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# Complete blood counts parameters and erythrocyte transfusions in predicting retinopathy of prematurity

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## Abstract

**Aim:** This study investigates the association of complete blood count parameters and erythrocyte transfusions with retinopathy of prematurity (ROP) requiring treatment in infants born prematurely under 32 weeks of gestation.

**Materials and Methods:** The single-center, retrospective, observational study included 130 patients with a gestational age between 24-32 weeks who were born in the same hospital and hospitalized in the neonatal intensive care unit of the hospital between 2016-2018.

**Results:** Mean complete blood count parameters at postnatal 0-24 hours and postnatal 24-72 hours as well as erythrocyte transfusions were compared in terms of retinopathy of prematurity requiring treatment. Mean hemoglobin, hematocrit and red blood cell count at postnatal 24-72 hours were significantly lower in patients with ROP requiring treatment than in those without.

**Conclusion:** The study suggests that low erythrocyte mass and an increased number of early erythrocyte transfusions are important risk factors for the development of ROP requiring treatment.



## Introduction

Despite scientific and technological developments in the field of health, morbidity and mortality rates are higher in babies born earlier than 32 weeks of gestation compared to other preterm and term babies [1]. The most important reason for this situation, which is caused by multifactorial reasons, is still preterm birth itself. The more preterm these babies are born, the more vulnerable they are and their risks of developing prematurity-related morbidities such as respiratory distress syndrome, patent ductus arteriosus, intraventricular hemorrhage, bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP) increase [2].

Although there are specialized laboratory methods in the literature for early prediction and prevention of the development of BPD and ROP, which are mainly long-term morbidities of these infants, most of them are expensive, invasive or inaccessible [3]. Additionally, although scoring systems including risk factors such as gestational age, gender, and need for mechanical ventilation are used, they do not perform individual risk analysis [4]. All these have led researchers to find accessible and inexpensive biomarkers.

This study investigates the role of complete blood count parameters (CBC), the most commonly used practical and relatively inexpensive laboratory test in clinical practice, in predicting the development of ROP, a long-term morbidity of prematurity. It aims to show the mean complete blood count parameters of these specialized infants and to investigate the effect of erythrocyte transfusions received during follow-up on ROP.

## Materials and Methods

The study was planned in a single-center, observational, retrospective design. All premature infants with a gestational age between 24 and 32 weeks who were born in the same hospital between January 2016 and December 2018 and admitted to the third level neonatal intensive

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care unit of the hospital were included in the study. Infants who were referred to another hospital for follow-up, had major congenital anomalies, received blood transfusion before complete blood count, died before the 36th postmenstrual week, and whose ROP follow-up data was not available were excluded from the study.

Data of the infants and their mothers were obtained from the patient information system of the hospital, patient files, and consultation notes of the ophthalmology department of the hospital. Demographic and clinical characteristics of mothers and infants; retinopathy and other morbidity and mortality data of infants were recorded. All complete blood count parameters obtained from infants in the first postnatal week according to the clinic protocol and clinician judgment were also recorded for comparison.

Complete blood count parameters; red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width (RDW), platelet count (PLT), mean platelet volume (MPV), plateletcrit (PCT), white blood cell count (WBC), absolute neutrophil count (ANC), lymphocyte count (LYM), monocyte count (MONO), eosinophil count (EOS), and basophil count (BASO) were evaluated. Only complete blood count parameters obtained before transfusion were recorded in patients who received blood transfusion in the first week.

The diagnosis and staging of ROP were recorded in accordance with the joint guidelines of the Turkish Neonatology Society and the Turkish Ophthalmology Society by reviewing the consultations made to the ophthalmology department of the hospital and the patient notes available until the 36th postmenstrual week [5]. Patients were categorized as presence of ROP, ROP stage and ROP requiring treatment according to the examination findings at follow-up.

Patients with and without ROP requiring treatment were compared in terms of gestational age, birth weight, presence of multiple pregnancies, duration of mechanical ventilation, duration of non-invasive ventilation, total oxygen time, presence of moderate to severe patent ductus arteriosus, late sepsis, intraventricular hemorrhage, and moderate/severe bronchopulmonary dysplasia, which are risk factors for the development of ROP. To evaluate the relationship between ROP development and complete blood count values in the first postnatal week, which was the primary outcome of the study, the mean values of complete blood count parameters at postnatal 0-24 hours and the mean values of complete blood count parameters at postnatal 24-72 hours were compared between the groups with and without ROP requiring treatment.

To evaluate the secondary outcome of the study, the number of erythrocyte transfusions given in the first three weeks and during the entire hospitalization were compared between these two groups. Threshold values showing high sensitivity and specificity for significant values were evaluated by receiver operating characteristic curve (ROC) analysis.

The first week transfusion limit of 11.5 g/dL hemoglobin in premature infants requiring respiratory support, the hemoglobin limit of 13.5 g/dL hemoglobin, which is accepted as anemia in newborns, and the hemoglobin cut-off values determined by ROC analysis were evaluated in terms of the risk of development of ROP requiring treatment with cross-tabulations. Significant parameters were tested by multivariate analyses.

The approval of Dokuz Eylül University Non-Interventional Clinical Research Ethics Committee was granted for the study (Decision no: 2018/20-12).

### *Statistical analysis*

IBM SPSS Statistics version 25 was used for statistical analysis. Categorical data were presented as numbers (n) and percentages (%). Based on the Shapiro-Wilk and Kolmogorov-Smirnov tests, continuous data that conformed to a normal distribution were expressed as mean (±SD), and non-parametrically distributed continuous data were expressed as the median (minimum-maximum) by considering skewness and kurtosis values. Student's t test was used for continuous data fitting to normal distribution and Mann-Whitney U test was used for non-parametric data. Chi-square and Fisher exact tests were used to compare categorical data. ROC analysis was performed on the tested continuous data and cut off values showing more than 80% specificity and sensitivity were determined if the area under the curve was more than 0.7. Logistic regression analysis was performed with Backward:LR method. $P<0.05$ was considered statistically significant.

## Results

Between January 2016 and December 2018, a total of 175 infants born between 24 and 32 gestational weeks and admitted to the third level neonatal intensive care unit of the same hospital were identified. Forty-five of these babies (29 babies who had died before the 36th postmenstrual week, 6 babies who received transfusion before the 3rd postnatal

**Table 1.** Demographic and clinical features.

| | ROP Treatment | No ROP Treatment | p |
|---|---|---|---|
| | N:7 (%) | N:123 (%) | |
| Gestational age (weeks) | 24.0 (23.3-25.6) | 29.6 (29.0-29.8) | **<0.001** |
| Birth weight (gram) | 618 (542-761) | 1216 (1188-1343) | **<0.001** |
| Multiplets | 3 (43%) | 29 (24%) | 0.24 |
| Male | 4 (57%) | 54 (44%) | 0.49 |
| Duration of NIV (days) | 29 (23-35) | 10 (11-15) | **<0.001** |
| Duration of MV (days) | 39 (28-58) | 1 (4-9) | **<0.001** |
| Duration of Oxygen | 77 (58-100) | 10 (0-91) | **<0.001** |
| Treatment (days) | | | |
| PDA | 4 (57%) | 25 (20%) | **0.04** |
| IVH | 5 (71%) | 21 (17%) | **<0.001** |
| Late sepsis | 7 (12%) | 52 (42%) | **<0.001** |
| BPD | 7 (100%) | 13 (11%) | **<0.001** |
| ERT times (n) | 7 (7-12) | 1 (1-3) | **<0.001** |

BPD: moderate/severe bronchopulmonary dysplasia, ERT: erythrocyte transfusions, IVH: intraventricular hemorrhage, MV: Mechanical ventilation, NIV: Non invasive ventilation, PDA: hemodynamically significant patent ductus arteriosus.

**Table 2.** Hemogram parameters in 0-24 hours after birth.

| | ROP Treatment | No ROP Treatment | p |
|---|---|---|---|
| | N:7 | N:123 | |
| HGB (g/dL) | 15.7 (±2.0) | 16.4 (±2.3) | 0.42 |
| HCT (%) | 49.1 (43.1-55.6) | 51.2 (49.4-52.0) | 0.51 |
| RBC ($x10^{12}$/L) | 3.97 (3.76-4.65) | 4.50 (4.29-4.54) | 0.35 |
| RDW (fL) | 17.4 (16.0-19.3) | 17.8 (18.1-19.1) | 0.35 |
| MCV (fL) | 121 (106-140) | 114 (114-117) | 0.17 |
| MCH (pg) | 37.2 (±2.6) | 37.3 (±2.6) | 0.87 |
| MCHC (g/dL) | 31.3 (30.8-33.0) | 32.8 (32.3-32.8) | 0.08 |
| WBC ($x10^9$/L) | 8.9 (5.2-12.1) | 8.8 (9.1-11.2) | 0.60 |
| NEU ($x10^9$/L) | 2.4 (1.2-9.3) | 4.0 (4.5-7.1) | 0.57 |
| LYM ($x10^9$/L) | 2.4 (0.6-6.6) | 3.2 (3.5-4.4) | 0.39 |
| MONO ($x10^9$/L) | 0.7 (0.2-2.0) | 0.8 (0.8-1.0) | 0.52 |
| EOS ($x10^9$/L) | 0 (0.1-0.2) | 0.1 (0.1-0.2) | 0.60 |
| BASO ($x10^9$/L) | 0 (0.1-0.2) | 0 (0-0.1) | 0.75 |
| PLT ($x10^9$/L) | 152 (124-174) | 198 (173-202) | 0.07 |
| MPV (fL) | 8.5 (7.6-9.1) | 8.1 (8.0-8.4) | 0.48 |
| PCT (%) | 0.12 (0.11-0.14) | 0.16 (0.14-0.16) | 0.08 |

ANC: absolute neutrophil count, BASO: basophil count, EOS: eosinophil count, HCT: haematocrit, HGB: haemoglobin, LYM: lymphocyte count, MCH: mean corpuscular haemoglobin, MCHC: mean corpuscular haemoglobin concentration, MCV: mean corpuscular volume, MONO: monocyte count, MPV: mean platelet volüme, ns: not significant, PCT: plateletcrit, PLT: Platelet count, RBC: red blood cell count, RDW: red blood cell distribution width, WBC: white blood cell count.

**Table 3.** Hemogram parameters in 24-72 hours after birth.

| | ROP Treatment | No ROP Treatment | p |
|---|---|---|---|
| | 6/7 (n/N) | 100/123 (n/N) | |
| HGB (g/dL) | 12.2 (±1.7) | 16.2 (±2.3) | **<0.001** |
| HCT (%) | 32.1 (±4.2) | 48.8 (±0.7) | **<0.001** |
| RBC ($x10^{12}$/L) | 3.21 (±0.16) | 4.35 (±0.06) | **<0.001** |
| RDW (fL) | 17.6 (15.2-23.3) | 17.8 (18.2-19.2) | 0.96 |
| MCV (fL) | 114 (93-130) | 113 (111-115) | 0.96 |
| MCH (pg) | 38.2 (33.1-43.2) | 38.0 (36.7-38.5) | 0.83 |
| MCHC (g/dL) | 35.0 (30.8-37.8) | 33.4 (32.9-34.0) | 0.29 |
| WBC ($x10^9$/L) | 6.7 (5.2-8.1) | 6.8 (7.1-9.2) | 0.70 |
| NEU ($x10^9$/L) | 3.7 (0.8-6.9) | 3.0 (3.0-4.9) | 0.86 |
| LYM ($x10^9$/L) | 2 (±0.6) | 3 (±1.2) | 0.15 |
| MONO ($x10^9$/L) | 0.9 (0.5-2.6) | 0.6 (0.4-1.5) | 0.37 |
| EOS ($x10^9$/L) | 0.1 (0.4-0.8) | 0.1 (0.1-0.2) | 0.49 |
| BASO ($x10^9$/L) | 0 (0-0.1) | 0 (0-0.1) | 0.90 |
| PLT ($x10^9$/L) | 81 (35-146) | 164 (139-206) | 0.05 |
| MPV (fL) | 9.3 (8.7-10.0) | 8.4 (8.3-8.8) | 0.03 |
| PCT (%) | 0.08 (0.03-0.14) | 0.13 (0.12-0.17) | 0.07 |

ANC: absolute neutrophil count, BASO: basophil count, EOS: eosinophil count, HCT: haematocrit, HGB: haemoglobin, LYM: lymphocyte count, MCH: mean corpuscular haemoglobin, MCHC: mean corpuscular haemoglobin concentration, MCV: mean corpuscular volüme, MONO: monocyte count, MPV: mean platelet volüme, ns: not significant, PCT: plateletcrit, PLT: Platelet count, RBC: red blood cell count, RDW: red blood cell distribution width, WBC: white blood cell count.

day, 7 babies who were referred to another center, and 3 babies whose ROP follow-up information could not be obtained in the same hospital) were excluded from the study. A total of 130 babies were included in the study.

ROP was detected in a total of 15 (11.5%) patients during the follow-up until the postnatal 36th week of life. Of these patients, 8 (53%) had ROP that did not require treatment [3 were stage 2 (20%), 5 were stage 1 (33%)] and retinopathy findings regressed during follow-up. A total of 7 patients (45%) had retinopathy that required treatment [5 were stage 3 (33%), 2 were aggressive ROP (13%)]. The demographic and clinical characteristics of ROP requiring treatment and other cases are shown in Table 1.

**Table 4.** Risk analysis for haemoglobin and ERT cut off values.

| | ROP Treatment | No ROP Treatment | RR | p |
|---|---|---|---|---|
| HGB <11.5 g/dL | 1 (17%) | 2 (2%) | 6.8 | 0.16 |
| HGB <13.5 g/dL | 5 (83%) | 12 (12%) | 26.7 | **<0.01** |
| HGB <14.2 g/dL | 5 (83%) | 19 (19%) | 4.9 | **<0.01** |
| ERT >4 times (n) | 2 (50%) | 56 (4%) | 12 | **0.01** |

ERT: erythrocyte transfusions, HGB: haemoglobin.

All 130 babies included in the study had a complete blood count obtained from umbilical cord, catheter, or vein on the first postnatal day. Complete blood counts were sent from 21, 59, and 44 patients on postnatal day 2, 3 and 4, respectively, and complete blood counts were not sent from 24 patients on those days. The complete blood count values of the patients at postnatal 0-24 hoursand postnatal 24-72 hours are given in Table 2 and Table 3.

No significant difference was found between the infants diagnosed with ROP requiring treatment and the others in HGB, HCT, RBC, RDW, MCV, MCH, MCHC, WBC, NEU, LYM, MONO, EOS, BASO, PLT, MPV, PCT values obtained at postnatal 0-24 hours. However, in the mean complete blood counts obtained at postnatal 24-72 hours HGB, HCT and RBC values were found to be significantly lower in babies who required ROP treatment compared to those who did not (HGB: 16.2±2.3 vs 12.2±1.7 g/dL; HCT: 48.8±0.7 vs 32.1±4.2 %; RBC: 4.35±0.06 vs 3.21±0.16 x106/mm3;P<0.001). No statistically significant difference was found in white blood cell counts (WBC, NEU, LYM, MONO, EOS, BASO) and platelet parameters (PLT, MPV, PCT)between the groups at postnatal 24-72 hours.

Erythrocyte transfusion decisions in the follow-up of the patients were made in accordance with the current guidelines of the Turkish Neonatology Society; all transfusions were made with 15 ml/kg of irradiated, filtered erythrocyte solution compatible with the blood group of the patient. Forty-four infants received erythrocyte transfusion in the first postnatal week and 83 infants received erythrocyte transfusion in the first three postnatal weeks. The total number of ERTs received in the first 3 postnatal weeks was compared between infants requiring and not requiring ROP treatment (Table 1). The median number of ERT given in the first three weeks was 1 (1-3) in the group not requiring ROP treatment, whereas it was statistically significantly higher at 7 (7-12) in the group requiring ROP treatment.

ROC analysis was performed to determine the value of erythrocyte indices in haemogram obtained at postnatal 24-72 hours in predicting ROP that requires treatment. Postna-

tal 24-72 hours' hemoglobin less than 14,2 g/dL was associated with the development of ROP that requires treatment with 84% sensitivity and 81% specificity [AUC:0.95 Cl(0.87-0.99)].

In addition, ROC analysis was performed to determine the value of the number of ERTs given in the first 3 postnatal weeks in predicting ROP requiring treatment. It was found that ERT given more than 4 times in the first 3 weeks was associated with the development of ROP requiring treatment with 82% sensitivity and 84% specificity [AUC:0.95 Cl(0.89-0.99)].

The relationship between hemoglobin cut-off values of 11.5 (transfusion cut-off), 13.5 (anemia cut-off), and 14.2 (investigated cut-off) in postnatal 24-72 hour hemograms and the development of ROP requiring treatment was evaluated separately using chi-squared. Hemoglobin levels below 14.2 g/dL and 13.5 g/dLin postnatal 24-72 hour hemograms were found to be associated with ROP requiring treatment. However, there was no significant difference between groups for hemoglobin levels below 11.5 g/dL. Similarly, the development of ROP requiring treatment was significantly higher in infants who received ERT more than 4 times in the first 3 weeks (Table 4).

In one-way analyses, a significant association was found between lower gestational age, low birth weight, presence of PDA, presence of intraventricular hemorrhage and ROP requiring treatment, but when these parameters and erythrocyte indices (HGB, HCT, RDW) were evaluated with binary and multiple logistic regression analysis, no significant difference was found for ROP requiring treatment.

## Discussion

This single-center study emphasized that approximately 12% of premature infants born before 32 weeks develop ROP and that the low hemoglobin levels of these infants in the first postnatal week and the number of blood transfusions in the early period are particularly indicative of the development of ROP that will require treatment.

In the clinic where the study was conducted, current scientific data and the recommendations of the Turkish Neonatology Society guidelines are taken into consideration in the management of very small preterm infants. Due to early CPAP from the delivery room, early extubation, rational use of antibiotics and close follow-up, it is believed that fewer cases of retinopathy of prematurity (ROP) are seen than in the literature [6].

All infants included in the study had hemograms at postnatal 0-24 hours.Only %18 of these babies did not have hemograms at postnatal 24-72 hours. Therefore comparisons were made from these studied hemograms.

The complete blood count values of the patients on the first day and the first postnatal week were found to be consistent with previous studies [7]. The erythrocyte indices (HGB, HCT, RBC) of the patients who would develop ROP requiring treatment were found to be significantly lower in the postnatal 24-72 hours than in the postnatal 0-24 hours. This may be due to the severe clinical condition of the patients or the higher volume of phlebotomy performed during this period. There are studies in the literature that found that anemia was more frequently observed and RBC transfusion was required earlier as the total volume of blood sample obtained by phlebotomy increased in preterm infants. However, in the study by Pin-Chun Su et al. investigating the effect of phlebotomy, no difference in ROP was found between infants who received restricted blood collection and those who received standard practice [8]. Because the standard approach was used for all infants in our study, the decrease in RBC indices at 24-72 hoursafter birth could not be related to the amount of phlebotomy.

In neonatal studies, 13.5 g/dL has been accepted as the cut-off for anemia [9]. In the study by Lundgren et al. anemia in the first postnatal week was found to be an independent risk factor for the development of ROP [10]. In this study, hemoglobin levels below than 14.2 g/dL in the first postnatal week found to be associated with the development of ROP requiring treatment. This study is consistent with the literature and suggests that hemoglobin levels higher than those accepted for anemia especially in the first week should be targeted for the development of ROP.

Current recommendations for the hemoglobin cut-off for transfusion range from 7.0 to-11.5 g/dL, depending on the postnatal age of the patient [11].The relationship between the accepted general anemia threshold (13.5 g/dL), the recommended maximum transfusion threshold (11.5 g/dL), and the HGB threshold recommended in this study (14.2 g/dL) and ROP requiring treatment is shown in Table 4. Although the debate on the cognitive consequences of restrictive and liberal transfusion policies is ongoing, studies have shown that early transfusion increases the risk of retinopathy [12]. It is argued that this is because the hemoglobin used in RBC transfusions is adult hemoglobin (HGBA) and the amount of fetal hemoglobin (HGF) decreases with each transfusion [13]. Since the oxygen holding capacity of HGBF is higher that of HGBA, the increased HGBA in the blood of a transfusion containing HGBA causes a greater fluctuation of free oxygen radicals. This may explain the lower incidence of oxidative stress and ROP in infants with higher HGBF and less need for transfusion. Randomized controlled trials investigating the effect of transfusion with fetal hemoglobin instead of HGBA on ROP have not been completed [14].

Another reason for more ROP with more transfusions is that glutathione turnover is higher and antioxidant enzymes are lower in neonatal erythrocytes [13]. Repeated transfusions increase oxidative stress in preterm infants through nitric oxide-mediated vasoregulation of free iron accumulation [15]. This may also play a role in the pathogenesis.

Although various relationships between platelet indices and ROP have been described in the literature, no statistically significant result was found between platelet count and ROP requiring treatment in this study. This may be due to the limited number of patients.

The main limitation of the study is its retrospective design. Although retrospective studies are very important for rare morbidities, they may influence the results due to the small number of patients. Considering all these, the importance of targeting high hemoglobin levels but not achieving them by transfusion is clear. To achieve this, the importance of

delayed cord clamping, which is widely accepted in current practice, cannot be denied. Due to the retrospective design of this study and the lack of data, the effect of delayed cord clamping practices could not be evaluated in this study.

In support of what is known, the study shows that low RBC mass and increased number of early RBC transfusions are independent risk factors for the development of ROP requiring treatment. The contribution of this study to the literature is that targeting hemoglobin levels above the generally accepted anemia cut-off when determining risk for ROP may be protective against ROP. Prospective studies in larger populations are needed to evaluate this.

*Ethical approval*

The approval of Dokuz Eylül University Non-Interventional Clinical Research Ethics Committee was granted for the study (Decision no: 2018/20-12).

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