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Red Cell Distribution Width to Platelet Count Ratio Reference Intervals in Premature Infants Beyond the First Week of Life

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ABSTRACT

Objective: Red cell distribution width (RDW) is a parameter of complete blood count (CBC). The RDW to platelet count ratio (RPR) is a new index that has been shown to reflect the severity of inflammation. We aim to determine the reference interval (RI) of RPR for premature newborns. **Study design:** The medical records of preterm infants who were followed up between January 2016 and December 2018 were reviewed. CBC levels were measured in 144 infants at <72 hours of age. **Results:** CBCs of infants (gestational age from 28 to 35weeks) had a RI of 0.038–0.126 for the RPR. The RI for RPR in infants with a gestational age of 32–35weeks was 0.042–0.129; and the RI for infants at 28–31weeks was 0.022–0.121. **Conclusion:** Establishment of RI for RPR in premature infants will allow clinical correlation of RPR alterations in this population.

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KEYWORDS
Automated cell counter; platelet; red blood cell; red cell distribution width; premature

Introduction

The complete blood count (CBC) test provides information about the number, shape and structural features of blood cells, and is widely used in the diagnosis, follow-up and screening of many diseases [1].

Red cell distribution width (RDW) is an automatically measured CBC parameter that reflects the degree of erythrocyte heterogeneity. Traditionally, RDW has been used to distinguish the causes of anemia. Recently, RDW has been shown to be associated with mortality and morbidity in critically ill children, regardless of disease severity [2]. RDW values are automatically calculated and no additional blood samples are required if a CBC is requested. The RDW can be a useful tool for evaluating the medical condition of newborns, especially preterm infants [1,2].

The RDW to platelet count ratio (RPR) is a novel index that has been shown to reflect the severity of inflammation in adults [3,4]. An elevated RPR is associated with

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increased inflammation [3]. It has recently been shown that RDW and RPR can contribute to the differential diagnosis of some diseases in children [5–9]. There are few studies showing the diagnostic value of RDW and RPR in preterm infants [5,10,11]. The range of values obtained by certain statistical methods from the distribution of test results according to reference individuals that separate healthy from diseased individuals is the reference interval (RI) [12]. RI values for CBC vary with age, gender, ethnicity, geographic location, and sociocultural differences, and therefore each parameter of the CBC should be evaluated using population-specific RIs [13,14].

The reference individuals for measurement of the values can be selected by direct, and indirect methods. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommends the direct selection method to determine the RIs. There are two types of direct selection methods: the priori (prospective) approach and the posteriori (retrospective) approach. In the priori approach, individuals are assessed first using inclusion criteria and those who are suitable are then tested. It is unethical to collect blood from healthy preterm infants for the sole purpose of determining RIs. Posterior approach requires a well-organized database. In this approach, clinical data is collected after analysis, and those values from individuals meeting clinical inclusion criteria are used to best approximate the true reference range [15].

In this study, we aimed to determine the RIs of RDW and RPR with direct posterior method for premature newborns.

Materials and methods

This retrospective study was approved by the Ethical Committee (2011-KAEK-25 2022/03-16). The medical files of premature neonates referred to our hospital's retinopathy of prematurity (ROP) outpatient clinic between January 2016 and December 2018 were retrospectively reviewed. The informed consent was waived because of the study design.

Premature infants who were normal on physical examination and had no maternal or intrapartum complications were defined as normal premature babies. Premature infants with any medical conditions such as infection, twin births, congenital malformations, retinopathy of prematurity (ROP), hematological abnormalities, extracorporeal membrane oxygenation, Rh and/or ABO incompatibility, previous transfusions, and those with sepsis were excluded from the study.

CBC samples which were drawn within 72 hours of birth into a pediatric blood collection tube with EDTA (Vacutainer; BD, Franklin Lakes, NJ) were eligible for inclusion in the study. Routine CBC test results were obtained with LH 780 Analyzers (Beckman Coulter Inc., Fullerton, CA) within 2 hours of sample collection and retrieved from the hospital data system. Internal and external quality control (KBUDEK External quality control program, Istanbul, Turkey) results of the devices were within acceptable limits during study period.

Statistics

MedCalc Statistical Software version 20.116 (MedCalc Software, Ostend, Belgium) was used to determine the reference interval between lower and upper levels. The

Box-and-Whisker plots were used to show the data distribution. The D'agostino-Pearson test was used to test normality. Outliers are detected using the Dixon–Reed test. Box-Cox transformation was performed then back-transformed to normalize the distribution of skewed data. The 95% confidence intervals of the lower and upper limits, as 2.5^{th} and 97.5^{th} percentiles, were calculated by the non-parametric percentile method according to the C28-A3 standard [15,16]. Premature infants were partitioned into two broad groups; 28–31 weeks (n = 65) and 32–35 (n = 79) weeks of gestation. The robust method was used to calculate the RIs for the partitions.

Results

Hemogram findings of 144 babies born at 28–35 weeks of age who met the study criteria from a total of 1045 premature infants were evaluated (Table 1). Gestational age at birth was 31.6 ± 1.9 (weeks; mean ± S.D); The study group consisted of 51.4% male and 49.6% female infants. Birth weight of the babies was 1740 ± 427 (g mean ± S.D). After excluiding outliers (n = 9); we found the lower reference limit of 0.038 and the upper reference limit of 0.126 for RPR for preterm newborns (Fig. 1). The RI for RPR in infants with a gestational age from 32 to 35 weeks was 0.042−0.129; and the RI for infants with a gestational age from 28 to 31 weeks was 0.022–0.121 (Fig. 2).

Discussion

The lower reference limit for RDW in premature infants is 14.2% and the upper reference limit is 21.8%. Similarly; Christensen found the RI of late preterm neonates between 15.5% and 23% [17]. The adult reference range for RDW is between 11% and 16% [18]. Prematurity is associated with ineffective erythropoiesis, leading to increased RDW, indicating variation in the size of circulating erythrocytes. For this reason, the availability of reliable RI is very important for the correct assessment, monitoring and diagnosis of preterm patient outcomes [19]. RDW value has a prognostic role in neonatal sepsis in infants diagnosed with patent ductus arteriosus [10,20].

Table 1. Reference range of complete blood cell parameters.

Parameter	Lowest value	Highest value	Median	Std Dev	95% Reference interval
RBC (×10^6/microL)	3.0	6.3	4.82	0.6	3.61–5.98
Hb (g/dL)	10.3	22.3	17.7	2.1	12.0–21.7
HCT (%)	30.3	66.0	52.4	6.5	39.2–64.8
MCH(picograms)	29.7	42.0	36.3	2.0	32.4–40.1
MCHC(g/dL)	30.5	37.7	33.2	1.2	30.8–35.8
MCV (fL)	87.3	122.1	109.4	5.6	97.8–120.0
RDW (%)	13.3	24.6	17.8	1.9	14.2–21.8
PLT (×10^3/microL)	105.0	462.0	255.0	70.8	119.9–397.8
MPV (fL)	5.1	10.9	7.7	0.9	5.8–10.9
PDW (%)	10.9	21.1	17.4	2.0	10.9–21.0
RPR	0.030	0.158	0.070	0.027	0.038–0.126

RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RDW, red cell distribution width; PLT, platelet; MPV, mean platelet volume; PDW, platelet distribution width; RPR, red cell distribution width to platelet.

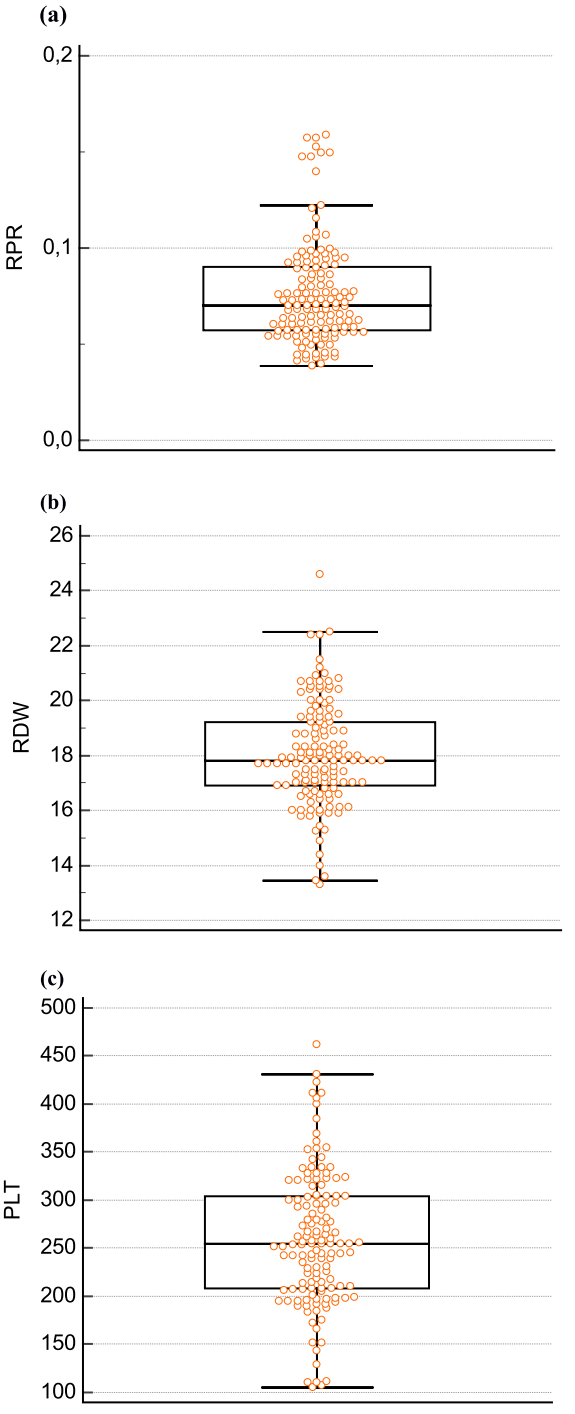

Figure 1. The range of values for red cell distribution width to platelet count ratio (a), red cell distribution width (%) (b), and platelet ($\times 10^3$/microL) (c) for neonates on the first week after birth among newborns 28–35 weeks gestation.
RPR: red cell distribution width to platelet count ratio; RDW: red cell distribution width; PLT: platelet
For each box-and-whisker plot, the central box covers the values from the lower to upper quartile (25 to 75 percentile). The middle line represents the median.

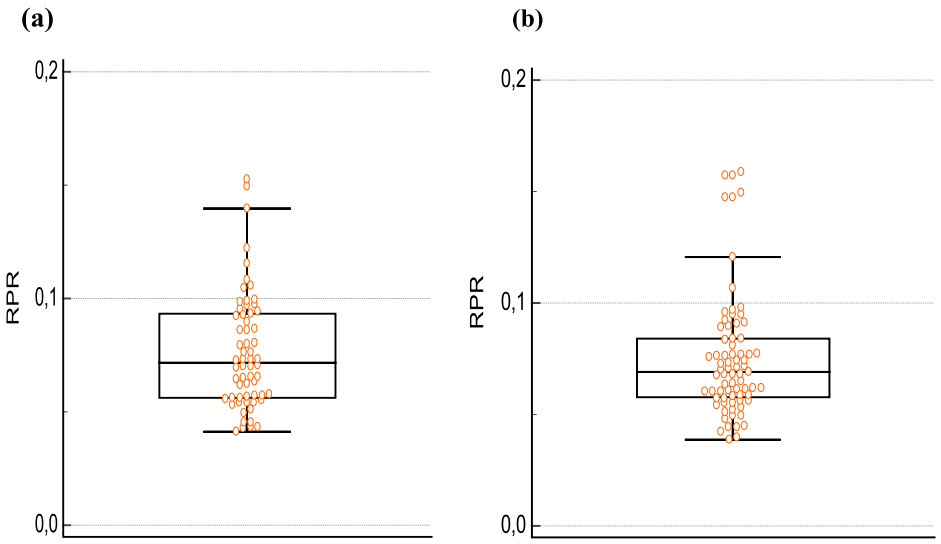

Figure 2. The range of values for red cell distribution width to platelet count ratio for neonates on the first week after birth among newborns 28–31 weeks gestation (n = 65) (a), among newborns 32–35 weeks gestation (n = 79) (b).
RPR: red cell distribution width to platelet count ratio.
For each box-and-whisker plot, the central box covers the values from the lower to upper quartile (25 to 75 percentile). The middle line represents the median.

We found the lower reference limit of 0.038 and the upper reference limit of 0.126 for RPR for preterm newborns. Imbalances between RDW and PLT counts serve as important components of hematologic pathophysiology in the course of the disease. RPR, a new risk marker, can be used in the diagnosis of early neonatal sepsis and may be a good alternative as an easily available biomarker used to aid in the diagnosis of sepsis/infection [6]. We suggest that an RPR > 0.129 in premature patients is abnormal, and should alert clinicians to search for a reason, such as sepsis. Upper RI limits were close in both gestational age groups, supporting the use of a single value. The difference between the groups in lower RI limits may be due to gestational age related stress but we are not able to explain the underlying mechanism.

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome that shares common features with sepsis in terms of clinical and laboratory features. Xi et al. [21] observed that RPR levels of the HLH patients were significantly higher than those of sepsis and normal controls. RPR may serve as an additional biomarker in distinguishing HLH from sepsis in children. Bekmez et al. [5] showed the predictive value (61% sensitivity and 92% specificity with a cutoff value of 0.13) of RPR in diagnosis of patent ductus arteriosus in the newborns (gestational age ≤ 30 weeks) and detection of the group that did not respond to ibuprofen treatment.

The diagnostic value of CBC parameters is useful for a wide range of conditions when compared with correct RIs [22,23].

Limitations

Unfortunately, there were several limitations in this study.

First, the current study relied on a small sample of 144 hemogram data, and the distribution of data across subgroups such as gestational age was uneven.

The small number of cases prevented the determination of accurate RI for different gestational weeks. A large number of data is an important rule that increases the reliability of the RI study [24]. Since premature infants have low blood volume and phlebotomy can cause complications such as anemia, this number of data consisting of healthy premature babies can be considered as a sufficient amount for the RI study [25].

Various factors can affect CBC, including the timing of sampling, and the health status of the newborn. Severe crying or exertion has an effect on hematological test results [26]. Maternal iron status, which can affect the iron status of neonates, was not assessed. This information was not available to us.

The RIs in our study require verification when transferred to other studies due to different analyzers, characteristics of the population studied, and differences in sample type.

Despite these limitations, establishment of a RI for RPR will allow clinical correlation of RPR alterations. Continued efforts are needed to further evaluate the importance of these RIs in routine clinical work and disease diagnosis.

Author contributions

EGK, YU, MA and KH contributed to the concept and design the work. EGK, YU, FY, EYA and KH drafted the work or revised it critically for important intellectual content. All the authors have acquisited, analyzed or interpretated of data for the work. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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