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Clinical and Demographic Characteristics of Treatment Requiring Retinopathy of Prematurity in Big Premature Infants in Turkiye: Report No. 1 (BIG-ROP Study)

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Clinical and Demographic Characteristics of Treatment Requiring Retinopathy of Prematurity in Big Premature Infants in Turkiye: Report No. 1 (BIG-ROP Study)

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Keywords
Retinopathy of prematurity · Neonatal care · Oxygen therapy · Retinopathy of prematurity screening

Abstract

Introduction: The aim of the study was to analyse the clinical and demographic features of infants with gestational age (GA) of 32–37 weeks and birth weight (BW) of >1,500 g who developed treatment requiring retinopathy of prematurity (ROP). ***Methods:*** Data on the infants with a GA of 32–37 weeks and BW >1,500 g who developed treatment requiring ROP (TR-ROP) were collected retrospectively from the 33 ROP centres in Turkiye. GA, BW, type of hospital, neonatal intensive care units (NICUs) level, presence of an ophthalmologist and neonatologist in the same hospital, length of stay in NICU, duration of oxygen therapy, comorbidities, type of ROP, and timing for TR-ROP development were analysed. ***Results:*** A total of366 infants were included in the study. Mean GA and BW were 33 ± 1 weeks and 1,896 ± 316 g, respectively. Duration of hospitalization was 3–4 weeks in 46.8% of them. The first ROP examination was performed at postnatal 4–5 weeks in 80.3% of infants, which was significantly later in level 2 and lower NICUs and non-university clinics. At the first ROP examination, any stage of ROP was detected in 90.9% and TR-ROP was detected in 15.3% of the infants. The mean postnatal week of TR-ROP development was 6.16 ± 2.04. ***Conclusion:*** Routine ROP screening thresholds need to be expanded in hospitals with suboptimal NICU conditions considering the development of TR-ROP in more mature and heavier preterm infants. The first ROP examination should be earlier than the fourth postnatal week.

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Plain Language Summary

Retinopathy of prematurity (ROP) is a serious eye condition that affects premature babies, sometimes leading to blindness. Babies born at more than 32 weeks of

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pregnancy or weighing over 1,500 g are generally considered less at risk. However, in low- and middle-income countries where neonatal intensive care is not optimal, these bigger and more mature babies can still develop severe ROP requiring treatment (TR-ROP). This study is the first of its kind to examine how having both an eye specialist (ophthalmologist) and a baby care specialist (neonatologist) in the same hospital affects the development of TR-ROP in different regions across Turkiye. The study found that bigger babies often show signs of ROP at their first eye exam and that the condition can worsen quickly. This aggressive form of ROP, similar to a severe type called A-ROP, progresses rapidly. The findings suggest that these bigger babies need to be screened earlier than 4 weeks after birth. The study recommends expanding ROP screening programs to include larger infants, especially in developing areas of Turkiye. These recommendations could also apply to other developing countries facing similar challenges.

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Introduction

Retinopathy of prematurity (ROP) is a sight-threatening, vasoproliferative disease affecting the immature peripheral retina in premature infants. ROP-related blindness can be potentially avoidable with advanced neonatal care and effective screening/treatment programs. The prevalence of ROP varies among countries and is influenced by the income of countries and the development of neonatal intensive care units (NICUs) [1]. Treatment requiring ROP (TR-ROP) typically occurs in bigger and more mature infants in low-/middle-income countries [1]. Therefore, national screening criteria are usually set according to the demographic features of infants developing ROP.

According to Turkiye ROP screening guideline, which was established in 2016, preterm infants with gestational age (GA) ≤32 weeks or birth weight (BW) ≤1,500 g or infants with a BW >1,500 g and GA >32 weeks with a defined extra-risk factor for ROP by paediatrician are screened for ROP [2]. A previous multicentre prospective study in Turkiye showed that the rates of severe ROP were higher in non-university NICUs, especially in private hospitals [3]. The study's findings also revealed that bigger and more mature infants are at increased risk of developing severe ROP in Turkiye. They indicated that screening criteria should be wide enough to detect the majority of infants developing TR-ROP [3]. In this study, we aimed to evaluate retrospectively the demographic and clinical features of TR-ROP seen in infants with a GA >32 weeks and BW >1,500 g in Turkiye.

Methods

This non-randomized, retrospective, multicentre study was conducted by the Turkish Ophthalmological Association (TOA) ROP commission to evaluate the demographic and clinical features of preterm infants with a GA >32 weeks and BW >1,500 g who developed TR-ROP. Members of the TOA who wish to contribute were requested to fill out the study-specific data entry forms for each patient treated for TR-ROP [4]. A total of 290 ophthalmologists were contacted through email. Submission of the fulfilled documents was made until December 2020. The study organizers (S.O., H.B.O.) received data of 713 eyes of 376 patients treated by 57 ophthalmologists (19.6%) from 33 centres. The Institutional Review Board of each centre and the Ethics Commission of Gazi University (No: 2020-191) approved the study protocol, which adhered to the tenets of the Declaration of Helsinki.

Infants with GA between 32 and 37 weeks and BW ≥1,500 g who developed TR-ROP were included in the study retrospectively. Infants with GA <32 weeks, BW <1,500 g, or bigger infants developing ROP who did not meet treatment criteria were excluded. Demographic data including GA, BW, city and region where the infant was born, city and region where the infant was hospitalized, level of NICU (between level 1 and 4) [5], and type of hospital defined as a university hospital, state hospital, or private hospital were collected for each case. University hospitals are defined as hospitals affiliated with a university that provide the highest level of service in academic and practical terms. State hospitals are divided into two as training clinics and service clinics, and academic staff and fellows are available in training clinics. In service clinics, NICU services are provided at a specialist level. Private hospitals can provide NICU services if they meet the Ministry of Health criteria. NICU services are not subject to special fees and are paid by general health insurance in all hospital types. The presence of neonatologists and ophthalmologists in the hospital was also questioned. If there was no ophthalmologist in the same hospital as NICU, the details of how the ROP examination was performed were requested, such as inviting an ophthalmologist from another centre or transferring the infant to another centre for ROP screening.

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All ROP examinations were performed by using binocular indirect ophthalmoscopy by ophthalmologist certified and experienced in ROP. Wide angle imaging was used as an additional tool in centres where available. Clinical features, including duration of hospitalization in NICU, mechanical ventilation, continuous positive airway pressure, and total oxygen therapy, were analysed. Comorbidities of prematurity such as the presence of respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia, sepsis, cardiac disease, anaemia, haematocrit levels, resuscitation history, phototherapy, surfactant treatment, extraocular surgery, total parenteral nutrition, duration of antibiotic use, presence and stage of intraventricular haemorrhage were also questioned for each case. Maternal risk factors such as age, presence of gestational diabetes, early membrane rupture, pre-eclampsia, multiple pregnancies, in vitro fertilization, and antenatal steroid treatment were collected. Even if the received data of neonatological assessment were not complete, the data sent were included if they were consistent and met the criteria of treatment.

Statistical analyses were performed using SPSS v22.0. The normal distribution of the continuous variables was tested using the Kolmogorov-Smirnov test and the homogeneity of variance was tested using Levene's test. Descriptive statistics as frequencies, percentages, mean (± standard deviation), and median values (minimum, maximum) were first calculated for all variables of interest. Pearson's χ^2, Fisher's exact, likelihood ratio, and McNemar's tests were used for comparisons of categorical data. Prospective selective multinomial logistic regression analysis was performed to identify important risk factors for the development of aggressive ROP (A-ROP). Statistical significance was set as a 2-tailed p value <0.05.

Results

Data of 376 infants treated between January 2003 and December 2020 from 33 reference centres for ROP were received. Ten patients were excluded due to insufficient data or duplication, and 366 patients were included in the study. The 33 participating centres had ophthalmology units for ROP screening, all of the centres performed laser photocoagulation and/or anti-vascular endothelial growth factor treatments, and one centre performed vitreoretinal surgery. Totally, 78.4% ($n = 287$) of the infants were accepted to the referral centres for treatment from another NICU.

The mean GA of infants was 33 ± 1 (32–37) weeks, and the mean BW was 1,896 ± 316 g (1,505–3,760 g). The distribution of hospitals where infants were born and received NICU care is given in Table 1. The demographic data and the duration and type of oxygen delivery are listed in Table 1. Maternal and prematurity-related comorbidities are presented in Table 2.

Most of the neonatal care was conducted by private NICUs (67.5%). The rate of private NICUs in high-income cities (74.1%) was higher than in low-income cities (50%) ($p < 0.0001$). There was at least one neonatologist in 49% of NICUs regardless of hospital type in the low-income cities and in 73.1% in the high-income cities ($p < 0.0001$). However, the rate of ROP examination by an ophthalmologist at the same hospital with NICU was 44% in low-income cities and 27.8% in high-income cities ($p < 0.0001$). The absence of neonatologists and ophthalmologists was statistically higher in non-university hospitals and lower levels of NICU ($p < 0.0001$ for all). The neonatologist was present in all level 3B and 4 NICUs but in only 68.5% of level 3A NICUs and in 39% of level 1 and 2 NICUs. The rate of presence of a neonatologist in the university hospitals was 95.5%, which was statistically significantly higher than that in the state hospitals (84%) and in the private hospitals (54.3%) ($p < 0.0001$). The rate of ROP examination by an ophthalmologist at the same hospital with NICU was 88.6% in university hospitals, 68% in state hospitals, and 11.3% in private hospitals ($p < 0.0001$).

In the present study, 294 infants (80.3%) were examined at the appropriate time according to Turkiye ROP screening guideline, which was postnatal 4–5 weeks. The first examination time was postnatal 6 weeks in 32 infants (8.7%) and postnatal 7 weeks in 40 infants (10.9%). The first examination timing was statistically significantly later in lower levels of NICU ($p = 0.001$), in the absence of an ophthalmologist at the same hospital with NICU ($p = 0.003$), and in non-university hospitals ($p = 0.025$). ROP was present in 328 infants (90.9%) at the first examination. The presence of ROP at the first examination was statistically significantly ($p < 0.05$) higher in lower levels of NICU and in the absence of an ophthalmologist at the same hospital (Table 3). There was no statistically significant difference between the prematurity-related comorbidities, such as RDS, NEC, anaemia, and thrombocytopenia, and maternal comorbidities listed in Table 2 and the presence of ROP at the initial examination ($p > 0.05$ for all parameters). TR-ROP developed in a mean of postnatal 6.16 ± 2.04 weeks (4–18 weeks). TR-ROP was detected at the postnatal 4th week

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Table 1. Demographic data of infants

	Patients, *n* (%)
Development status of the cities	
High-income cities	266 (72.7)
Low-income cities	100 (27.3)
Hospital type	
University hospital	44 (12.0)
State hospital	75 (20.5)
Private hospital	247 (67.5)
Level of NICU	
Level 1–2	77 (21.0)
Level 3	243 (66.4)
Level 4	46 (12.6)
Neonatologist present at NICU	
Yes	226 (66.1)
No	116 (33.9)
ROP screening by	
Ophthalmologist in the same hospital	118 (32.2)
Invited ophthalmologist from another centre	176 (48.1)
Referring the infant to another hospital	72 (19.7)
Total stay at NICU (*n*: 363)	
0–2 wks	57 (15.7)
3–4 wks	170 (46.8)
5–8 wks	94 (25.9)
>8 wks	42 (11.6)
Total oxygen treatment duration (*n*: 218)	
<1 wk	30 (13.7)
1–3 wks	105 (48.2)
>3 wks	83 (38.1)
Duration of mechanical ventilation (*n*: 203)	
<1 wk	132 (65.0)
1–3 wks	45 (22.2)
>3 wks	26 (12.8)
Duration of CPAP (*n*: 196)	
<1 wk	144 (73.5)
1–3 wks	43 (21.9)
>3 wks	9 (4.6)

CPAP, continuous positive airway pressure; wks, weeks.

in 56 infants (15.4%). ROP type was A-ROP in 60 infants (16.4%) and type 1 ROP in 306 infants (83.6%).

The frequency of A-ROP was higher in Southeastern Anatolia than in other regions ($p < 0.001$) (Fig. 1). The frequency of A-ROP was lower in state hospitals than in university and private hospitals ($p = 0.037$, $p = 0.001$, respectively). The frequency of A-ROP was lower in the level 4 NICUs than in level 3 NICUs ($p = 0.016$). There was no statistically significant difference between the prematurity-related comorbidities, such as RDS, NEC, anaemia, and thrombocytopenia, and maternal co-morbidities listed in Table 2 and the presence of A-ROP ($p > 0.05$ for all parameters). The comparisons according to the presence of neonatologists and ophthalmologists are presented in Table 4. Multinomial logistic regression analysis was performed to identify hospital-related risk factors in the development of A-ROP (Table 5).

Discussion

It is well known that the incidence and severity of ROP increase with decreasing GA and BW [6]. It is unusual to see a TR-ROP development in infants with a GA of >30

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Table 2. Maternal and prematurity-related comorbidities

Comorbidity, *n*	Patients, *n* (%)
Prematurity-related comorbidities	
RDS (*n*: 217)	137 (63.1)
BPD (*n*: 217)	31 (15.2)
Sepsis (*n*: 245)	84 (34.3)
IVH (*n*: 213)	26 (12.2)
NEC (*n*: 217)	10 (4.6)
Cardiac disease (*n*: 207)	33 (15.9)
Anaemia (*n*: 206)	79 (38.3)
Thrombocytopenia (*n*: 206)	57 (27.6)
TPN (*n*: 178)	57 (32)
Phototherapy (*n*: 209)	67 (32.1)
Resuscitation (*n*: 190)	34 (17.9)
Surgery except for ocular conditions (*n*: 205)	25 (12.2)
Maternal comorbidities	
Multiple pregnancies (*n*: 332)	90 (27.1)
Gestational diabetes (*n*: 191)	28 (14.7)
Pre-eclampsia/eclampsia (*n*: 179)	33 (18.4)
Early membrane rupture (*n*: 225)	42 (18.7)
Antenatal steroid (*n*: 112)	56 (50)
Assisted reproductive techniques (*n*: 145)	25 (17.2)

BPD, bronchopulmonary dysplasia; TPN, total parenteral nutrition; IVH, intraventricular haemorrhage.

Table 3. Comparison of NICUs according to different criteria for the presence of ROP in the first examination

Criteria	Level of NICU (*n*: 361)				Presence of neonatologist in the NICU (*n*: 337)			ROP examination type (*n*: 361)			
	level 1–2	level 3	level 4	*p* value	present	absent	*p* value	examiner in the same hospital	invited examiner	referring to another centre	*p* value
Percentage of patients with ROP in the first examination	96%	90.8%	82.6%	**0.046**	88.8%	94.7%	0.056	85.5%	91.4%	94.3%	**0.038**

weeks or a BW >1,500 g in optimum NICU conditions, which is usually available in high-income countries [7]. However, there is a significant number of infants with a GA of >32 weeks and BW >1,500 g in suboptimal NICU conditions in low- to middle-income countries. Our study reveals the demographic and clinical findings of TR-ROP in preterm infants with a GA of >32 weeks and BW of >1,500 g and aims to point out possible risk factors that need improvement.

Gilbert et al. [1] reported that more mature infants are developing TR-ROP in low-/middle-income countries compared with high-income countries, and ROP screening programs should be structured according to the socio-economical characteristics of the countries and their populations. Shah et al. [8] reported that developing countries such as India are facing a new epidemic similar to the first epidemic of ROP, which was related to high oxygen delivery and also called oxygen-induced retinopathy. They named the increasing incidence of TR-ROP in mature and heavier infants as the third epidemic of ROP [8]. This was confirmed by other authors from China and India [9, 10]. Bas et al. [3] evaluated the incidence, risk factors, and severity of ROP with a prospective, multicentric study in Turkiye and showed that

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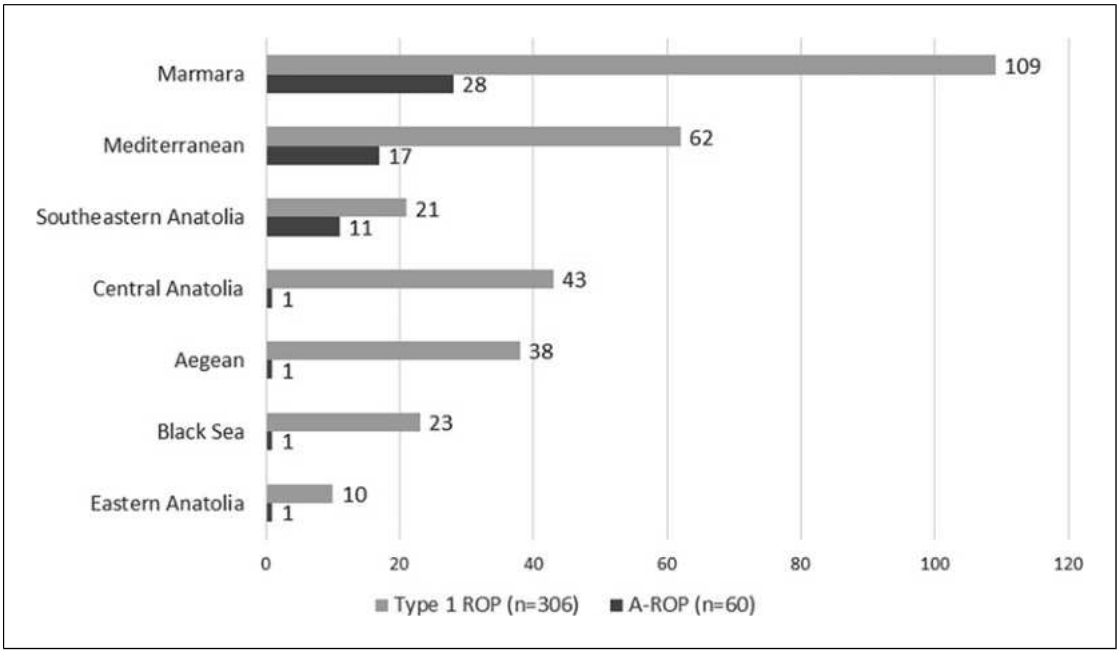


Fig. 1. The numbers of aggressive ROP (A-ROP) and type 1 ROP in TR-ROP of each region are presented. Although the number of A-ROP cases is higher in Marmara and Mediterranean Regions, the rate of A-ROP is statistically higher in Southeastern Anatolia Region, which is socio-economically developing.

more mature and heavier infants were at risk for TR-ROP. The study included 6,115 infants, 1,151 of whom (19%) were with a GA >32 weeks any stage of ROP was found in 61 infants (5.3%), and TR-ROP was detected in 6 infants (0.5%). They have suggested that the ROP screening program in Turkiye should be expanded to include premature infants with a BW <1,700 g or GA <34 weeks to detect all infants requiring treatment [3]. Similarly, Yildiz Ekinci et al. [11] reported that incidence of ROP in babies with BW ≥2,000 g is higher in Turkiye compared to developed countries.

The rate of ROP may be considered an indicator of the quality of neonatal care [12]. Bas et al. [3] reported that the rates of TR-ROP were lower in the university hospital NICUs, where neonatal care is likely to be better, and reported more mature and heavier infants developing TR-ROP, especially in private hospitals. Similarly, in our study, the presence of ROP at the first examination was higher with TR-ROP in lower levels of NICU. Shah et al. [8] indicated that increasing preterm births and survival rates, inadequate oxygen therapy, and failure to comply with the ROP screening program may increase the incidence of ROP in big infants.

Our study included infants without the major risk factors related to GA and BW. Several risk factors such as length of stay in NICU, RDS, bronchopulmonary dysplasia, NEC, anaemia, thrombocytopenia, transfusion, sepsis, intracranial haemorrhage, cardiac problems, nutrition, extraocular surgery, and maternal risk factors such as maternal diabetes, pre-eclampsia, assisted conception had been associated with the development of TR-ROP in the literature [13–21]. We have evaluated the rates of such risk factors in our patients such as RDS, anaemia, and thrombocytopenia, and we found similar or lower rates as compared to other cohorts in the literature [3, 22–24]. We did not include patients without TR-ROP; therefore, we could not compare the effect of these factors on the development of ROP.

Recently, the Turkish ROP guideline was revised and recommended screening all infants <34 weeks and ≤1,700 g for ROP. The ROP screening guidelines in India and China suggest that preterm infants with GA ≤34 weeks and/or BW ≤2,000 g should be screened for ROP [25]. Screening guidelines in Thailand suggest examining infants with GA <33 weeks and/or BW <1,500 g [25]. Developed western countries such as the USA recommend screening infants with BW ≤1,500 g or GA ≤30 weeks [7]. In the UK, infants with BW ≤1,500 g or GA ≤32 weeks are screened for ROP [26]. The socio-economic status of the country and NICU conditions are the most essential factors in determining the ROP screening criteria. Although ROP screening

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criteria have recently been revised in Turkiye, if the NICU conditions are not improved, they may need to be expanded further, such as in China and India.

Shah et al. [27] reported loss of retinal vessels from zone II to zone I in relatively mature preterm infants (GA of 31.7 weeks [range 28–35 weeks]) and progression to A-ROP with 100% oxygen exposure. The number of A-ROP cases was higher in Marmara, the Mediterranean Sea, and Southeastern Anatolia regions. The higher number of A-ROP cases in the socio-economically developed Marmara and Mediterranean Regions may be related to the higher rates of private NICUs in these regions. In our country, in the socio-economically developed regions, immigration and refugee rates are higher. This situation jeopardizes the health system in these regions and may stimulate more private hospitals to be opened without sufficient equipment and health care staff, and as a result, the quality of intensive care becomes lower in these regions. Further studies are needed to reach a more definite conclusion on this topic. However, it is very well known that decreased quality of neonatal care promotes the development of A-ROP, which may be assumed as a kind of oxygen-induced retinopathy. This topic was discussed with the neonatologists, and they informed that oxygen saturation data are very difficult to be determined exactly since they may not be stable during the whole NICU period, especially in a retrospective study. Future studies with detailed information on the follow-up of the oxygen saturation level of neonates are needed to conclude.

Prolonged oxygen therapy was found to be a risk factor for the development of ROP not at the initial examination but at subsequent examinations in the present study. This may be caused by inadequate oxygen delivery or non-compliance to target saturation levels, or comorbidities that increase the development of ROP. Lack of neonatologists and shortage of nurses controlling the saturation levels may result in lower quality of NICU service, which may lead to the development and progression of ROP and A-ROP, which may be linked to a kind of oxygen-induced retinopathy in more mature and heavier preterm infants. In our study, the lack of neonatologists was found to be statistically significantly higher in low-income cities, in lower levels of NICU, and in non-university clinics, especially private hospitals.

In our study, ROP was present in 90.9% of patients at the first examination, which was performed in the fourth postnatal week, and TR-ROP developed in a mean period of 6.16 weeks. This finding may indicate that the onset of ROP corresponds more closely with postmenstrual age than with postnatal age [6]. ROP onset was reported to begin at roughly 30 weeks of PMA and peaked at a PMA

Table 4. Comparison of (A-ROP) frequency according to different NICU characteristics

Criteria	Development status (*n*: 366)			Hospital type (*n*: 366)			Level of NICU (*n*: 366)				The presence of neonatologist (*n*:342)			The presence of ophthalmologist (*n*:366)		
	high income (*n*: 266)	low income (*n*: 100)	*p* value	university (*n*: 44)	state (*n*: 75)	private (*n*: 247)	*p* value	level 1 and 2 (*n*: 77)	level 3 (*n*: 243)	level 4 (*n*: 46)	*p* value	present (*n*: 226)	absent (*n*: 116)	*p* value	present (*n*: 118)	absent (*n*: 248)	*p* value
Percentage of A-ROP eyes	15%	19%	0.046	16%	4%	20%	0.004	16%	19%	4%	0.049	17%	15%	0.720	8%	21%	0.003

A-ROP, aggressive ROP; NICU, neonatal intensive care unit.

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Table 5. Risk factors for A-ROP development, multinominal logistic regression analysis

	β coefficient	Standard error	*p* value	OR	95.0% CI for OR	
Southeastern Anatolia Region	1.228	0.418	0.003	3.413	1.505	7.742
Absence of ophthalmologist	1.209	0.387	0.002	3.350	1.568	7.154
Constant	−2.689	0.363	<0.001	0.068		

Dependent variable: A-ROP; Nagelkerke R^2 = 0.085; accurate forecast rate = 83.61%. OR, odds ratio; CI, confidence interval.

of 36–38 weeks in infants with BW <1,251 g, irrespective of GA at birth [28]. In a study conducted by Zarei et al. [24] in Iran, the rate of any stage ROP at the first examination has been reported as 27.3% in 543 patients with a mean GA of 32.29 weeks and a mean week of delivery of 1,758 g. In this study, 33% of patients required treatment. Our study revealed that ROP was already present at a PMA of 36 weeks, and TR-ROP developed at a mean of 38 weeks similarly. The high rates of ROP in the first examination in the present study may suggest that the first ROP examination may be done earlier (even before the fourth postnatal weeks) in bigger premature infants, especially in low-income countries, and they should be followed up closely if there is any ROP.

The present study has shown that 19.7% of the infants could not be screened for ROP on time, and this was more prevalent in hospitals where there is no ophthalmologist in the same hospital. In such hospitals, the first and ongoing ROP examinations were performed by an invited ophthalmologist from another centre or with the referral of the infant to another hospital for ROP screening. The timing of the first ROP examination was postnatal 4–5 weeks in 90.7% of the infants in the hospitals where an ophthalmologist was in charge. However, this rate was 75% if there was no ophthalmologist in the same hospital. The presence of an ophthalmologist in the same hospital seems to increase the proper conduction of ROP screening by letting timely examinations and preventing delays in the detection of ROP. When the ophthalmologist performing the ROP screening is present in the same hospital, both the screening and treatment can be planned as soon as possible when necessary. However, examinations may tend to be grouped together when it is to be done by an invited ophthalmologist from other hospitals. This may cause some delay in the screening programs, e.g., to postpartum 5–7 weeks instead of 4 weeks, which may explain the detection of a higher rate of ROP at the first examination. Similarly, Mousavi et al. [29] reported that late examination increases the prevalence of ROP and the incidence of TR-ROP in preterm infants. There is also a relationship between the absence of ophthalmologists and A-ROP rates, which is parallel to the quality of neonatal care. The lack of ophthalmologists was more prominent in non-university clinics and especially in private hospitals in the present study. Our study suggests that hospitals with NICU must have an ophthalmologist trained in ROP screening as well as a neonatologist. In hospitals without ophthalmologists, patients should be transferred to an NICU with full staff including an ophthalmologist when ROP in any stage was detected to prevent progression of the disease. This may also prevent seeking a treatment centre and transferring the patient, which may cause a delay in treatment in case of TR-ROP.

This study has some limitations because of its retrospective nature. First, some of the data about systemic parameters in the NICU were lacking in some infants. The most important of these was the lack of oxygen saturation levels, as we mentioned above. Second, since only infants with TR-ROP were included in the study, we could not make comparisons for the risk factors for ROP development in these bigger infants. Another limitation is the variability of experience among the ophthalmologists performing the screening and the variability of equipment in different facilities. Both factors can affect the quality and accuracy of diagnoses and create a potential bias in the results. Additionally, the lack of genetic mutation screening is a drawback of this study, which may be the cause of TR-ROP development in some of these cases. On the other hand, the strength of this study can be listed as follows: this is the first study analysing the regional differences in the same country and the effect of the presence of an ophthalmologist and neonatologist in the same hospital as NICU on the development of TR-ROP in a nationwide study in Turkiye. This study emphasizes the detection of a high rate of ROP at the first examination in these bigger infants and progression to

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TR-ROP in a short time. The results of our study suggest the need for a timely (even earlier) screening for bigger infants and a revision to expand the limits of the ROP screening program to bigger infants in at least developing parts of Turkiye. This may be generalized to all developing countries. The high frequency of TR-ROP in bigger infants, the missed cases due to disruptions in screening, the role of socio-economic development in the occurrence of A-ROP in bigger infants, and the importance of having an ophthalmologist at the exact centre in timely recognition of TR-ROP are the main findings, which are emphasized for the first time in the present study.

In conclusion, more mature and heavier preterm infants may develop TR-ROP, primarily when the ideal NICU conditions cannot be provided. Revision for screening criteria for ROP in Turkiye may not be enough to detect the TR-ROP in bigger infants if NICU conditions are not improved. The ROP in these infants may be more aggressive like A-ROP and may progress rapidly in a short time. The first examination for ROP should be even before the fourth postnatal week with a close follow-up. Babies should be transferred to an NICU with full staff including an ophthalmologist when ROP at any stage was detected to prevent progression and a delay in treatment. Increasing the number of well-educated neonatologists and ophthalmologists, as well as improving NICU conditions, will improve neonatal care for ROP to the standards of high-income countries.

Appendix

BIG-ROP Study Group

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Statement of Ethics

This study was approved by the Ethics Commission of the Gazi University (Approval No. 2020-191). We adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from participants' parents or legal guardians.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.O. and Z.O.T. designed the study. S.O. and H.B.O. collected the data and verified the raw dataset and labels. H.B.O. labelled the data. S.O., H.B.O., Z.O.T., S.E.B., E.A.S., N.K., and E.K. developed the algorithm, analysed the data, drafted the manuscript, and interpreted the results. All authors contributed to cases and the manuscript revision. All authors approved the submitted version.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author (H.B.O.). The data are not publicly available due to privacy or ethical restrictions. A preprint version of this article is available on medRxiv [30].

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