The Incidence of Retinopathy in Preterm Infants with Birthweight Above 1500 Grams

Doğum Ağırlığı 1500 Gramın Üstündeki Preterm Yenidoğanlarda Retinopati Sıklığı

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ABSTRACT

Objective: To investigate the incidence of retinopathy of prematurity (ROP) and assess risk analysis in infants of birth weight (BW) ≥1500 grams.

Material and Methods: Retrospective, single-center, cohort included preterm intensive-care admissions who were screened for ROP between 2010-2019. Exclusion criteria were BW <1500 grams, congenital anomalies, death or postnatal transfers before ROP-screening. Data were extracted for maternal/neonatal characteristics, clinical features, retinopathy's grade–zone, plus-disease and treatment. Multivariate regression analysis determined risk factors for developing retinopathy.

Results: ROP incidence was 7.6% in 1431 infants with the largest-one born 2450 grams at 36th gestational weeks (BW between 1500–1599 gr: 17.1%, 1600–1699 gr: 13.8%, 1700–1799 gr: 8.8%, 1800–1899 gr: 8.2%, 1900–1999gr: 2.9%, ≥2000 gr: 1.3%). Small for gestational age (SGA; OR:2.52, 95% CI:1.48-4.30), neonatal resuscitation (OR:3.23, 95% CI:1.87-5.57), low Apgar score (OR:2.08, 95% CI:1.03-4.20), congenital heart disease (OR:2.25, 95% CI:1.38-3.69), hemodynamic instability (OR:3.67, 95% CI:1.92-7.02), intraventricular hemorrhage (OR:2.86, 95% CI:1.40-5.86) were associated with ROP. In the multivariate logistic regression, prolonged mechanical ventilation (duration >2 days) and oxygen supplement (duration >9 days) were identified as independent risk factors that presented highest odds for retinopathy (OR:8.79, 95% CI: 5.53-13.99 and OR:4.67, 95% CI: 2.26-9.66). Therapy was warranted in 22 (1.5%) neonates (Type-1 ROP in eighteen, aggressive-ROP in four patients). Four infants with BW ≥1800 grams delivered ROP-treatment.

Conclusion: ROP incidence is 7.6% and treatment-warranted retinopathy is 1.5% in neonates born ≥1500 grams. Preterm-infants with SGA, neonatal resuscitation, congenital heart disease and hemodynamic instability requiring

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inotropes, intraventricular hemorrhage and the ones necessitating prolonged mechanical ventilation and oxygen supplement are more likely to develop ROP.

Key Words: Intravitreous injections, Photocoagulation, Retinopathy of prematurity, Risk factors

ÖZ

Amaç: Doğum ağırlığı (DA) 1500 gram ve üstündeki yenidoğanlarda prematüre retinopatisi (ROP) sıklığının ve risk faktörlerinin değerlendirilmesi

Gereç ve Yöntemler: Retrospektif, tek-merkezli, kohort olarak planlanan çalışmaya 2010-2019 yıllarında yoğun bakıma yatırılan ve ROP taraması yapılan preterm yenidoğanlar alındı. Doğum ağırlığı <1500 gram, konjenital anomalisi olan, tarama öncesi kaybedilen, dış merkeze yönlendirilenler çalışma dışı bırakıldı. Olguların maternal-neonatal özellikleri, klinik verileri, retinopati-tarama bulguları (evre, bölge, plus-hastalık), uygulanan tedaviler kaydedildi. Çoklu regresyon analiziyle ROP gelişimindeki risk faktörleri değerlendirildi.

Bulgular: Genel ROP insidansı 1431 yenidoğanda %7.6 bulundu. En büyüklerini 36. gebelik haftasında doğan 2450 gram ağırlığındaki pretermin oluşturduğu retinopati olgularının doğum ağırlığına göre sıklığı 1500–1599 gr: %17.1; 1600–1699 gr: %13.8; 1700–1799 gr: %8.8; 1800–1899 gr: %8.2; 1900–1999 gr: %2.9; ≥2000 gr: %1.3 bulundu. Gestasyonel haftasına göre DA 10 persentilin altında doğum (SGA; OR: 2.52, %95CI: 1.48-4.30), neonatal resusitasyon ihtiyacı (OR:3.23, %95 CI: 1.87-5.57), Apgar düşüklüğü (OR:2.08, %95 CI: 1.03-4.20), kalp hastalığı (OR:2.25, %95CI: 1.38-3.69), hemodinamik bozukluk (OR:3.67, %95 CI: 1.92-7.02), intraventriküler hemoroji (OR: 2.86, %95 CI:1.40-5.86) varlığıyla retinopati gelişimi arasında ilişki saptandı. Çoklu regresyon analizinde uzamış mekanik ventilasyon (>2 gün) ve oksijen desteğinin (>9 gün) en yüksek olasılığı veren bağımsız risk faktörleri olduğu saptandı (OR:8.79, %95 CI: 5.53-13.99; OR: 4.67, %95 CI: 2.26-9.66). Yirmi iki (%1.5) hastada tedavi ihtiyacı doğdu (Tip-1 hastalık: onsekiz hastada, agresif-ROP: dört hastada). Doğum kilosu 1800 gram ve üstündeki beş bebekte tedavi ihtiyacı doğdu.

Sonuç: Doğum ağırlığı 1500 gram ve üstündeki bebeklerde retinopati %7.6, tedavi ihtiyacı %1.5 sıklığındadır. Neonatal resusitasyon, SGA, intraventriküler hemoroji, uzamış solunum ve mekanik ventilasyon desteği, kalp hastalığı, inotrop ihtiyacı gösteren hemodinamik bozukluklar retinopati gelişimini artıran risk faktörleridir.

Anahtar Sözcükler: İntravitreal enjeksiyonlar, Fotokoagülasyon, Prematürite retinopatisi, Risk faktörleri

INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the retina that occurs due to various insults during the development of the organ in the preterm infant (1). If left unrecognized and not treated promptly, the disease proceeds to future childhood blindness. A 2010-study including ten countries (Turkey, USA, China, India, Indonesia, Brazil, Iran, Russian Federation, Mexico, Thailand) showed ROP is the cause of approximately two-thirds of visual impairments (2). The same data estimated 30.000 impaired visual functions in 184,700 preterm infants developing ROP (2).

The vascularization of the retina starts at prenatal 15-18 gestational weeks and is completed around 36th gestational weeks at the nasal region and 40th gestational weeks at the temporal region of the retina (can be delayed up to postmenstrual 48-52 gestational weeks (3). Until then, the retina of the preterm infants is not fully vascularized and is vulnerable to specific insults that may interrupt the normal physiological vascularization. In the routine practice of ROP screening, the classification of disease severity (ROP stage I to stage V) is based on the 2005 International Committee for the Classification of Retinopathy of Prematurity (ICROP) classification (4). Stages III and higher stages are described as advanced stages; plus-disease represents the dilatated and tortuous vessels. Partial or complete retinal detachment can occur at stages IV ve V and proceeds to visual impairment (4).

Infants with earlier gestational age (GA) and low birth weight (BW) are susceptible to this potential cause of childhood blindness (3). The greater survival of the immature infant brings along the increased risk of retinopathy. The socioeconomic status of the countries, accessibility of health care facilities and the quality of neonatal care influence ROP incidence (5). Moreover, suboptimal care in developing countries results in developing ROP in more mature preterm neonates (6). ROP remains to be a problem in neonates born less than 28 gestational weeks in developed countries; but, it can appear in the newborn of later gestations (7). In a Turkish, multicentered study, ROP incidence is documented 13.3% and severe ROP 0.4% in infants born after 32 gestational weeks (8). Regarding this fact, the current study is conducted to investigate the incidence of ROP in infants of BW ≥1500 grams in a highly-populated, tertiary neonatal intensive care unit (NICU). The second outcome was to assess risk analysis for developing ROP in this specific group of neonates.

MATERIAL and METHODS

This retrospective, single-center, observational cohort was conducted in a highly-referral, level-III NICU following the ethical approval of the study (ethics committee of Istinye University Antalya Medical Park Hospital; IRB approval no: 2019/1, date: 23.04.2019). All preterm neonatal intensive care admissions, who were born less than 37th gestational weeks, delivered cardiorespiratory support (oxygen requirement ≥ 40% to attain pulse oxygenation at 90%, invasive mechanical ventilation – MV, prolonged oxygen therapy, hemodynamic instability) and screened for ROP between 2010 and 2019 were reviewed.

Infants of BW <1500 grams, congenital anomalies, those who died or transferred to another facility before ROP screening and lack of patient data were excluded from the study.

Following the national ROP guideline, our local institutional policy is to screen all preterm infants born above 32 gestational weeks at postnatal 4th weeks before hospital discharge if they require cardiorespiratory support (ROP screening was performed after 4th weeks if they were discharged earlier) (3). We have to mention indirect binocular ophthalmoscopes are used for the retinal screening following the dilatation of the eye 1-hour before examination with phenylephrine 0.1% and cyclopentolate 0.1%. The findings for each eye are recorded according to i) the location of the involvement, ii) the extend by clock hour, iii) stage at the vascular-avascular junction and iv) the presence of plus-disease (at least 2 quadrants of dilation and tortuosity of the posterior retinal vessels) defined by 2005 ICROP classification (4). Severe ROP is defined as grade-3 ROP or more advanced stages including plus-disease. Agressive posterior ROP is another term that describes the rapidly evolving plus-disease at posterior locations (zone-1 or posterior zone-2) with flat intraretinal neovascularization and vascular loops (5). The patient follow-up is guided by the recommendations of Turkish Neonatal and Turkish Ophthalmology Societies consensus guideline on the retinopathy of prematurity and treatment is warranted for retinal findings that characterize Type-1 ROP such as: zone-1, grade-3 without plus disease or in zone-1, any stage with plus disease, or ROP in zone-2, grade-2 and 3 with plus disease and APROP (3,9). The maximum stage of ROP for each infant was recorded from the medical files accordingly.

Maternal (hypertension, diabetes mellitus and rupture of the membranes) and neonatal factors such as BW and GA, small for gestational age (SGA; BW >2 SD below the mean or <10th centile for gestational week, gender, multiple gestations, mode of delivery, assisted reproductive technology (ART) and neonatal resuscitation were retrieved from the medical database. The clinical variables including respiratory distress syndrome (RDS), invasive MV and oxygen requirement (via hood and noninvasive ventilation), echocardiographically-confirmed congenital heart disease (both cyanotic and left-to-right shunting cardiac anomalies), hemodynamic instability (any systolic blood pressure < 3rd percentile for age) that requires the use of inotropes (sympathomimetic drugs: dopamine, dobutamine, adrenaline infusions), intraventricular hemorrhage (IVH), sepsis (early and late-onset sepsis), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD; persistent oxygen dependency up to 28 days of life) and if received, packed red blood cell (PRBC) transfusions were recorded (10).

SPSS version-21 (IBM Statistical Package for the Social Sciences) was used for statistical analysis. Following the normality assumption for numerical variables, the results were presented as percentage (%), mean±standart deviation (SD) or median (interquartile range: IQR, 25%-75%). Mann-Whitney U test (for nonparametric variables) or independent sample t-test was used to compare the differences. Chi-squared test or Fischer exact test was performed for categorical variables. Receiver operating characteristic (ROC) analysis calculated the cutoff values, the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) for the duration of invasive MV and oxygen supply using Medcalc statistical program (free-trial version). Logistic regression determined the odds ratio (OR) and 95% confidence intervals (CI) for proceeding ROP and a P-value of 0.05 was used as the threshold for statistical significance.

RESULT

Overall ROP incidence was 7.6% in 1431 infants with the largest one born 2450 grams at 36th gestational weeks and treatment was warranted in 1.5% of the population (Table I). In respect to categorical birthweights, the rates were 17.1%, 13.8%, 8.8%, 8.2%, 2.9% ve 1.3% in every 100 grams increase in BW (1500–1599 grams, 1600–1699 grams, 1700–1799 grams, 1800–1899 grams, 1900–1999 grams and ≥2000 grams, respectively; Figure 1). According to ROP grades and zones, grade-1 disease was observed in 65.1% (71/109), grade-2 in 19.3% (21/109), grade-3 in 11.9% (13/109) and zone-1 in 13.8% (15/109), zone-2 in 17.4% (19/109), zone-3 in 68.8% (75/109) of retinopathic infants. Plus-disease occurred in five neonates with BW <1700 grams, while four (3.7%) infants developed rapidly evolving APROP.

The maternal and neonatal characteristics are shown in Table II. The demographic outcome demonstrated ROP was not associated with any maternal risk factors, but inversely related with BW (OR:0.99, 95% CI: 0.99-1.00), and GA (OR: 0.39, 95% CI: 0.31-0.49). Infants born SGA had a 2.5-fold increase in developing retinopathy (OR: 2.52, 95% CI:1.48-4.30). Univariate logistic regression identified increased retinopathy risks with several clinical variables such as neonatal resuscitation at birth (OR: 3.23, 95% CI: 1.87-5.57), Apgar score <7 (OR: 2.08, 95% CI: 1.03-4.20), oxygen delivery (OR: 2.40, 95% CI: 1.59-3.61), invasive MV (OR: 2.72, 95% CI: 1.65-4.48), congenital heart diasease (OR: 2.25, 95% CI: 1.38-3.69), hemodynamic instability necessitating inotrope use (OR: 3.67, 95% CI: 1.92-7.02), and IVH (OR: 2.86, 95% CI: 1.40-5.86) (Table III).

Invasive MV more than two days and oxygen supply exceeding nine days had the sensitivity of 91.3% and 72.3%, but low-to-moderate specificity of 57.6% and 79.2% in ROC analysis (invasive MV: AUC: 0.78, sensitivity: 91.3%, specificity: 57.6% PPV: 29.6%, NPV: 97.1% and oxygen therapy: AUC: 0.74, sensitivity: 72.3%, specificity: 79.2%, PPV: 29.9%, NPV: 96%) (Figure 2). In the multivariable regression model, prolonged invasive MV (duration >2 days) and oxygen supply (duration >9 days) were identified as the independendant risk factors with highest odds ratios for developing retinopathy (OR: 8.79, 95% CI: 5.53-13.99 and OR 4.67, 95% CI: 2.26-9.66, respectively; Table IV).

Table I: ROP incidence according to categorical birthweight.

Birthweight (grams)	1500 – 1599 (n=199)	1600 – 1699 (n=188)	1700 – 1799 (n=297)	1800 – 1899 (n=147)	1900 – 1999 (n=206)	≥ 2000 gr (n=394)	Total (n=1431)
ROP (any grades)	34 (17.1%)	26 (13.8%)	26 (8.8%)	12 (8.2%)	6 (2.9%)	5 (1.3%)	109 (7.6%)
Grade-1	16 (47.1%)	19 (73.1%)	20 (76.9%)	9 (75%)	3 (50%)	4 (80%)	71 (65.1%)
Grade-2	9 (26.5%)	4 (15.4%)	2 (7.7%)	2 (16.7%)	3 (50%)	1 (20%)	21 (19.3%)
Grade-3	6 (17.6%)	2 (7.7%)	4 (15.4%)	1 (8.3%)	-	-	13 (11.9%)
Plus-disease	3 (8.8%)	2 (7.7%)	-	-	-	-	5 (4.6%)
APROP	3 (8.8%)	1 (3.9%)	-	-	-	-	4 (3.7%)
Zone-1	5 (14.7%)	3 (11.5%)	5 (19.2%)	2 (16.7%)	-	-	15 (13.8%)
Zone-2	4 (11.8%)	8 (30.8%)	5 (19.2%)	-	2 (33.3%)	-	19 (17.4%)
Zone-3	25 (73.5%)	15 (57.7%)	16 (61.5%)	10 (83.3%)	4 (66.7%)	5 (100%)	75 (68.8%)
TW-ROP	9 (4.5%)	4 (2.1%)	5 (1.7%)	2 (1.4%)	2 (1.0%)	-	22 (1.5%)
Anti-VEGF therapy	6 (3.0%)	4 (2.1%)	3 (1.0%)	2 (1.4%)	1 (0.5%)	-	16 (1.1%)
Laser photocoagulation	3 (1.5%)	-	2 (0.7%)		1 (0.5%)	-	6 (0.4%)
Postmenstrual age (weeks)*	39 (37.75-40)	40 (37.5-41)	40 (38-41)	40.5 (40-41)	40 (39 – 42)	40(39.5-41.5)	-

ROP: *Retinopathy of prematurity,* ***APROP:*** *Aggressive posterior ROP,* ***TW – ROP:*** *Treatment warranted ROP,* ***VEGF:*** *vascular endothelial growth factor -* ***Anti-VEGF therapy*** *refers to intravitreous injection of Bevacizumab (Avastin®), ranibizumab (Lucentis®) or aflibercept (Eylea®).* *******Median (interquartile range 25%-75%)*

Table II: Maternal and Neonatal Characteristics.

	No ROP (n=1322)	ROP (n=109)	Univariate logistic regression		
			OR	95% CI	p
Maternal Factors					
Maternal age, (years)*	29.84 ± 6.37	28.93 ± 6.27	0.978	0.948-1.008	0.152
Hypertension,†	131 (9.9%)	7 (6.4%)	0.624	0.284-1.370	0.240
Placental problems,†	39 (3.0%)	4 (3.7%)	1.253	0.439-3.574	0.673
Rupture of membrane,†	48 (3.6%)	3 (2.8%)	0.751	0.230-2.452	0.636
Diabetes mellitus,†	104 (7.9%)	14 (12.8%)	1.726	0.951-3.131	0.073
Antenatal steroid,†	507 (38.4%)	32 (29.4%)	0.668	0.436-1.024	0.064
ART, †	79 (6.0%)	6 (5.5%)	0.917	0.390-2.153	0.841
Natal Characteristics					
Mode of birth delivery					
Caesarean section†	1043 (78.9%)	88 (80.7%)			
Vaginal birth†	279 (21.1%)	21 (19.3%)	1.121	0.684-1.837	0.651
Multiple birth,†	86 (6.5%)	7 (6.4%)	0.986	0.445-2.187	0.973
Gestational age* (weeks)	33.90 ± 1.33	32.82 ± 0.79	0.395	0.312-0.498	<0.001
Birthweight‡ (grams)	1886 (1700 - 2210)	1659 (1575 - 1787.5)	0.999	0.999-1.000	0.002
SGA,†	102 (7.7%)	19 (17.4%)	2.525	1.480-4.309	0.001
Gender,†					
Male	668 (50.5%)	57 (52.3%)	0.932	0.630-1.378	0.723
Female	654 (49.5%)	52 (47.7%)			
Postnatal transfers,†	438 (33.1%)	41 (37.6%)	1.217	0.812-1.823	0.341

*******mean ± SD, †%, ‡median (interquartile range [IQR]: 25%-75%). Postnatal transfers refer to the infants given birth in a health facility other than the center where the neonatal care will be delivered.* ***ART:*** *assisted reproductive technology, SGA: small for gestational age (birthweight >2 SD below the mean or <10th centile for gestational week)*

The therapy (intravitreous anti-vascular endothelial growth factor-antiVEGF therapy and laser photocoagulation) was warranted in 22 (1.5%) neonates with Type-1 ROP in eighteen infants (13 patients: zone-1 grade-3 ROP without plus-disease; 5 patients: zone-2, grade 2 with plus-disease) and APROP in four infants. Four newborns with ≥1800 grams received retinopathy treatment (all infants were born with low Apgar scores and necessitated neonatal resuscitation; two infants had left-to-right shunted cardiac disease and presented the signs of severe cardiac failure; another one acquired grade-2 IVH).

DISCUSSION

Until recently, the screening of retinopathy in premature babies was restricted to infants born less than 1500 grams or 30 gestational weeks; however, increasing reports of ROP developing in larger neonates have obliged the American Academy of Pediatrics and American Academy of Ophthalmology societies to reconsider their recommendations (11). The recent ROP guideline revised in 2018, advised the screening of infants of BW between 1500grams and 2000

Table III: Neonatal Complications Related to Prematurity.

	No ROP (n=1322)	ROP (n=109)	Univariate logistic regression		
			OR	95% CI	p
Neonatal resuscitation, †	81 (6.1%)	19 (17.4%)	3.234	1.878-5.570	<0.001
Apgar score <7, †	61 (4.6%)	10 (9.2%)	2.088	1.038-4.202	0.039
O_2 therapy, †)	592 (44.8%)	72 (66.1%)	2.400	1.591-3.619	<0.001
Days on O2 therapy (days)*	7 (6-9)	10 (8.5-13)	1.238	1.156-1.325	<0.001
Invasive MV, †	118 (8.9%)	23 (21.1%)	2.729	1.659-4.487	<0.001
The length of invasive MV (days)*	2 (1-4)	4 (3-5)	1.234	1.010-1.506	0.039
RDS, †	101 (7.6%)	14 (12.8%)	1.782	0.981-3.235	0.058
BPD, †	11 (0.8%)	2 (1.8%)	2.228	0.487-10.180	0.302
Congenital heart disease, †	140 (10.6%)	23 (21.1%)	2.258	1.380-3.694	0.001
Hemodynamic instability–inotropes †	47 (3.6%)	13 (11.9%)	3.674	1.921-7.025	<0.001
IVH prior to ROP, †	45 (3.4%)	10 (9.2%)	2.866	1.402-5.860	0.004
Sepsis, †	95 (7.2%)	8 (7.3%)	1.023	0.483-2.165	0.953
NEC, †	-	3 (2.8%)	-	-	-
Blood (PRBC) transfusion, †	129 (9.8%)	11 (10.1%)	1.038	0.542-1.987	0.910

***median (interquartile range [IQR]:25%-75%), †%, **MV:** Mechanical ventilation, **RDS:** Respiratory distress syndrome, **BPD:** Bronchopulmonary dysplasia, **IVH:** Intraventricular hemorrhage, **ROP:** Retinopathy of prematurity, **NEC:** Necrotizing enterocolitis, **PRBC:** Packed red blood cell*

Table IV: Multiple logistic regression model for developing ROP.

Variables	Exp (B)	95% C.I. for EXP(B)		p
		Lower limit	Upper limit	
SGA	3.188	1.729	5.880	<0.001
Neonatal resuscitation	2.521	1.339	4.748	0.004
Duration of O_2 therapy >9 days	4.677	2.263	9.666	<0.001
Invasive MV >2 days	8.799	5.533	13.992	<0.001
Congenital heart disease	2.442	1.266	4.708	0.008

***Nagelkerke R^2 of the multivariate regression model: 0.420. **SGA:** Small for gestational age (birthweight >2 SD below the mean or <10th centile for gestational week), **invasive MV:** Invasive mechanical ventilation*

grams who fulfill certain criteria (9). This suggestion was applicable for many developing countries since the incidence varied upon the socioeconomic status, birth conditions and the quality of neonatal care (5,12). Data suggest that more mature preterm babies can develop severe ROP and screening guidelines might not be appropriate to detect retinopathy in middle-to-low income societies (13). Numerous publications from different countries point out the concern for developing retinopathy in infants of BW >1500 grams: a Mexican study demonstrated 19.9% of the screened newborns fell out of the American Academy of Pediatrics 2018-guidelines and 38% of these outliers required ROP treatment (11). In another study from Lithuania, ROP therapy was applied to 54% of infants with BW >1500 grams (14). Several reports featuring retinopathy in neonates of BW between 1500 grams and 2000 grams and GA 32 weeks and 37 weeks share similar data in Turkey (8,15-20). A retrospective study evaluating 5920 ROP screening between 2011 and 2015 from Zeynep Kamil Maternity and Children's Disease Training and Research Hospital demonstrated 36 infants (0.61%) with BW >1500 grams developed ROP in Istanbul (largest infant with GA 36 weeks and 2900 grams) (15). Kola et al. (20) studied all preterm infants of GA ≤36 weeks in the Eastern Black-Sea region of Turkey and reported 46.9% rate of retinopathic patients were above 1500 grams. The authors also suggested screening preterm neonates born ≤33 gestational weeks and ≤1770 grams. The incidence is highly variable: 9.3% retinopathy rate in Western- Black-Sea region, 11.1% in Central Anatolia, 17.8% in İstanbul (16,20,21). In 2015, the ROP Neonatal Study group reported the incidence as 14.5% for all grades of ROP, 0.06% for grade-3 and higher grades and 0.067% for laser photocoagulation therapy (8). Three years after, another multicentered, prospective study (TR-ROP) involving 69 Turkish NICUs evaluated 6115 preterm infants (19% of the population were above 32 gestational weeks) (7). TR-ROP study demonstrated the incidence as 10.3% and 3.8% for infants of BW 1500-2000 grams and BW >2000 grams. Moreover, the authors observed 1% of the infants (BW: 1500-2000 grams) required treatment and concluded the screening of preterms born ≤34 gestational weeks or BW<1700 grams in Turkey. In the present study, 1431 ROP screening was performed at one of the highest-referral healthcare facility in the city of Antalya to

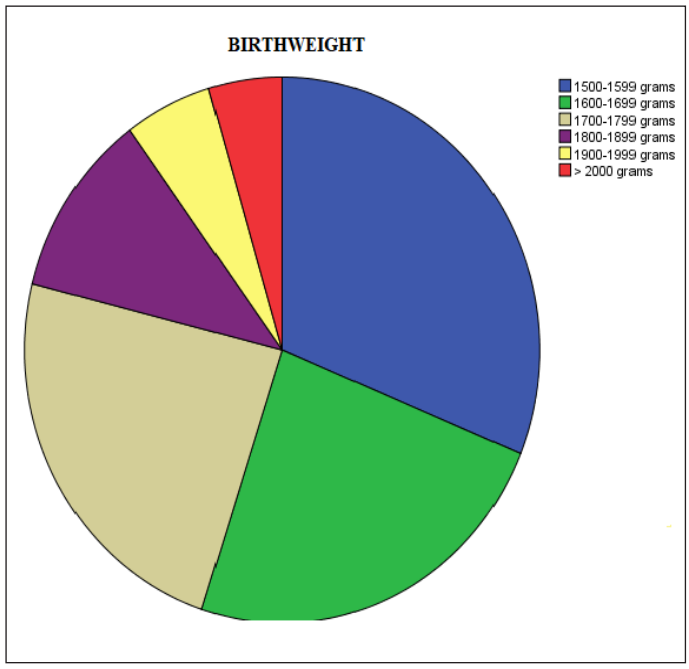


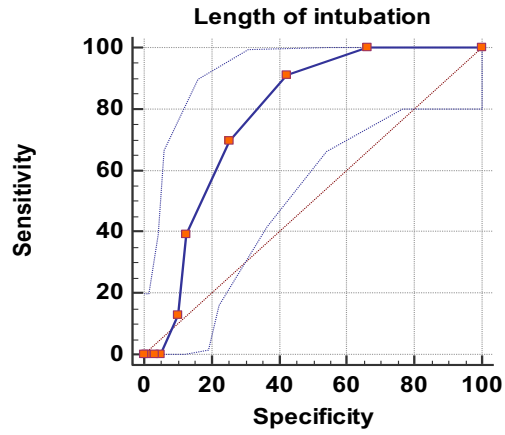
Figure 1: ROP incidence according to birthweight.

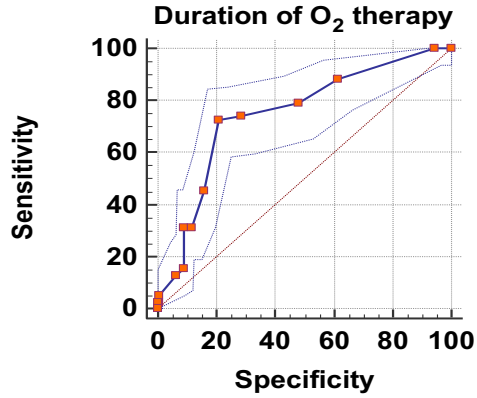
the infants with BW ≥1500 grams within 10 years period. A total of 109 neonates (7.6%) developed retinopathy (including all grades) and 22 (1.5%) of the patients required therapy (1.7%, 1.4% and 1% in infants of BW 1700-1799 grams, 1800-1899 grams and 1900-1999 grams, respectively). We observed five infants were above 2000 grams, with the largest one born 2450 grams and 36th gestational weeks. Given the facts, Turkish Neonatal and Turkish Ophthalmology Societies suggested screening for retinopathy in neonates with BW >1500 grams or GA >32 weeks who require cardiopulmonary support or at risk for ROP (3). Our findings confirmed the study of Chen et al. (23), that retinopathy screening varies greatly between intensive care units and each neonatal care facility should develop its screening criteria in light of the environmental characteristics.

Several prenatal-perinatal factors other than BW and GA have been identified in the development of retinopathy. Excessive and/or inappropriate oxygen therapy appears to be the major contributor of ROP in more mature infants (15,20). Maternal diabetes mellitus, intraventricular hemorrhage, sepsis and pneumonia, pulmonary disease, mechanical ventilation, hypotension requiring inotropes, birth in a health-facility other than the center where the neonatal care will be delivered are some of the risk factors in larger neonates (9,12,15,23-25). Hungi et al. (26) identified increased risks with sepsis, neonatal jaundice, RDS and oxygen therapy in developing severe ROP in more mature infants. Our findings confirmed that infants with SGA, hemodynamic instability, IVH, congenital heart disease and those who required neonatal resuscitation at birth, invasive MV and oxygen supply were likely to develop ROP. However, the highest odds for retinopathy occurred when the infants delivered invasive MV more than two days and oxygen supply exceeding nine days in the multivariate regression. The influence of oxygen supply has been demonstrated in previous studies (7,27,28). Supplemental oxygen insults the vasculature during the vasoconstrictive phase (phase-I) and vasoproliferative phase (phase-II) proceeds after postmenstrual 32 weeks but has a wide range of onset. In very low birthweight neonates, prolonged mechanical ventilation for more than 7 days is identified as a risk factor, while each day of oxygen supply increases the risk of retinopathy 1.023-fold in infants of BW >1500 grams (7 ,28). The findings supported the role of oxygen on retinopathy regardless of BW. Acute and chronic respiratory conditions like RDS and BPD, which are known to influence retinopathy in preterm infants, did not have any impact on developing ROP in this study (29,30).

The subject of cardiac disease is a matter of debate in developing ROP. Previous research reported an association with cyanotic heart disease (31). Conversely, reduced perfusion due to by-pass of systemic blood flow in left-to-right shunting conditions like PDA might cause retinal hypoxia and attribute to developing ROP (32-34). Increased pulmonary circulation and systemic infections contribute to the pathophysiological process of retinopathy (35). Our data also suggested increased risks for congenital heart disease (OR: 2.25, 95% CI: 1.38-3.69) and hemodynamic instability requiring inotrope use (OR: 3.67, 95% CI: 1.92-7.02). Moreover, we observed, treatment-warranted ROP (TW-ROP) occurred in infants with BW ≥1800 grams who possess mostly left-to-right shunted cardiac conditions. Our findings confirmed the study of Thomas et al. (31), who reported any hemodynamic alterations resulting in reduced systemic perfusion, oxygenation and the following reperfusion contributed to ischemic damage of retinal tissue. The authors also identified hypotension and the use of inotropes were more likely to develop severe ROP. However, the reason behind this fact remained unclear. Future research should encompass the influence of hemodynamic alterations and inotrope administrations, whether if retinopathy can occur due to insufficient perfusion, retinal ischemia-reperfusion, or a direct impact of sympathomimetic drugs (inotropes) on retinal vasculature. Nevertheless, close monitoring of hemodynamic status and delicate optimization of oxygen saturation shields a protective mechanism for ROP development.

Predictive models have been developed to define an infant at risk for retinopathy (12). However, screening infants born >1500 grams is open to dispute because the majority of NICU admissions require cardiorespiratory support and screening them all (born <37 weeks) are not feasible in the daily practice of neonatal care. That's why the decision of retinal screening is left to the discretion of the neonatologist in both national and international guidelines (3,9). Hence, the attending physician needs to incorporate additional data other than BW, lower gestations or cardiorespiratory support. We observed a strong relationship between SGA infants and retinopathy in the present study. However, the literature search appointed controversial data on the topic of SGA. Previous investigations found out SGA as an independent predictor of ROP, lower risk of ROP or no indicator of ROP at all (35-39). Chronic uterine hypoxia,





AUC: 0.781 (95% CI: 0.704 -0.846) **Sensitivity**: 91.3% (95% CI: 72% - 98.9%) **Specificity:** 57.6% (95% CI: 48.2% - 66.7%) **Likelihood ratio**: 2.15 (95% CI: 1.7 - 2.8) **Positive predictive value**: 29.6% (95% CI: 19.3% - 41.6%) **Negative predictive value**: 97.1% (95% CI: 90.1% - 99.0%)	**AUC:** 0.748 (95% CI: 0.714 - 0.779) **Sensitivity:** 72.3% (95% CI: 61.4% - 82.3%) **Specificity:** 79.2% (95% CI: 75.9% - 82.3%%) **Likelihood ratio:** 3.5 (95% CI: 2.9 – 4.3) **Positive predictive value**: 29.9% (95% CI: 23.5% - 37.1%) **Negative predictive value:** 96.0% (95% CI: 93.9%-97.5%)

Figure 2: ROC analysis demonstrating length of endotracheal invasive mechanical ventilation and the duration of total days in O_2 therapy.

nutrient restriction and antioxidant deficiency might contribute to SGA in developing ROP (7,37). A 2.52-fold increase in SGA of this study suggested, screening recommendations should narrow down the frequency of follow-up for early ROP detection in these newborns. The second risk assessment for retinopathy should include Apgar scores and the need for resuscitation at birth; because both parameters influenced developing ROP in the present study. Low Apgar scores, which is generally an indicator of poor neonatal health, retinal screening should be considered in infants of BW >1500 grams (28). The authors of the present study oppose this suggestion. Low Apgar scores do not diagnose asphyxia and predict individual neurologic outcomes alone (40). It should be embodied in other neonatal variables in the decision-making process of retinal screening.

The limitations of this study were retrospective nature for the potential risk of bias. Designing single-center research also limited the study outcomes to generalize conclusions. The absence of long-term treatment outcome was another limitation. However, much of the previous research focuses on risk analysis of neonates born at gestations 32 weeks and earlier and the subject of retinopathy is a relatively rare investigated area for more mature preterm infants. Hence selecting a preterm population of BW ≥1500 grams from a highly-referral neonatal center within ten years period and obtaining risk analysis for this group was the strength of this study. The results emphasized the need for ROP screening criteria in resourced-limited settings to become wider than highly-income countries.

CONCLUSION

ROP remains a leading cause of childhood blindness and can develop in more mature neonates. The overall incidence is 7.6% and treatment-warranted retinopathy is 1.5% in neonates born ≥1500 grams. Preterm infants with SGA, neonatal resuscitation, congenital heart disease and hemodynamic instability requiring inotropes, intraventricular hemorrhage and the ones necessitating prolonged mechanical ventilation and oxygen supplement are more likely to develop ROP.

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