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Incidence, risk factors and severity of retinopathy of prematurity in Turkey (TR-ROP study): a prospective, multicentre study in 69 neonatal intensive care units

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ABSTRACT

Background To evaluate the prevalence, risk factors and treatment of retinopathy of prematurity (ROP) in Turkey and to establish screening criteria for this condition.

Methods A prospective cohort study (TR-ROP) was performed between 1 April 2016 and 30 April 2017 in 69 neonatal intensive care units (NICUs). Infants with a birth weight (BW)≤1500 g or gestational age (GA)≤32 weeks and those with a BW>1500 g or GA>32 weeks with an unstable clinical course were included in the study. Predictors for the development of ROP were determined by logistic regression analyses.

Results The TR-ROP study included 6115 infants: 4964 (81%) with a GA≤32 weeks and 1151 (19%) with a GA>32 weeks. Overall, 27% had any stage of ROP and 6.7% had severe ROP. A lower BW, smaller GA, total days on oxygen, late-onset sepsis, frequency of red blood cell transfusions and relative weight gain were identified as independent risk factors for severe ROP in infants with a BW≤1500 g. Of all infants, 414 needed treatment and 395 (95.4%) of the treated infants had a BW≤1500 g. Sixty-six (16%) of the treated infants did not fulfil the Early Treatment for Retinopathy of Prematurity requirements for treatment.

Conclusions Screening of infants with a GA≤34 weeks or a BW<1700 g appears to be appropriate in Turkey. Monitoring standards of neonatal care and conducting quality improvement projects across the country are recommended to improve neonatal outcomes in Turkish NICUs.

Trial registration number NCT02814929, Results.

INTRODUCTION

Retinopathy of prematurity (ROP), a vasoproliferative disorder of the immature retina in premature infants, is a significant cause of blindness in many middle-income countries. The prevalence of ROP is lower in high-income countries, where risk factors such as oxygen administration and blood oxygen saturation are strictly monitored.[1] Severe ROP is typically found in infants with a very low gestational age (GA) at birth in developed countries.[1 2] Heavier and more mature babies can also develop ROP in developing countries, because there is insufficient awareness of the risk factors of the disease process, a shortage of skilled professionals and/or a shortage of essential equipment to care for infants.[3]

In recent years, Turkey has been developing programmes to improve neonatal health. This study (TR-ROP) determined the prevalence and treatment modalities of infants with ROP in Turkey and was the first multicentre study to analyse risk factors for ROP development in the country. Based on data obtained from infants, criteria for ROP screening in Turkey were evaluated. Because Turkey has received many refugees in recent years, this study also evaluated the prevalence of ROP in preterm infants born to refugees.

METHODS

The TR-ROP study was promoted by the Turkish Neonatology Society and included preterm infants screened for ROP between 1 April 2016 and 30 April 2017. In Turkey, the total number of neonatal intensive care units (NICUs) including neonatologists on the medical staff is 134 (22 private, 40 university and 72 state hospitals). In total, 69 NICUs (8 private, 39 university and 22 state hospitals) agreed to take part in the study (51% of all). Heads of the NICUs and directors of hospitals gave written consent to participate in the research. It was approved by the ethics committee and informed consent was obtained from the parents before the initial screening.

Study population

This prospective cohort study evaluated the incidence and severity of ROP in relation to GA, birth weight (BW) and treatment modalities. The independent risk factors for the development of severe ROP in infants with a BW≤1500 g and for any ROP in infants with a BW>1500 g were assessed.

Infants with a BW≤1500 g or GA≤32 weeks and those with a BW>1500 g or GA>32 weeks, who were determined by the attending clinician to be at risk for ROP development, were screened. Then the medical records of retinal examinations of preterm infants who met the screening criteria were evaluated. The data on refugee infants were also recorded. Examinations took place in the NICU or outpatient facility (for discharged infants). Eligible infants who were discharged before the first screening and missed or did not complete all screening sessions were excluded from the study. The data are restricted to all babies who underwent all the screening sessions. Infants with congenital anomalies, chromosomal abnormalities and

those who died before the first ophthalmic examination were excluded from the study.

Dataset

Neonatologists who agreed to participate in this study provided data regarding ROP in their NICUs. A case report form (CRF) for each enrolled patient was completed by the participating neonatologist. Data were collected through an online data entry system via a special network named the 'Trials-Network'. All the questions in the CRF were required to be answered. The data entry system did not allow the collaborator to proceed and submit the data if no response was received for any question in the CRF. Anonymous data were entered into password protected database to maintain confidentiality. The records from 69 NICUs were pooled together and analysed at the end of the study.

Clinical characteristics

Antenatal, natal and postnatal risk factors for the development of ROP including maternal age, use of antenatal corticosteroids, preeclampsia/eclampsia, infants of diabetic mothers, chorioamnionitis (clinical or histopathological), in vitro fertilisation, multiple births, mode of delivery, sex, GA, BW, small for gestational age (SGA; 10th percentile),[4] resuscitation in the delivery room, respiratory distress syndrome (RDS), surfactant treatment, duration of invasive/noninvasive mechanical ventilation and oxygen therapy, intracranial haemorrhage >Grade II according to Papile staging,[5] haemodynamically significant patent ductus arteriosus (PDA), early/late neonatal sepsis (clinically proven or culture positive), necrotising enterocolitis (NEC)≥Stage II in accordance with the modified Bell criteria,[6] the number of red blood cell (RBC) transfusions (15 mL/kg for each transfusion), bronchopulmonary dysplasia (BPD), oxygen requirement at 36 weeks postmenstrual age, relative weight gain and breastfeeding were recorded on the CRF for each patient.

Ophthalmic examinations

The International Classification of ROP guidelines were used to record the stage of the disorder, location by zone and signs of plus disease.[7] All infants meeting the screening criteria were scheduled to have their first examination at between 4 and 6 weeks of life. Ophthalmic examinations were continued until full retinal vascularisation and the maximum stage of ROP for each infant was reported. The data were analysed for the most advanced stage of ROP in the eye with the most severe disease.

Severe ROP was defined as ROP needing treatment. Criteria for treatment of ROP were based on the Early Treatment for Retinopathy of Prematurity (ETROP);[8] however, not all treated patients met this criteria and were defined as the 'unclassified' group. The study also investigated the need for laser photocoagulation, intravitreal bevacizumab (IVB) and vitreoretinal surgery for ROP.

The NICUs having no treatment options transferred the infants to other facilities where ROP treatment is available. The referring neonatologists completed the CRF forms for these patients after being in contact with the receiving facilities.

Statistical analyses

Statistical analyses were conducted using SPSS statistical software for Windows, V.21.0 (SPSS, Chicago, Illinois, USA). The results are presented as numbers (n), frequencies (%), means with the respective SDs and medians with their IQRs. Parametric tests were used to analyse variables. The χ^2 test was used to compare categorical variables. A two-tailed value of $p \leq 0.05$ was considered statistically significant. Multiple logistic regression analyses were used to evaluate risk factors for any degree of ROP (BW>1500 g) and severe ROP in infants (BW≤1500 g), using the selection of factors associated ($p \leq 0.05$) with ROP determined by univariate analyses. In the model, no ROP versus severe ROP (BW≤1500 g) and no ROP versus any degree of ROP (BW>1500 g) were compared. Variables with a $p \leq 0.05$ using logistic regression analyses were accepted as independent risk factors. The OR and 95% CI for each risk factor were determined. The one-way analysis of variance was performed to determine the statistical significance for GA and BW among NICUs in university, state and private hospitals.

Table 1 ROP in relation to gestational age and birth weight

Gestational age (weeks)	Screened infants (n)	Any ROP (n, %)	Severe ROP (n, %)
≤28	1539	968 (62.9)	332 (21.6)
29–32	3425	666 (19.4)	76 (2.2)
Subtotal (≤32)	4964	1634 (32.9)	409 (8.2)
33–35	1030	56 (6.1)	6 (0.6)
>35	121	5 (4.1)	–
Total	6115	1695 (27)	414 (6.7)
Birth weight (g)	**Screened infants (n)**	**Any ROP (n, %)**	**Severe ROP (n, %)**
≤1000	1109	761 (68)	288 (26)
1001–1250	1085	438 (40)	74 (6.8)
1251–1500	1296	269 (20.8)	33 (2.5)
Subtotal (≤1500)	3490	1468 (42)	395 (11)
1501–2000	1944	201 (10.3)	19 (1)
>2000	681	26 (3.8)	–
Total	6115	1695 (27)	414 (6.7)

ROP, retinopathy of prematurity.

RESULTS

During the study period, data from 69 centres including NICUs of 39 university hospitals (2823 infants), 22 state hospitals (2605 infants) and 8 private hospitals (687 infants) were obtained. All of the participating centres had ophthalmology units for ROP screening, but only 41/69 performed laser photocoagulation and/or antivascular endothelial growth factor (anti-VEGF) treatments and 5/69 centres performed vitreoretinal surgery.

The TR-ROP study included 6115 preterm infants: 4964 (81%) with a GA≤32 weeks and 1151 (19%) with a GA>32 weeks. The mean BW and GA for the total cohort were 1,457±479 g and 28.9±6.3 weeks, respectively. There were 3163 (51.7%) females and 2952 (48.3%) males in the study group. The mean postnatal day and postmenstrual age at the initial diagnosis of ROP were 49.2±16 days and 33.8±2.9 weeks, respectively. Overall, 27% of the patients were found to have any stage of ROP and 6.7% had severe ROP. The incidences of ROP and severe ROP in relation to GA and BW are shown in table 1. The majority (96%) of infants with any stage of ROP had a GA≤32 weeks and 80% of the infants with severe ROP had a GA≤28 weeks.

Of the total study cohort, a total of 551 infants (9%) were born to refugees. There were no statistically significant differences in any degree of ROP and severe ROP between very low birth weight (VLBW) infants of citizens (n=3193) and refugees (n=297).

Univariate analyses identified several risk factors as potential markers. Table 2 shows the relationships between severe ROP and risk factors in infants with a BW≤1500 g.

Table 2 Univariate analyses of covariates for severe ROP development in infants with a BW≤1500 g

	Infants BW≤1500 g		Univariate analysis (Severe ROP vs No ROP)		
Covariates	**No ROP (n=2022)**	**Severe ROP (n=395)**	**P value**	**95% CI**	**OR**
Maternal age (years)*	28.9±6.4	28.7±6.2	0.565	0.979 to 1.012	0.995
Antenatal steroid, two doses	870 (43%)	145 (36.7 %)	0.02‡	0.614 to 0.959	0.767
Preeclampsia	544 (26 %)	83 (21%)	0.015‡	0.556 to 0.938	0.722
Gestational diabetes	106 (5 %)	23 (5.8 %)	0.640	0.702 to 1.777	1.117
Chorioamnionitis	165 (8 %)	56 (14 %)	<0.001‡	1.343 to 2.570	1.858
IVF pregnancy	247 (12%)	41 (10 %)	0.832	0.586 to 1.180	0.832
Multiple births					
Twins	424 (21%)	80 (20.3 %)	0.728	0.729 to 1.248	0.953
Triplets	76 (3.8 %)	14 (3.5%)	0.810	0.519 to 1.668	0.931
Vaginal delivery	236 (12 %)	83 (21 %)	<0.001‡	1.524 to 2.656	2.012
Gestational age (weeks)*	29.8±2.2	26.5±1.9	<0.001‡	0.441 to 0.511	0.475
BW (g)*	1215±215	888±228	<0.001‡	0.994 to 0.995	0.994
Male gender	934 (46 %)	207 (52 %)	0.028‡	1.035 to 1.593	1.284
SGA	520 (25.7 %)	50 (12.7 %)	<0.001‡	0.306 to 0.572	0.418
Resuscitation at birth	853 (42 %)	306 (77 %)	<0.001‡	3.667 to 6.070	4.717
RDS	1228 (83 %)	361 (91 %)	<0.001	4.820 to 9.957	6.928
Surfactant treatment	959 (47 %)	340 (86 %)	<0.001‡	5.092 to 9.240	6.859
Duration of invasive mechanical ventilation (days)†	0±2 (0–148)	17±40 (0–308)	<0.001‡	1.063 to 1.080	1.071
Duration of noninvasive ventilation (days)†	3±7 (0–87)	18±22 (0–120)	<0.001‡	1.079 to 1.100	1.090
Total days on oxygen†	10±23 (0–171)	65±53 (0–308)	<0.001‡	1.047 to 1.057	1.052
PDA requiring treatment	349 (36 %)	210 (53 %)	<0.001‡	4.326 to 6.837	5.438
Intracranial haemorrhage (>Grade II)	73 (3.6 %)	70 (17.7 %)	<0.001‡	4.057 to 8.142	5.748
Early-onset neonatal sepsis	433 (21 %)	167 (42 %)	<0.001‡	2.149 to 3.378	2.694
Late-onset neonatal sepsis	677 (33 %)	294 (74 %)	<0.001‡	4.537 to 7.394	5.792
NEC (≥Stage II)	142 (7 %)	84 (21 %)	<0.001‡	2.680 to 4.840	3.601
BPD	273 (13 %)	266 (67 %)	<0.001	10.324 to 16.884	13.203
Frequency of RBC transfusions					
Once	426 (21 %)	41 (10%)	<0.001‡	2.637 to 7.503	4.448
Twice and more	532 (26 %)	331 (83%)	<0.001‡	18.607 to 44.438	28.756
Breastfeeding more than 80% of feeding at PN 28 days, (n, %)	1347 (66 %)	162 (41 %)	<0.001‡	0.279 to 0.434	0.348
Age of regain BW (days)*	11.3±5.1	14.5±6	<0.001‡	1.080 to 1.121	1.100
Relative weight gain at 28 days (g)*	382±180	229±135	<0.001‡	0.993 to 0.995	0.994

*The values are presented as mean±SD.
†The values are presented as median±IQR, min-max values are given in parentheses.
‡The variables that were put in the logistic regression model.
BPD, bronchopulmonary dysplasia; BW, birth weight; IVF, in vitro fertilisation; n, number of patients; NEC, necrotising enterocolitis; p, significant difference between patients with severe ROP versus those with no ROP, defined as p<0.05; PDA, patent ductus arteriosus; PN, postnatal; RBC, red blood cell ; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; SGA, small for gestational age.

All risk factors found to be significant were analysed using a multivariate logistic regression model. Table 3 shows the independent risk factors for severe ROP in VLBW infants.

Using multivariate logistic regression analyses, the following were independent risk factors for any ROP in infants with BW>1500 g: GA (for every 100 g) (OR, 0.863; 95% CI 0.775 to 0.960; p=0.007), BW (for every week) (OR, 0.997; 95% CI 0.996 to 0.998; p<0.001), RBC transfusion (≥once) (OR, 1.545; CI 1.067 to 2.237; P=0.021) and total days on oxygen (for each day on oxygen) (OR, 1.023; CI 1.014 to 1.032; p<0.001).

Of all of the infants screened for ROP, 414 (6.7%) needed treatment. A total of 395 (95.4%) of the treated infants had a BW≤1500 g and treatment was performed in 19 infants with a BW of 1501–2000 g. Severe ROP was diagnosed in five babies with BW>1500 g and GA>32 weeks who required treatment. Treatment was applied bilaterally in 385 patients and was performed in one eye in 29 cases. Five infants with a GA≤28 weeks underwent vitreoretinal surgery. Table 4 lists the severities and treatment modalities of ROP in the treated patients.

The incidence of severe ROP in university hospitals, in state hospitals and in private hospitals was 6.2%, 6.8% and 8.4% respectively. Mean GA and mean BW of infants with severe ROP varied between different types of NICU (table 5).

Appropriate criteria for screening for the NICUs in university hospitals should be <1700 g or ≤32 weeks and for the NICUs in state hospitals and private hospitals should be <1700 g or ≤34 weeks (figure 1).

DISCUSSION

ROP is a serious morbidity of prematurity, whose incidence and severity increase with decreasing GA and BW. Studies conducted in high-income countries have shown that infants born at ≥32

Table 3 Independent risk factors for severe retinopathy of prematurity in infants with a birth weight≤1500 g

	Adjusted OR	95% CI	P value
Gestational age (weeks)*	0.812	0.726 to 0.910	<0.001
Birth weight (g)†	0.998	0.997 to 0.999	<0.001
Small for gestational age	0.471	0.277 to 0.799	0.005
Total days on oxygen‡	1.025	1.019 to 1.031	<0.001
Late-onset sepsis	1.423	1.016 to 1.994	0.04
Frequency of red blood cell transfusions≥twice	2.384	1.389 to 4.092	0.002
Relative weight gain at 28 days (grams)	0.998	0.997 to 0.999	<0.001

P<0.05 represents statistical significance.
*OR for every week.
†OR for every 1 g.
‡OR for each day on oxygen.

weeks are not at risk for developing ROP and most infants born at >28 weeks who develop ROP have a mild disease that spontaneously regressed without treatment.[9] The findings of the TR-ROP study were comparable to those from other developing countries and showed that more mature and heavier babies were at risk for severe ROP.[10]

There were no differences in any ROP and severe ROP development between VLBW infants of refugees and citizens in our study. The Ministry of Health of Turkey has been involved in direct healthcare services in the refugee camps and through the referral of refugees to Turkish hospitals. The 2015 report of the Turkish Neonatology Society reported a mortality rate of

Table 4 Severity and treatment modalities of ROP in treated patients

Severity of ROP	Only IVB	Only laser treatment	IVB and laser treatment	Total N, (%)
APROP	45	26	15	86 (20.8%)
Type 1 ROP	93	145	24	262 (63.3%)
Zone I, any stage of ROP with plus	28	9	7	44
Zone I, stage 3 without plus	6	2	2	10
Zone II, stage 2 or 3 with plus	59	134	15	208
Type 2 ROP	20	24	-	44 (10.6%)
Zone I, stage 1 or 2 without plus	4	5	-	9
Zone II, stage 3 without plus	16	19	-	35
Unclassified	6	15	1	22 (5.3%)
Zone II, stage 1 with plus	4	5	-	9
Zone III, stage 2 with plus	1	6	1	8
Zone III, stage 3 with plus	1	4	-	5
Total N, (%)	164 (39.6%)	210 (50.7%)	40 (9.7%)	414 (100%)

APROP, aggressive posterior retinopathy of prematurity; IVB, intravitreal bevacizumab; N, number of patients; ROP, retinopathy of prematurity.

Table 5 Mean BWs and GAs of infants with severe ROP according to types of units

	University hospitals (n=192)	State hospitals (n=164)	Private hospitals (n=58)	P value*
Mean GA (weeks)	26.3±2	26.7±2.2	27.9±2.1	<0.05
Mean BW (g)	878±250	905±273	1128±299	<0.05

*The values are significantly higher in private hospitals than in university and state hospitals.
BW, birth weight; GA, gestational age; n, number of patients; ROP, retinopathy of prematurity.

26% for babies with a BW<1500 g, according to data obtained from 59 NICUs.[11] However, there were insufficient data on the neonatal mortality of refugees in this report.

GA, BW and oxygen therapy are well-known major risk factors in the development of ROP.[12] In this study, a lower BW, shorter GA and total days on oxygen were found as independent risk factors for severe ROP in infants with a BW≤1500 g and for any ROP in infants with a BW>1500 g.

Some previous studies have reported that the prevalence of ROP was higher in SGA infants compared with appropriate for GA preterms, while SGA was not found to be a risk factor for ROP in other reports.[13 14] Factors that are considered an increased risk for severe ROP in SGA babies include chronic uterine hypoxia, abnormal growth factor levels, nutrient restriction and antioxidant deficiency.[15] However, in our study, SGA was surprisingly associated with a decreased incidence of severe ROP in VLBW infants when using a multivariate logistic regression model.

There was a relationship between poor postnatal weight gain and an increased risk for ROP.[16] Poor postnatal weight gain was also found as an independent risk factor for severe ROP in infants with a BW≤1500 g in our study. Using univariate analyses, several risk factors including RDS, respiratory support, sepsis, NEC, PDA, intracranial haemorrhage and BPD were significantly associated with severe ROP in VLBW infants in our cohort. These perinatal morbidities may have decreased postnatal weight gains.

This study showed that RBC transfusions had strong effects on the development of ROP. Transfusions may increase oxygen delivery to the retina because of the lower oxygen affinity of adult haemoglobin in packed red cells. Repeated transfusions may also cause free iron accumulation, which may result in increased production of free hydroxyl radicals as assessed by the Fenton reaction, resulting in damage to the retina.[17] Although the role of blood transfusions as a risk factor for ROP was suggested by numerous reports,[18 19] several studies have reported that a transfusion limitation policy did not reduce the prevalence of ROP.[20] Our data suggested that limiting blood transfusion in regards to threshold haemoglobin values in guidelines could contribute to reducing the prevalence of ROP.

Multiple studies have reported the role of neonatal sepsis in the development of ROP.[21 22] In this study, late onset sepsis was an independent risk factor for severe ROP in VLBW infants. Sepsis may act through cytokines and endotoxins, which directly affect retinal angiogenesis. This process is frequently accompanied by hypotension, which can cause tissue perfusion impairment and retinal ischaemia.[23]

Treatment was performed in 6.7% of the infants screened for ROP in the current study. In nearly half of the infants with severe ROP, the treatment modality involved laser photocoagulation and IVB was performed in the other half as the first choice.

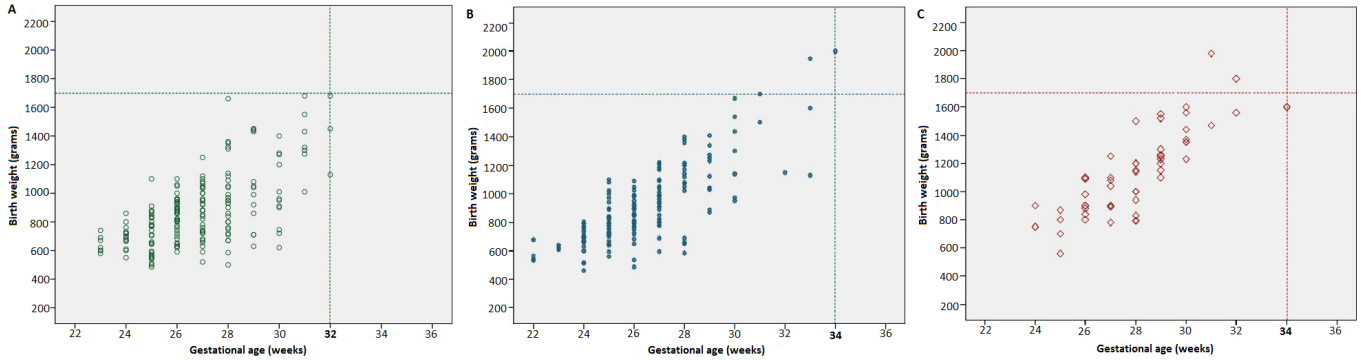

Figure 1 Plots of BW versus GA for infants treated for ROP in three different types of NICU. (A) University hospitals. (B) State hospitals. (C) Private hospitals. BW, birth weight; GA, gestational age; NICU, neonatal intensive care unit; ROP, retinopathy of prematurity.

A nationwide population-based study from the UK reported that diode laser photocoagulation was performed in 90.5% of infants requiring treatment.[1] The higher usage of IVB in our study may be due to ease of administration (typically at the bedside). In addition, paediatric anaesthesia for performing laser photocoagulation was not available in some NICUs in our study.

Notably, 66 (16%) of 414 infants were treated earlier than type 1 ROP and did not fulfil the ETROP requirements for treatment in our study. Twenty-six of these 66 infants were treated with IVB. The popularity of anti-VEGF agents is increasing in Turkey; however, the long-term safety and efficacy of these agents are still not definitively known. The risk of progression to retinal detachment in type 1 ROP is around 15%, but is much lower with less severe disease.[8] Evidence-based data are not available to confirm a favourable risk–benefit ratio of IVB usage in cases earlier than type 1 ROP.

In our study, the incidence of severe ROP varied between the three types of NICU which reflects the differences in neonatal care. The rates of severe ROP were lower in university hospital NICUs, where practices for newborn care are likely to be better than non-university NICUs. Based on the results of present study, the screening criteria for ROP need to be wider in state and private hospitals than applied in the university hospitals. ROP programmes in Turkey should adopt the criteria of <1700 g or ≤ 34 weeks to capture all babies requiring treatment.

The strength of the TR-ROP study was that it was a large multicentre cohort study that allowed us to prospectively obtain data via a special network. However, the neonatologists did not go through any training in order to standardise definitions of potential risk factors before the study started. Similarly, the participating ophthalmologists also did not undergo any processes to standardise how they graded ROP. These situations are the limitations of the study.

In conclusion, screening criteria for ROP in Turkey needs to be wider than developed countries. The high incidence of infants with ROP in our study emphasised the need for aggressive measures for prevention and control of the disease. The safe implementation of oxygen therapy with appropriate monitoring, better antenatal and neonatal care, meticulous attention to hygienic procedures and control of sepsis may reduce the prevalence of ROP. Therefore, monitoring standards of neonatal care and conducting quality improvement projects across the country are essential for improving neonatal outcomes in Turkish NICUs.

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