Zeynep Kamil Med J 2023;54(2):106–111
DOI: 10.14744/zkmj.2022.04764

ORIGINAL ARTICLE

Retinopathy of prematurity requiring treatment; incidence and risk factors in a tertiary center

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ABSTRACT

Objective: While retinopathy of prematurity (ROP) is the leading cause of blindness in children, understanding the pathogenesis and protection from the risk factors are crucial in neonatal practice. In this retrospective study, we aimed to evaluate our clinic's incidence and risk factors for ROP cases requiring treatment.

Material and Methods: Preterm babies with gestational age ≤34 weeks and birth weight ≤1700 g who underwent ROP examination were included in the study. Demographic data, antenatal risk factors, and clinical features of patients with ROP requiring treatment and patients with no treatment requirement were compared. Logistic regression analyses were made to determine independent risk factors.

Results: The study included 214 patients with a median of 1550 g birth weight and 33 weeks of gestational age. Treatment was required for 26 of the patients. BW and GA were significantly lower (p<0.01, p<0.01, respectively), and ventilation support duration, need for resuscitation in the delivery room, surfactant administration, grade ≥2 intraventricular hemorrhage, premature-preterm rupture of membranes, bronchopulmonary dysplasia (BPD), and need for red blood cell transfusions (p<0.01, p<0.01, p=0.04, p<0.01, p=0.023, p=0.027, p<0.001, p<0.001; respectively) were significantly higher in the treatment-requiring group. Lower gestational age (95% CI: 0.442–0.921, p=0.02) and BPD (95% CI: 1.117–11.01, p=0.032) are determined as independent risk factors. No patient between BW of 1500–1700 gr and GA of 32–34 weeks required treatment for ROP.

Conclusion: Risk factors must be clearly identified to reduce the incidence of ROP, and the need for treatment and precautions must be taken to prevent preterm babies from developing visual disturbances.

Keywords: Bronchopulmonary dysplasia, prematurity, retinopathy of prematurity.

Cite this article as: Dincer E, Kızılay O, Çelik G, Karatekin G. Retinopathy of prematurity requiring treatment; incidence and risk factors in a tertiary center. Zeynep Kamil Med J 2023;54(2):106–111.

Received: August 04, 2022 **Revised:** December 06, 2022 **Accepted:** December 30, 2022 **Online:** June 16, 2023
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Zeynep Kamil Medical Journal published by Kare Publishing. Zeynep Kamil Tıp Dergisi, Kare Yayıncılık tarafından basılmıştır.

INTRODUCTION

Retinopathy of prematurity (ROP) is a disease characterized by abnormal vasoproliferation in the retinal vessels of premature infants, the pathogenesis of which is still not fully elucidated. ROP is the most important cause of blindness in these infants, and its incidence increases as gestational age (GA) and birth weight (BW) decrease.[1] However, the frequency of ROP increases in older infants in units where oxygen applications, shown as the most important risk factor, are not monitored strictly and in regions where awareness is low on this issue. While ROP is an important problem in babies born under 28 weeks in developed countries, it is observed that ROP requiring treatment develops in infants up to 34 weeks of GA in developing countries.[2]

According to the American Academy of Pediatrics (AAP) and the American Academy of Ophthalmology, ROP screening is recommended for babies younger than 30 weeks of gestation and <1500 g.[3] On the other hand, in 2016, the Turkish Neonatal Society (TNS) guideline recommended screening all babies born with a GA of ≤32 weeks or a BW of ≤1500 g and preterm babies with a GA of >32 weeks or BW of >1500 g who received cardiopulmonary support therapy or who were deemed at risk by the clinician following the baby for the development of ROP.[1]

In the TR-ROP study conducted in our country, ROP was reported in infants over 2000 g in some centers, and in this study, "severe ROP" was reported to occur at a rate of 1% in infants with GH>32 weeks and BW>1500 g.[2] Therefore, as a result of this multicenter study, in the 2021 update of the joint guidelines of the Turkish Neonatology and Ophthalmology Societies, it is recommended to screen babies with a BW of ≤34 GW and ≤1700 g.

Low GA and BW are the most important risk factors for ROP. Besides, the need for prolonged and high oxygen treatment, hemodynamic disorders, hyperoxia/hypoxia, hypocapnia/hypercapnia, asphyxia, hypothermia, metabolic acidosis, bronchopulmonary dysplasia (BPD), intracranial hemorrhage, and blood transfusions are shown as risk factors for ROP.[1,4,5]

In this retrospective study, we aimed to determine the frequency of severe ROP requiring treatment and evaluate the risk factors in infants who met the criteria of the gestational week and BW for ROP screening in our unit. In addition, we aimed to evaluate the ROP screening results of babies with a BW between 1500 and 1700 g and a GA of 32–34 who were added to the screening program with the 2021 update.

MATERIAL AND METHODS

This retrospective study was conducted in a 42-bed neonatal intensive care unit of a tertiary hospital with 1,200 annual admissions. The Local Ethical Review Board approved the study (Date: July 06, 2022, Number: 2022-80), and parental consent was obtained for all patients before the initial screening examination. The study was conducted in agreement with the Declaration of Helsinki.

Study Population

Patients who underwent ROP screening between June 2017 and December 2018 were enrolled in the study. Our unit screens all newborns with a BW of ≤1800 grams or GA of ≤34 weeks for ROP. In addition, patients with a GA of >34 weeks who are considered to have a risk for ROP due to risk factors such as long-term oxygen use are screened. This study only evaluated patients with ≤1700 g of BW and ≤34 weeks of GA.

Table 1: Demographic data and clinical features of the patients

n=214	Mean±SD
Gender, male n, (%)	111, (51.9)
Birth weight*, grams	1500 (785)
Gestational age*, weeks	32 (5)
Maternal age, years	29.4±6.1
C/s n,(%)	168 (78.5)
SGA, n(%)	74 (34.6)

SD: Standard deviation; C/s: Caesarean section; SGA: Small for gestational age.

Data Recording

Demographic data and antenatal risk factors (preeclampsia, gestational diabetes, antenatal steroids, chorioamnionitis, and premature-prolonged rupture of membranes) were recorded from patients' registries.

The diagnosis of sepsis was made by blood culture positivity. The transfusion risk factor was defined as the administration of one or more erythrocyte suspensions. Transfontanel ultrasonography was performed in all infants, and intraventricular hemorrhage was classified according to the Papile Classification.[6] The diagnosis of patent ductus arteriosus was made by echocardiography. The bell classification was used to diagnose necrotizing enterocolitis.[7] Finally, Bancalari criteria were used for BPD diagnosis.[8]

ROP Screening and Examination

ROP screening is performed at the postmenstrual 30th week in those born between 22 and 26 gestational weeks and at the end of the postnatal 4th week in those born at ≥27 gestational weeks.[1] ROP examinations were performed with an indirect ophthalmoscope by an experienced ophthalmologist (OK or GÇ) specializing in neonatal ophthalmology.

The International Classification for ROP is used to evaluate the disease's severity and staging. Aggressive ROP (A-ROP) was described as a severe, rapidly progressive form of ROP in posterior zones I or II and beyond. Dilation and tortuosity of retinal vessels are defined as "Plus disease," and abnormal vascular dilation, tortuosity insufficient for plus disease, or both were defined as "pre-plus disease." Treatment indications are defined as follows; (1) Stage 2 or 3 ROP in zone II and "plus disease," (2) Stage 1 or 2 ROP in zone II and "plus disease," (3) Stage 3 ROP in zone I and (4) A-ROP.[9]

Statistical Analyses

Using the SPSS 20.0 program, categorical values were compared with the Chi-square test. In addition, non-parametric numeric values were compared with Mann–Whitney U tests and parametric

Table 2: Comparison of numerical data between treatment required and no-treatment group

Variable	No treatment required (n=188)		Treatment required ROP (n=26)		p
	Mean (*Median)	±SD (*IQR)	Mean (*Median)	±SD (*IQR)	
Gestational age, weeks*	32	3	27	3	**<0.01**
Birth weight, grams	1550	716	832	283	**<0.01**
Maternal age, years	29.6	6.2	28.1	7	0.281
Invasive MV, days*	0	3	16	51	**<0.01**
Non-invasive MV, days*	2	4	10	14	**<0.01**
Total oxygen support, days*	10	19	75	123	**<0.01**
Day of regaining birth weight*	11	5	11	7	0.710
Weight on 28th days, grams*	1750	723	1137	456	**<0.01**

Values with normal distribution are shown in mean and standart deviations, values not normally distributed are shown in medains and interquartile ranges and marked with*; SD: Standard deviation; ROP: Retinopathy of prematurity; IQR: Interquartile range; MV: Mechanical ventilation.

values with student t-tests. The risk factors with a significant difference were analyzed by logistic regression, and independent risk factors were determined.

RESULTS

During the study period of 18 months, 256 patients were screened for ROP. 14 patients were excluded as these patients' follow-up was continued in different centers. In addition, 28 patients were excluded because their GA was >34 GW or their BW was >1700 g. Two hundred and fourteen patients were eligible for the study. Of 216 patients, 26 were indicated for treatment.

The median BW was 1500 g (interquartile range [IQR]: 785), and the median GA was 32 weeks (IQR: 5). (The demographic data of the patients are depicted in Table 1). GA and BW were significantly lower in patients requiring treatment for ROP (Table 2).

Resuscitation in the delivery room, RDS, PPROM, IVH >grade II, need for surfactant treatment, red blood cell transfusions, and BPD were found as risk factors for ROP (Table 3), while only GA and BPD (%95 CI: 0.442–0.921, p=0.02, 95% CI: 1.117–11.01, p=0.032, respectively) were found as independent risk factors (Table 4).

Considering the patients with BW between 1500 and 1700 grams and GA between 32 and 34 weeks, three patients had stage 1 ROP, and one had stage 2 ROP. None of them required treatment for ROP.

ROP incidence was higher in patients with lower GA and BW and gradually decreased as they increased (Table 5).

DISCUSSION

In our study's results, we observed that in the group of patients (BW 1500–1700 g, GA 32–34 weeks) who were added to the screening recommendation in the 2021 guidelines, different from 2016, none of these patients required ROP treatment, but four patients had stage 1 or 2.

Although developed countries lead the others in developing treatment, patient screening, and follow-up systems, all countries create local treatment and screening guidelines for many diseases, considering their conditions and patient populations.[10] For example, many countries have established comprehensive guidelines on ROP because it is the most important cause of blindness in preterm babies, and this situation can be prevented with early and appropriate screening and treatment.[4] While these local guidelines ensure that all babies at risk are screened, they also prevent the unnecessary screening of risk-free babies.[11]

Considering major guidelines for screening ROP, the guideline with the lowest GA as the screening limit is the AAP guideline. AAP guidelines recommend ROP screening for babies younger than 30 weeks of gestation and <1500 g.[3] However, Canadian guidelines have the smallest BW criteria for ROP screening; screening all infants born ≤30 6/7 weeks' GA (regardless of BW) and infants with a BW ≤1250 g is recommended.[12]

In India, it was suggested that preterm babies ≤2000 g BW and ≤34 weeks GA should be screened for ROP.[13] On the other hand, studies conducted in China have shown that screening babies with GA ≤33 weeks and BW ≤1750 g may still detect all treatable ROP.[14]

Conducting multicentric national studies is vital to identifying the screening limits for ROP. The TR-ROP study, published in 2018, is the largest and most recent study in our country, and in light of this study's results, the criteria for our current guidelines were determined.[2]

Our country has made important neonatal health developments with many projects in recent years. Although developed countries' standards have not been reached yet, high-level care services are provided in many centers in our country. Nevertheless, because of the heterogeneity, the TNS has increased the ROP screening criteria to BW ≤1700 and GA ≤34 weeks in the 2021 update of the national guidelines.[1,2]

Table 3: Comparison of categorical data between treatment required and no-treatment group

Variable	No treatment required (n=188)		Treatment required ROP (n=26)		p
	n	%	n	%	
Gender, male	96	51.1	15	57.7	0.336
SGA	69	36.7	5	19.2	0.058
C/s	144	76.6	24	92.3	0.049
IVF	8	4.3	0	0	0.340
Multiple pregnancy	49	26.1	5	19.2	0.313
Antenatal steroid	53	28.2	12	46.2	0.054
Preeclampsia	42	22.3	5	23.1	0.552
Gestational diabetes	16	8.5	2	7.7	0.662
Chorio-amnionitis	11	5.9	3	11.5	0.233
Resuscitation in DR	75	39.9	18	69.2	**0.004**
RDS	75	39.9	21	80.8	**<0.001**
Surfactant treatment	73	38.8	21	80.8	**<0.001**
PPROM	15	8.0	6	23.1	**0.027**
IVH > grade II	3	1.6	3	12	**0.023**
Treatment required PDA	18	9.6	6	23.1	0.520
EOS	24	12.8	6	23.1	0.133
LOS	26	13.8	9	34.6	0.120
NEC	9	4.8	2	7.7	0.306
BPD	16	8.5	12	46.2	**<0.001**
Transfusions	9	5.5	17	34.7	**<0.001**
Excitus	0	0	1	4.3	0.479

SGA: Small for gestational age; C/s: Caesarean section; IVH: Intraventricular hemorrhage; DR: Delivery room; RDS: Respiratory distress syndrome; PPROM: Preterm premature rupture of membranes; EOS: Early onset sepsis; LOS; Late onset sepsis; NEC: Necrotizing enterocolitis; BPD: Broncho-pulmonary dysplasia.

In this context, it is important to identify the risk factors for ROP to lower the incidence. Furthermore, raising awareness will protect preterm babies from the risk factors. In our study, the longer need for ventilation and oxygen support, lower weight on the 28th day of life, resuscitation in the delivery room, RDS, need for surfactant treatment, PPROM, IVH >grade II, BPD, and need for red blood cell transfusions were found to be the risk factors for treatment-required ROP. On the other hand, patients requiring ROP treatment have significantly lower GA and BW.[4,5] These results were coherent with the current literature.

The longer need for ventilation and oxygen support, resuscitation in the delivery room, RDS, and demand for surfactant treatment are directly related to a higher risk of hyperoxia, which suppresses VEGF and erythropoietin at the early stage of ROP development.[1,2] On the other hand, lower weight gain on the 28th day of life is associated with persistently low insulin-like growth factor levels in premature infants, causing later elevation of VEGF, which is a prime determinant of ROP.[15] Blood transfusions are also a well-known risk factor for ROP, as adult red blood cells are rich in 2,3 DPG and adult hemoglobin binds less firmly to oxygen, thus releasing excess oxygen to the retinal tissue and causing hyperoxia in the immature retina.[16]

Table 4: Evaluation of independent risk factors

	OR	RR 95% CI	p
Gestational age, weeks	0.638	0.442–0.921	0.02
Birth weight, grams	0.998	0996–1.001	0.234
BPD	4.027	1.117–11.01	0.032
PPROM	3.129	0.731–14.58	0.063

OR: Odds ratio; RR: Relative ratia; CI: Confidence interval; PPROM: Preterm premature rupture of membranes; BPD: Broncho-pulmonary dysplasia.

Besides these risk factors, asphyxia, hypothermia, metabolic acidosis, systemic fungal infections, hyperglycemia, and multiple pregnancies are also risk factors for ROP.[1,4,5]

In our study, lower GA and BPD were independent risk factors for treatment requiring ROP. However, prematurity is the most important risk factor for ROP, as we know that the more immature retina is at

Table 5: Treatment requirement incidences in terms of birth weight and gestational age

Gestational age, weeks	Treatment required ROP		No ROP		Total	Birth weight, grams	Treatment required ROP		No ROP		Total
	n	%	n	%	n		n	%	n	%	n
<24	4	100	0	0	4	500–750	8	62	5	38	13
24–25	7	35	13	65	20	750–1000	11	44	14	56	25
26–28	10	33.3	20	66.7	30	1000–1500	5	8.6	53	91.4	58
28–30	4	12	28	87	32	1500–1700	1	2.1	45	97.8	46
30–32	1	1,7	55	98.2	56	>1700	1	1.3	71	98.6	72
>32	0	0	72	100	72						

ROP: Retinopathy of prematurity.

greater risk of developing abnormal vasoproliferation. On the other hand, as BPD is directly identified as having a longer need for oxygen and ventilation support, the longer oxygen therapy may result in severe ROP development.[4,5] However, in addition, growth factors such as vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), and transforming growth factor β (TGF-β) are also important in the pathogenesis of BPD. These growth factors regulate the process of lung morphogenesis in both the prenatal and postnatal periods. Disorders in the secretion of VEGF, IG F-1, and TGF beta may play a role in developing typical BPD. It is well known that VEGF regulates angiogenesis, formation, differentiation, maturation, and repair processes of the blood vessels. Furthermore, it has been shown that IGF-1 concentration is lowerin patients without BPD at the same post-conceptional age, and IGF-1 is an important factor in the maturation and repairment of the lungs. Lower IGF-1 levels cause disrupted angiogenesis and reduced VEGF synthesis. These interactions and altered growth factors' levels are important in both the developments of BPD and ROP.[17,18]

This study is important as it presents a tertiary center's ROP results with relatively high annual admissions. On the other hand, a larger number of patients may provide more significant results with a longer study period.

CONCLUSION

Clinicians must be aware of the risk factors to reduce ROP incidence. In the era of the tiniest babies' survival, oxygen, and ventilation therapies must be strictly monitored, and extensive precautions should be taken to prevent diseases with multifactorial pathogenesis, such as ROP.

Statement

Ethics Committee Approval: The Zeynep Kamil Maternity and Children's Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 06.07.2022, number: 80).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – ED, OK, GÇ, GK; Design – ED, OK, GÇ, GK; Supervision – ED, OK, GÇ, GK; Resource – ED, OK; Materials – ED; Data Collection and/or Processing – ED; Analysis and/or Interpretation – GÇ, OK, GK; Literature Search – ED, OK; Writing – ED; Critical Reviews – GK.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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