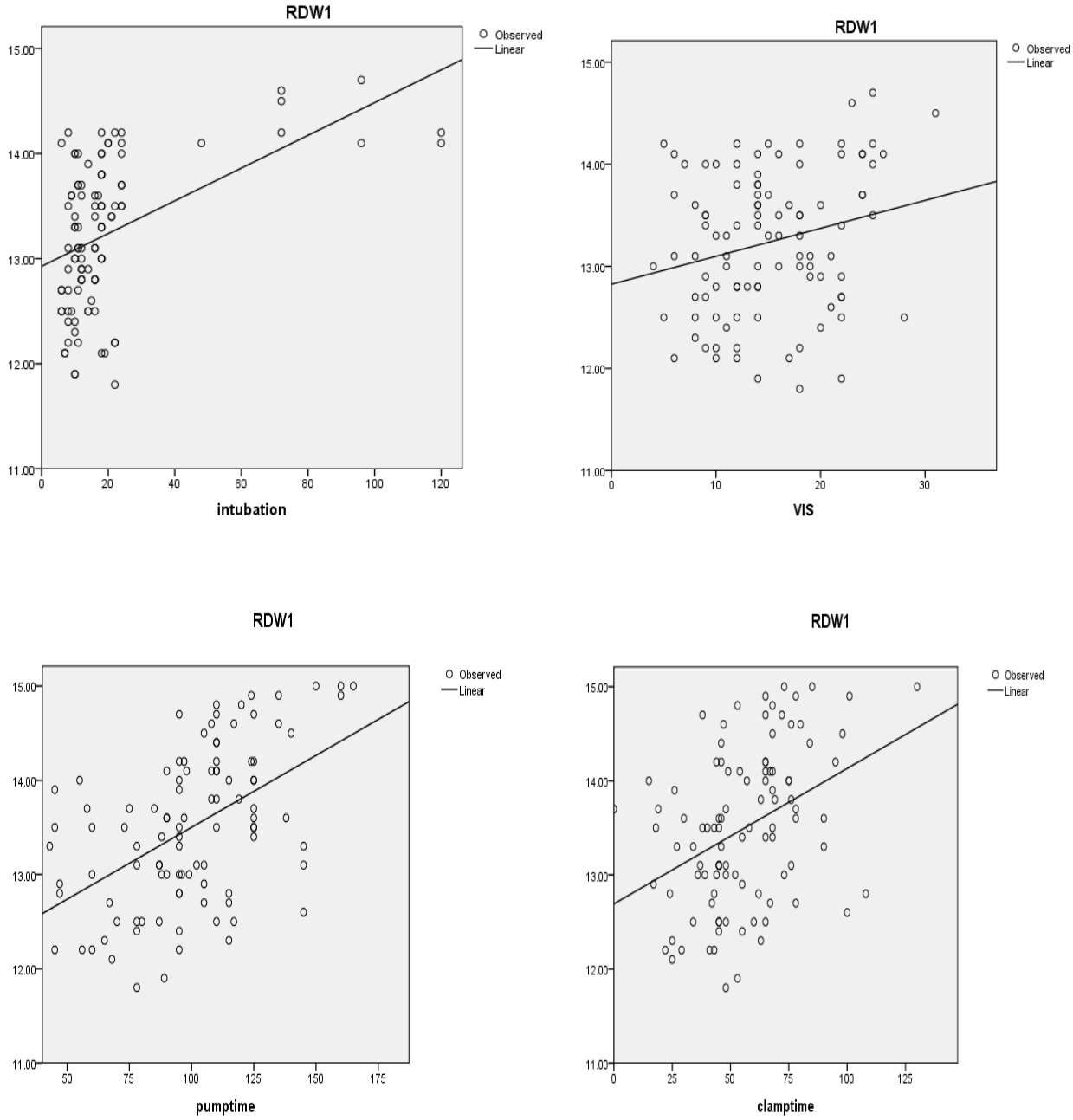

Figure 1. Relationship between RDW1 and intubation time, VIS, CPB time and ACC time.

can be used as a screening criterion for those at risk of developing PAD (14).

Poludasu S. et al., Felker G. et al., and Allen L.et al. found in patients with coronary artery disease (CAD) and those with heart failure, RDW has been revealed to be an independent predictor of mortality and morbidity. Patients with higher RDW levels risk developing diabetes mellitus, LV dysfunction, and ESRD. They also demonstrated that the predictability of RDW in outcome correlates with hemoglobin levels. In patients with normal hemoglobin, RDW can be used as a prognostic factor, but in those with low hemoglobin levels, RDW is not useful (12, 15, 16).

In patients with CAD, people with diabetes have higher morbidity and mortality rates. In diabetic patients, RDW has a relationship with microvascular and macrovascular complications. Those with higher RDW values are at a greater risk for diabetic

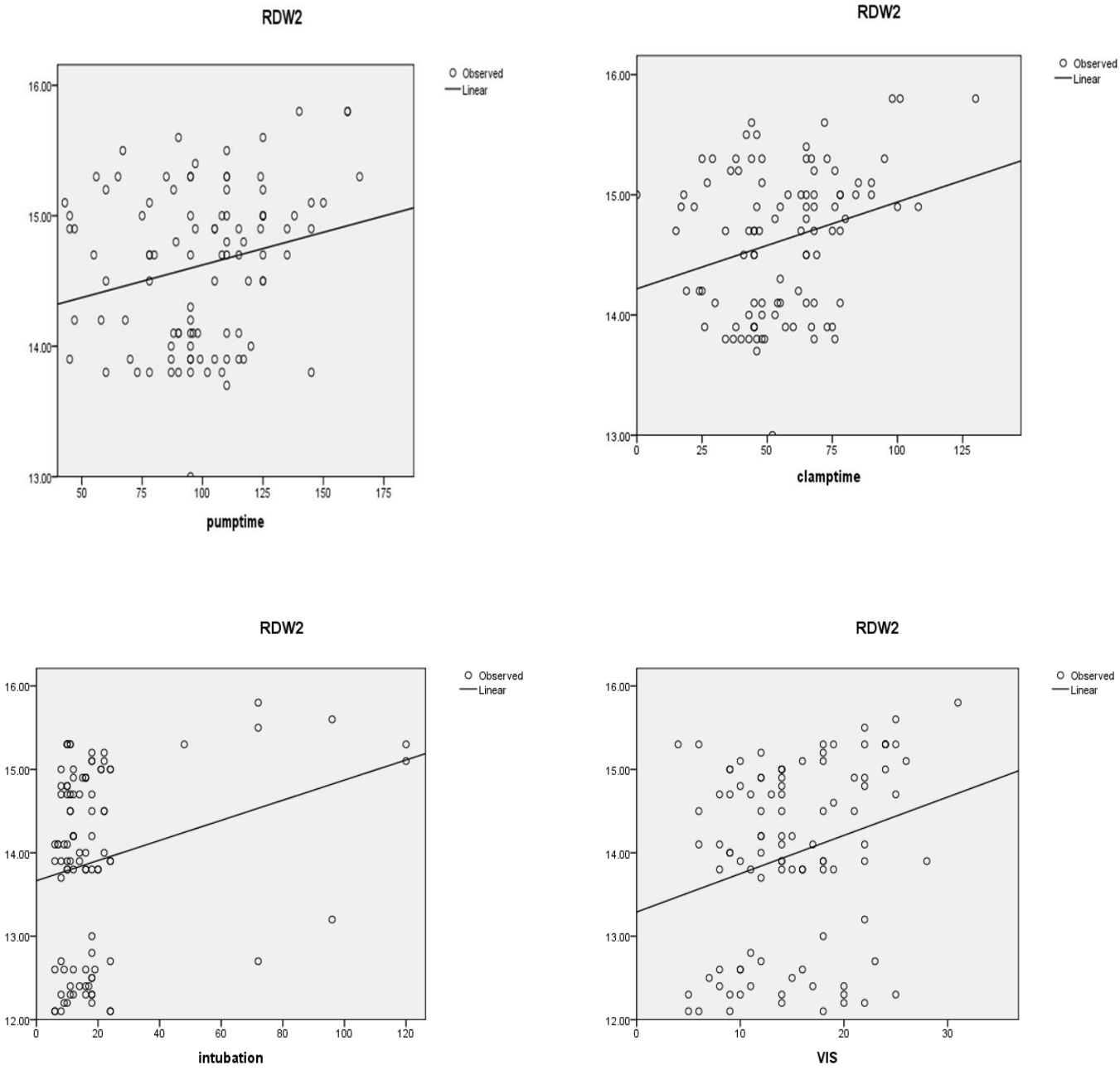

Figure 2. Relationship between RDW2 and intubation time, VIS, CPB time and ACC time.

nephropathy and cardiovascular events. Increased RDW is related to increased all-cause mortality in diabetic patients after elective PCI. Therefore, RDW can be used in daily practice to evaluate patients' oxidative stress and inflammatory condition after elective PCI (17).

RDW and Framingham risk score (FRS) is higher in patients with CAD. FRS is a tool for evaluating the risk of CAD over ten years. Higher levels of RDW were associated with increased FRS. Therefore, RDW is associated with an increased risk of heart events in patients with CAD (20).

CABG can play an essential role in the treatment of patients with CAD. In this procedure, we can use arterial or saphenous vein grafts. Degeneration and occlusion of saphenous grafts are major concerns, and these complications are caused by atherosclerosis, especially after one year of the CABG. Recent studies showed that RDW is related to the atherosclerosis process, diabetic nephropathy, and carotid plaque development in patients. It was found that the values of RDW were higher in those with saphenous vein graft disease (SVGD) than in patients with standard saphenous venous grafts; thus, RDW can be used as a predictor for SVGD (13).

In a recent study by Richard Warwick, RDW is a predictor of mortality and prolongation of hospitalization in patients who have undergone CABG. They demonstrated that besides other prognostic factors such as age, diabetes, peripheral vascular disease, and ejection fraction, RDW is a determinant of in-hospital mortality and long-term survival after CABG (7).

Table 1: Baseline clinical characteristics and data.

Variable	
Gender (f/m)	55/45
Age (month)	21.45 ± 13.01
Weight (kg)	10.92 ± 2.3
Height (cm)	67 ± 13
Intubation time (hour)	20 ± 2.15
ICU stay (hour)	86 ± 21
Hospital stay(day)	6.5 ± 1.6
CPB time (min)	99 ± 27
ACC Time (min)	56 ± 22
VIS	15.13±5.9
EF (%)	45 ± 10
Mortality (expired/alive)	11 / 89

It seems that higher pump time and clamp in patients with higher RDW levels may be since RDW itself is an inflammatory agent that exacerbates inflammation during CPB. Seth HS et al. demonstrated that the increased RDW was significantly accompanied by a higher risk of severe inflammatory response after CPB. Thus, RDW could be a useful test to predict severe inflammatory responses in patients undergoing cardiac surgery with CPB. Therefore, more sophisticated attention to its values could prevent postoperative morbidity and mortality (10).

Inflammation might play a role in cytokines-induced changes in the red cell membrane, leading to an increased RDW. Erythrocyte malformation and increased RDW may be caused by oxidative stress, inflammation, and increased cholesterol levels in the erythrocyte membrane. Inflammation or oxidative stress may cause increased RDW by impairing iron metabolism, inhibiting the production of or response to erythropoietin, and shortening red blood cell survival. RBCs and PLTs are sensitive to the presence of pro-inflammatory cytokines like interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-1β (IL-1β). These and other cytokines could simultaneously affect circulating RBCs and PLTs during inflammation and are closely related to cardiovascular and vascular risks.

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Table 2: Relationship between RDW and variables.

variable	Intubation Time (hour)	ICU stay (hour)	Hospital stay (day)	VIS	CPB time (minute)	ACC time (minute)	EF (%)	mortality	arrhythmia
RDW1(before surgery)	P=0.001	P=0.76	P=0.01	P=0.01	P=0.004	P=0.029	P=0.001	P=0.01	P=0.01
RDW2(24 hours after surgery)	P=0.001	P=0.09	P=0.06	P=0.024	P=0.04	P=0.015	P=0.006	P=0.01	P=0.01
RDW3(discharge from hospital)	P=0.2	P=0.97	P=0.6	P=0.03	P=0.98	P=0.68	P=0.9		P=0.2

simultaneously affect circulating erythrocytes and PLTs during inflammation and are closely related to cardiovascular and vascular risks (22-26).

There are not as many studies related to RDW and adult cardiac surgery as in pediatric cardiac surgery. According to Polat, et al. study, RDW is important in predicting mortality and morbidity after heart surgery in children. It can be used in the preoperative stage to predict the outcome of the surgery and also in a postoperative state as a follow-up marker of a patient's condition (1).

In a recent study by Massin, 688 children with CHD with a mean age of 12 months were evaluated. As a result, the RDW was significantly higher in patients who died during the postoperative hospital stay (mean, 18.34 ± 4.69 vs. 16.12 ± 2.84; p = 0.004). It was also found that the risk of postoperative death was five times higher in patients with an RDW of 16% or more. Accordingly, RDW is an inexpensive and accessible test for predicting mortality and morbidity in children after heart surgery (3).

Our study showed a significant correlation between pre and postoperative RDW levels, with intubation time and hospital stay, CPB time, ACC time, VIS, and complications such as mortality and arrhythmia. These findings indicate that higher RDW levels are associated with longer intubation time, hospital stay, duration of the CPB and ACC, and the need for inotropes (VIS).

We evaluated patients with cyanotic heart disease in a particular range of age (between 6 and 60 months). Cyanotic congenital heart diseases are among the most complex heart lesions with significant morbidity and mortality. On the other hand, we choose this age range because it is our country's usual age for corrective surgery.

Although more emphasis was placed on mortality and other related complications in previous studies, in this study, intraoperative and postoperative items such as longer pump time, clamp time, and VIS were investigated. Meanwhile, we suggest that RDW is an important marker for predicting mortality, morbidity, and perioperative complications such as pump time, clamp time, and VIS. The results of our study related to patients' outcomes follow previous studies.

The most important shortcoming of this study was the limited time and sample size.

Conclusion

The elevated RDW was associated with higher mortality and morbidity rates. As it is inexpensive and easy to measure, we suggest monitoring RDW before and after pediatric cardiac surgery as an inflammatory factor to predict complications.

Acknowledgment

None.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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