RESEARCH ARTICLE

A promising, novel index in the diagnosis and follow-up of patent ductus arteriosus: Red cell distribution width-to-platelet ratio

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Background: The role of red cell distribution width-to-platelet ratio (RPR) has not previously been mentioned in reports on patent ductus arteriosus (PDA). Our objective was to evaluate whether RPR would have a role in the diagnosis and/or prediction of pharmacological closure of PDA.

Methods: Preterm infants' gestational age ≤ 30 weeks and ≤ 1500 g who were given first ibuprofen treatment in the first week of life for hemodynamically significant PDA (hsPDA) were included in the study. The patients were matched for gestational age, birthweight, and sex. Patients were subdivided into two groups based on the response to medical treatment (open and closed PDA). Hemogram parameters were recorded before and after medical therapy. Groups were compared with regard to demographic and clinical characteristics and for three sequential hematological parameters. RPR was calculated. Patients with sepsis, anemia, perinatal asphyxia, and congenital/chromosomal anomaly were not included in the study.

Results: A total of 112 infants had medically treated hsPDA. Of those, ductus closed in 70 neonates (closed PDA). A total of 96 infants constituted the control group. Mean gestational age and birthweight of the patients were 28.9 ± 2.4 weeks and 1207 ± 372 g. While RPR was significantly increased, PCT was lower in both hsPDA and open PDA groups ($P < 0.05$ and $P < 0.05$, respectively). In multivariate analysis, high RPR (OR 3.3, 95% CI 1.438-5.872, $P < 0.05$) and RDS (OR 2.9, 95% CI 1.903-4.811, $P < 0.01$) were detected as independent risk factors for hsPDA.

Conclusion: Red cell distribution width-to-platelet ratio and PCT may be promising supportive tools for the diagnosis and prediction of pharmacotherapy success.

KEYWORDS

ductal patency, patent ductus arteriosus, plateletcrit, red cell distribution width-to-platelet ratio, response to pharmacotherapy

1 | INTRODUCTION

Patent ductus arteriosus (PDA) is a significant challenge in preterm infants. This patency is related to higher rates of serious morbidities, including respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), pulmonary hemorrhage, and mortality.¹ Despite the current debate regarding whether urgent closure is beneficial or not, pharmacological and/or surgical intervention is still widely used in neonatal intensive care units.^{2,3} Although Doppler echocardiographic assessment is the principal method for diagnosis and follow-up, researchers continue to search for alternative tools for prediction of PDA and/or response to medical treatment.

The role of platelets in ductal closure became of interest following the results of an animal study.⁴ Later, the association of PDA with platelet count and indices was investigated several times but with conflicting results. A recent meta-analysis by Simon et al⁵ that included 3479 preterm infants from 11 studies demonstrated that thrombocytopenia in early life was a modest but significant risk factor for persistent PDA. Also, in another meta-analysis, platelet count appeared lower in premature infants who did not respond to the first medical treatment.⁶ In the following limited number of studies, the role of platelet indices in ductal patency was investigated, but no clear relationship was found.⁷⁻¹¹ There is also scant data regarding the value of plateletcrit (PCT) in PDA.

Red blood cell distribution width (RDW) is a parameter that measures the range of variation of red blood cell volume. The critical role of RDW has been revealed in a variety of inflammatory diseases in adults.¹²⁻¹⁶ The normal ranges of RDW values were identified in neonates.^{17,18} It was shown that there was an inverse relationship between gestational age and RDW, but data on the association of RDW with neonatal morbidities are limited. Only one study inferred a correlation between high RDW and neonatal morbidities such as PDA and BPD.¹⁹ The rise of PDA rates in the presence of chorioamnionitis or sepsis indicated the presence of inflammation in the etiology. This inflammatory state was speculated to raise RDW values.

Red cell distribution width-to-platelet ratio (RPR) is a quite new, easily calculated parameter that was demonstrated to have a high predictive value in inflammatory diseases of adults.²⁰⁻²² We hypothesized that this index may be supportive in the diagnosis of hemodynamically significant PDA (hsPDA) and prediction of ductal closure with pharmacotherapy, in addition to echocardiography.

Therefore, the aim of this study was to assess whether RPR would be useful in the diagnosis and follow-up of the response to treatment.

2 | METHODS

In this retrospective cohort study, data of newborn infants admitted to the tertiary neonatal intensive care unit of Zekai Tahir Burak Women's Health Education and Research Hospital in

Ankara, Turkey, between December 2014 and December 2016 were collected. Our center is a huge perinatal center that has approximately 18 000 annual births and 130 NICU beds. Infants with echocardiographic diagnosis of hsPDA with gestational age ≤ 32 weeks, birthweight ≤ 1500 g, postnatal age < 7 days, and who were given first oral ibuprofen treatment for hsPDA were included in the study. Patients with similar demographic and clinical characteristics without PDA constituted the control group. Infants with hsPDA were subcategorized as "open" and "closed" according to response to treatment. This study was approved by the local ethical committee.

Prenatal, demographic, and clinical characteristics including gender, birthweight, gestational age, APGAR scores, RDS (requirement for surfactant administration), severe IVH (Grade 3-4), moderate-severe BPD, and duration of respiratory support were obtained from the files. Patients with sepsis, anemia, hemodynamic instability, perinatal asphyxia, or major congenital and/or chromosomal anomalies were excluded from the study.

Doppler echocardiographic examination was routinely performed by a pediatric cardiologist 48-72 hours following birth in extremely preterm infants with a GE Vivid 7 Pro, 10S transducer (GE Healthcare, Salt Lake City, UT, USA). The markers indicating hsPDA were the presence of ductal diameter ≥ 1.5 mm and/or a left atrial-to-aortic root (LA:Ao) ratio ≥ 1.5 . The patients with hsPDA were treated with oral (Dolven, Zentiva) ibuprofen at a dosage of 10 mg/kg on the first day, 5 mg/kg on the second and third day, or oral paracetamol (Calpol; GlaxoSmithKline, Istanbul, Turkey) at a dose of 15 mg/kg every 6 hours for 3 days. After completion of medical treatment, Doppler echocardiography was performed again to evaluate the closure of the PDA. The medical therapy was repeated in the presence of ductal patency. A complete blood count was gathered just before the start of the therapy to exclude the contra-indication of thrombocytopenia ($\leq 50\,000/\text{mm}^3$). All patients were evaluated for complete blood count following completion of pharmacotherapy, and afterward, a weekly routine clinical examination was conducted. Blood counts were obtained using a twice-daily calibrated Cell-Dyn 3700 automated hemocytometer (Abbott, Abbott Park, IL, USA).

Platelet count, indices, and RDW were acquired, and RPR was calculated from the samples. The formula of RDW-to-platelet ratio was used for the calculation. Sequential indices were compared between the groups and subgroups.

2.1 | Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS), version 20.0 (SPSS Inc, Chicago, IL, USA). Kolmogorov-Smirnov test was used to determine whether the sample values fit a normal distribution. Descriptive statistics are given as mean and standard deviation for normally distributed variables or median and interquartile range (IQR) for variables that were not normally distributed. Categorical data are presented as number and/or percentage. Chi-square for categorical variables and independent samples *t* test (for parametric continuous variables)

or Mann-Whitney *U* test (for nonparametric continuous variables) were used for univariate analysis. Statistical significance was set at $P < 0.05$. Multiple logistic regression analysis was performed to evaluate variables that were most probably associated with hsPDA. Odds ratios and 95% confidence intervals were used in this analysis. The cutoff for RPR values was calculated with a receiver operating characteristic curve. Multivariate analysis was performed to explore the individual effects of each variable on raising RPR above the cutoff value.

3 | RESULTS

A total of 305 neonates, ≤ 32 weeks and ≤ 1500 g, were accepted to the NICU during the study period. A total of 209 patients were evaluated for eligibility and 93 patients were excluded due to paracetamol administration ($n = 31$), sepsis ($n = 30$), nonsignificant PDA ($n = 22$), anemia ($n = 8$), or congenital and/or chromosomal anomalies ($n = 2$). A total of 116 had hsPDA. While ductus was closed in 70 patients after first medical treatment, ductal patency was observed in 46 patients. A total of 96 preterm neonates constituted the control group. Demographic and clinical characteristics of the patients are shown in Table 1. Gestational ages and birthweights of the neonates were 28 ± 2 weeks and 1207 ± 372 g in the study group and 29 ± 2 weeks and 1275 ± 218 g in the control group, respectively ($P > 0.05$; Table 1).

TABLE 1 Demographic characteristics of hsPDA and non-PDA groups

	hsPDA (n = 116)	Non-PDA (n = 96)	P*
Gestational age (wk) ^a	28.9 ± 2.4	29.2 ± 2.0	>0.05
Birthweight (g) ^a	1207 ± 372	1275 ± 218	>0.05
Gender (male), n %	70 (60)	56 (58)	>0.05
APGAR 1st min ^a	6 ± 2	6 ± 2	>0.05
APGAR 5th min ^a	8 ± 2	8 ± 2	>0.05
Severe RDS, n (%)	59 (59)	36 (37.5)	<0.01
IVH, n (%) (Grade ≥ 3)	29 (30)	21 (21.8)	<0.01
BPD, n (%) (moderate-severe)	31 (27)	10 (10.9)	<0.01
Survival, n (%)	74 (63)	66 (69)	>0.05

BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; RDS, respiratory distress syndrome.

^aMean $\pm$ standard deviation.

*Statistically significant *P* values are highlighted.

The comparison of hematological parameters between hsPDA and non-PDA infants is shown in Table 2. PCT was lower in the hsPDA group as compared to non-PDA patients (0.185 ± 0.055 vs 0.214 ± 0.066 , $P = 0.025$). While the RDW and platelet count was similar between groups, RPR was higher in the hsPDA group and the difference was statistically significant (0.084 ± 0.069 and 0.068 ± 0.024 in study and control groups, respectively; $P < 0.01$).

Hematological parameters were compared between responders and nonresponders (Table 3). Gestational age and birthweight were similar between the subgroups. There was no difference in terms of other morbidities and mortality. While RPR was higher in the open group both before and after therapy (0.086 ± 0.087 vs 0.071 ± 0.024 , $P < 0.01$; 0.093 ± 0.076 vs 0.069 ± 0.037 , $P < 0.01$; respectively), PCT was lower in the open PDA group (0.185 ± 0.076

TABLE 2 The hematological parameters of hsPDA and non-PDA group

	hsPDA (n = 116)	Non-PDA (n = 96)	P*
RPR, %	0.084 ± 0.069	0.068 ± 0.024	<0.01
RDW, %	15.75 ± 1.15	16.85 ± 1.49	>0.05
Platelet count, $10^3/\mu\text{L}$	243 ± 98	259 ± 82	>0.05
PDW, %	13.03 ± 2.12	12.95 ± 1.44	>0.05
MPV, fL	7.8 ± 1.0	8.2 ± 1.4	>0.05
PCT, %	0.185 ± 0.055	0.214 ± 0.066	0.025

All values are given as mean $\pm$ standard deviation.

*Statistically significant *P* values are highlighted.

TABLE 3 The hematological parameters of open and closed PDA groups

	Open PDA (n = 46)	Closed PDA (n = 70)	P*
PCT, %	0.185 ± 0.076	0.220 ± 0.095	0.009^a
	0.208 ± 0.120	0.262 ± 0.106	0.015^b
	0.272 ± 0.134	0.330 ± 0.134	0.017^c
RPR, %	0.086 ± 0.087	0.071 ± 0.024	0.003^a
	0.093 ± 0.076	0.069 ± 0.037	0.009^b
	0.093 ± 0.096	0.067 ± 0.064	0.012^c
MPV, fL	7.6 ± 0.7	7.9 ± 1.3	$>0.05^a$
Platelet count, $10^3/\mu\text{L}$	247 ± 116	259 ± 82	$>0.05^a$
PDW, %	12.6 ± 1.7	13.4 ± 2.3	$>0.05^a$
RDW, %	16.1 ± 1.1	16.2 ± 1.5	$>0.05^a$

All values are given as mean $\pm$ standard deviation.

^aP = before treatment.

^bP = after treatment.

^cP = one week later after completion of treatment.

*Statistically significant *P* values are highlighted.

vs 0.220 ± 0.095 in open and closed PDA groups respectively; $P < 0.01$).

ROC analysis was performed to evaluate the utility of RPR (Figure 1). Cutoff values are demonstrated in Table 4. A cutoff value

of 0.13 showed 61% sensitivity and 92% specificity for the prediction of hsPDA [area under curve (AUC) 0.781, 95% confidence interval (CI): 0.625–0.767]. With 71% sensitivity and 90% specificity, a value of 0.15 was detected as the cutoff for nonresponsiveness to medical treatment (AUC 0.786, 95% CI: 0.714–0.893).

Multivariate analysis demonstrated that while RDS and high RPR (>0.13) were associated with hsPDA, gestational age and birthweight had no effect on hsPDA (OR 2.9, 95% CI 1.903–4.811, $P < 0.01$ for RDS; OR 3.3, 95% CI 1.438–5.872, $P < 0.05$ for RPR). Gestational age, birthweight and RDS had no association with a cutoff of >0.13 ($P > 0.05$).

4 | DISCUSSION

Our aim was to evaluate the value of RPR in hsPDA diagnosis and prediction of ductal closure with medical treatment in preterm infants. This study revealed that RPR may be a supportive tool for both diagnosis and responsiveness to medical therapy. Also, high PCT was found to be associated with hsPDA and a worse response to medical therapy.

We found no association of platelet count with hsPDA or responsiveness to medical therapy. Despite the conflicting results of scientific articles, a recent meta-analysis showed that thrombocytopenia in early life was a moderate and significant risk factor for PDA in very preterm infants.⁵ For a variety of reasons, including the retrospective nature of these studies, concerns regarding the definition of hsPDA and neonatal thrombocytopenia, differences in the dates of platelet count evaluation, and the sick state of the preterm infants were the reasons why a clear association or causality link could not be made.

A point of interest is the relationship between platelet count and response to pharmacotherapy. The fact that these studies were planned with other primary objectives as well as divergence in the timing of platelet count evaluation minimized the reliability of the results. Subsequently, researchers claimed that not only the number, but mainly the function of platelets may be fundamental in ductal closure.

We established that PCT was lower in both hsPDA and nonresponders with normal platelet counts. PCT, an indicator of platelet mass, is the volume occupied by platelets in the blood. PCT was detected to be low in nearly half of the patients, despite normal platelet count.²³ Tvedten et al²⁴ proposed the superiority of PCT rather than count in the evaluation of platelet status. This platelet index has been minimally searched and therefore undervalued in neonates. Normative ranges were identified as 0.19 ± 0.05 in 30 preterm

FIGURE 1 Receiver Operating Characteristic Curves for hsPDA Group vs Control Group (A) and Open PDA Group vs Closed PDA Group (B) Using the RDW-to Platelet Ratio

	AUC	Cutoff level	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)
RPR ^a	0.781	0.13	92	61	89	63
RPR ^b	0.786	0.15	90	71	88	72

^ahsPDA vs non-PDA.

^bResponder vs nonresponder.

TABLE 4 AUC, cutoff value, specificity, sensitivity, PPV, and NPV of RPR

neonates, similar to our study, and additionally, a linear relationship between gestational age and PCT was demonstrated in the same study.⁹ This may actually be related to morbidities of prematurity, not gestational age. The link between platelet mass and responsiveness to pharmacotherapy was investigated in a limited number of studies, but with conflicting results. The direct relationship between PDA and PCT has not been studied previously. We speculated that low PCT may reflect increased consumption and a defective role of platelets in ductal closure. Again, platelet volume deficiency may have inhibited the success of medical therapy.

The RDW values were similar in the groups and subgroups. Yčas et al²⁵ put forward a hypothesis that acute hypoxia results in increased red blood cell size variability. Apart from the hypoxia, current studies indicate a link between high RDW and inflammation. However, there is limited data regarding whether a similar relationship is present in critically ill neonates or not. Normative ranges were identified in both term and preterm infants, and an inverse link was shown between gestational age and RDW values.^{17,18} A correlation was demonstrated between high RDW and mortality in septic newborns.²² Garofoli et al¹⁹ showed that RDW had a prognostic role for neonatal morbidities, such as PDA and mortality, in preterm and IUGR infants. The speculation was that inflammation and hypoxia are involved in the pathogenesis of PDA.

A new index, namely RPR, which possesses a good predictive property for inflammatory liver and cardiac diseases in adults, was put forth.²⁰⁻²² General sterile inflammation was thought to have a part in PDA pathogenesis.²⁶ This systemic inflammation was overt during the first 3 days of life independent of sepsis, probably due to intensive care.²⁷ As a result of this inflammation, prostaglandin E2 and prostacyclin release, with stimulation of the cyclooxygenase pathway, have a substantial role in ductal patency.²⁷ This implication was supported by the claim that intrauterine inflammation, namely chorioamnionitis, was an independent risk factor for PDA.²⁸ Depending on the connection of high RDW and low platelet number to the presence of inflammation, we speculated that RPR may be a valuable index in hsPDA. We demonstrated a high predictive value of RPR both in diagnosis and for the unresponsive group to ibuprofen treatment.

To the best of our knowledge, this is the first study that has mentioned the RPR index in preterm infants. Moreover, the question is raised whether PCT may be a more valuable platelet index than previously thought. While several studies evaluated the hemogram parameters once in the first days of life, we further analyzed these values three times. We also attempted to determine the predictive value of these parameters and of RPR for both hsPDA diagnosis and the monitoring of ductal closure through sequential assessments. We excluded infants who were given paracetamol treatment due to debatable issues related to this therapy. The reliability of the outcomes was enhanced using the same hematology counter in this period. However, the retrospective nature and modest sample size are limitations of this study. Although we excluded infants with a sepsis diagnosis, the general sick state

or other accompanying morbidities of the newborns may have influenced the results. We are not able to claim that the parameters are solely linked with hsPDA. Future studies must focus on these confounding factors in prospectively randomized controlled studies in large-scale populations.

5 | CONCLUSION

RPR may be a supportive tool in the both diagnosis and prediction of ductal closure in addition to Doppler echocardiography. The fact remains that this study may be a touchstone for future studies on the prognostic value of PCT and RPR in preterm infants.

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