Frequency, risk factors and outcomes of retinopathy of prematurity in a tertiary care hospital in Turkey

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SUMMARY: Küçükevcilioğlu M, Mutlu FM, Sarıcı SÜ, Ceylan OM, Altınsoy Hİ, Kılıç S, Çekmez F. Frequency, risk factors and outcomes of retinopathy of prematurity in a tertiary care hospital in Turkey. Turk J Pediatr 2013; 55: 467-474.

The aim was to report outcomes of retinopathy of prematurity (ROP) screening conducted between March 1999 and March 2012 in a retrospective manner before October 2005 (Group 1) and prospective manner thereafter (Group 2). Data of the neonates with either a gestational age of 34 weeks or less or with a birth weight of less than 1501 g were analyzed to elucidate the frequency of ROP, ROP-related risk factors and population characteristics. Of the 640 neonates, 240 (37.5%) had any stage of ROP. Gestational age ≤32 weeks, birth weight <1500 g, oxygen therapy, respiratory distress syndrome, and sepsis were found as independent determinants for any stage of ROP. Gestational age ≤28 weeks, mechanical ventilation, intraventricular hemorrhage, and outborn infant status were found as independent determinants for treatment-requiring severe ROP (8.6%). Frequency of ROP did not seem to follow a decreasing trend; however, neonates in Group 2 were more immature and sicker. Therefore, check-backs seem to be necessary to follow the dynamic nature of ROP.

Key words: frequency, outcome, retinopathy of prematurity, risk factors.

Retinopathy of prematurity (ROP) is an ocular disorder involving vascular proliferation in premature infants[1]. Despite substantial advances in the management of ROP and in understanding of the fundamental pathophysiology, it still stands as a leading cause of childhood blindness throughout the world[2]. Low birth weight (BW) and short gestational age (GA) have been the most emphasized risk factors for development of ROP[3,4]. Currently, more immature babies have an increasing chance to survive due to the recent advances in neonatal nursing care. Neonatologists now have to handle sicker and more immature babies who are at risk for developing severe ROP[5]. Thus, early recognition is of particular importance for the further management of ROP. Some screening strategies have been offered by institutions mostly from developed countries[6,7]. In developing countries, while some centers have adopted one of them and reported a high applicability, others have noted severe ROP in more mature neonates and called for a new screening protocol covering these neonates[8-11]. Both the characteristics of neonates developing severe ROP and treatment rates differ among countries[12]. This suggests that the varying levels of neonatal nursing care and socioeconomic status of the population may affect the frequency of ROP.

We herein report a 13-year combined prospective and retrospective study describing the frequency, disease characteristics, risk factors, and treatment outcomes of infants screened and treated for ROP, managed at a third level neonatal intensive care unit situated in central Turkey.

Material and Methods

This combined retrospective and prospective study was based on institutional data collected between March 1999 and March 2012 in a retrospective manner before October 2005

Table I. Baseline Characteristics of the Study Cohort

Total cohort	650
Dropouts	10
Original cohort	640
Birth weight (mean±SD, g)	1521.43±423.2
Gestational age (mean±SD, weeks)	30.84±2.20
Gender (Male, %)	50.9
Multiple births (%)	
Single	58.9
Twin	31.6
Triplet	9.5
Referral from different center (%)	2.8
ROP (%)	37.5
Treatment (%)	8.6

ROP: Any stage of retinopathy of prematurity.

(Group 1), and in a prospective manner thereafter (Group 2) at Gülhane Military Medical Academy and Faculty of Medicine, which serves as a teaching and reference hospital for the Armed Forces in the capital of Turkey, Ankara. Screening and treatment algorithms were based on the recommendation of Cryotherapy for Retinopathy of Prematurity (CRYOROP)13 before October 2005 and on the Early Treatment for Retinopathy of Prematurity (ETROP)14 thereafter in our hospital. Approval was obtained from the Institutional Ethics Committee of Gülhane Military Medical Academy for the present study. All efforts were made to comply with the guidelines of the Declaration of Helsinki Principles.

Neonates, inborn or outborn and referred, with either a BW of <1501 g or a GA of ≤34 weeks, and selected infants with an unstable clinical course were included. Each neonate underwent an initial eye examination at 4 to 6 weeks after birth or at a postconceptional age of 31-33 weeks, which was performed by one of the two senior pediatric ophthalmologists. The retinal findings were recorded based on the standard international classification of ROP[15]. Follow-up examinations were done in accordance with the guidelines described before[15-17]. Neonates who met the treatment criteria received ablative therapy (laser photocoagulation or cryotherapy) within 72 hours. The treatment criteria was threshold ROP before October 2005 and pre-threshold ROP thereafter[11,13,14]. Intravitreal vascular endothelial growth factor (VEGF) antibody injections were also performed in aggressive posterior ROP cases as an adjunct to the ablative therapy. Neonates with an advanced disease (stage 4-5) were treated with vitreoretinal surgery. Written informed consent was obtained from the parents before all treatments.

Data including gender, BW, GA, presence of ROP, oxygen therapy, mechanical ventilation, respiratory distress syndrome (RDS), sepsis (culture-proven), multiple births, blood transfusion, intraventricular hemorrhage (IVH), surfactant, and steroid therapies were recorded. Data were analyzed using the Statistical Package for the Social Sciences version 15 (SPSS Inc., Chicago, IL). Independent sample t-test and chi-square test were used as appropriate. Univariate logistic regression analysis was performed to identify significant risk factors for any degree of ROP and severe ROP requiring treatment. Variables for which the unadjusted p value was less than 0.05 in logistic regression analysis were identified as potential risk markers and included in the multivariate logistic regression

Table II. Retinopathy of Prematurity and its Treatment in Relation to the Birth Weight and Stage Distribution

BW (g)	No. of infants			Stage (No.)			
	Subtotal	with ROP (%)	with treatment (%)	1	2	3	4-5
<1000	77	63(81.8)	26(33.7)	19	26^{-1}	18^{-2}	0^{+3}
1000-1249	103	64(62.1)	15(13.5)	30	25^{-1}	9^{-2}	0^{+3}
1250-1499	123	58(47.1)	9(7.3)	33	21^{-1}	3^{-1}	1^{+2}
≥1500	337	55(16.3)	5(1.4)	40	11	4	0
Total	640	240(37.5)	55(8.6)	122	83	34	1^{+8}

BW: Birth weight. ROP: Any stage of retinopathy of prematurity.
†Superscripts indicate the number of neonates who showed progression to stage 4-5 despite first-line ablative therapy.

Table III. Retinopathy of Prematurity and its Treatment in Relation to the Gestational Age and Stage Distribution

	No. of infants			Stage (No.)			
GA (weeks)	Subtotal	with ROP (%)	with treatment (%)	1	2	3	4-5
≤28	106	87(82)	36(33.9)	27	41[-1]	18[-4]	1[+5]
29-32	385	137(35.5)	19(4.9)	79	42	16[-3]	0[+3]
>32	149	16(10.7)	0(0)	16	0	0	0
Total	640	240(37.5)	55(8.6)	122	83	34	1[+8]

BW: Birth weight. ROP: Any stage of retinopathy of prematurity.
†Superscripts indicate the number of neonates who showed progression to stage 4-5 despite first-line ablative therapy.

model. Steroid and surfactant therapies were not included in the full model, though they were statistically significant on univariate regression analysis, because these variables were closely related to the presence of RDS. The model was reduced by using backward elimination, and we eliminated potential risk markers by using likelihood ratio tests. Differences were considered significant when the p value was <0.05.

Table IV. Univariate and Multivariate Analyses of the Risk Factors for Any Stage of ROP

Risk Factors	Crude OR	95% CI	P	Adjusted OR	95% CI	P
GA (weeks)						
≤28	38.062	18.567-78.029	< .001	5.162	2.140-12.449	< .001
29-32	4.592	2.626-8.031	<.001	1.877	1.010-3.489	.046
>32	1.0			1.0		
BW (g)						
<1000	23.07	12.079-44.072	<.001	6.212	2.821-13.676	<.001
1000-1249	8.414	5.145-13.761	<.001	5.141	2.966-8.909	<.001
1250-1499	4.575	2.897-7.225	<.001	3.059	1.831-5.110	<.001
≥1500	1.0			1.0		
Gender	1.126	0.817-1.552	.467			
Multiple births	0.837	0.606-1.157	.282			
Oxygen therapy	4.898	2.956-8.116	<.001	2.128	1.180-3.838	.012
Mechanical ventilation	3.996	2.842-5.619	<.001	1.229	0.735-2.054	.43
RDS	5.375	3.664-7.884	<.001	2.393	1.448-3.955	.001
Blood transfusion	4.451	2.925-6.773	<.001	1.508	0.892-2.552	.12
Sepsis	4.881	3.215-7.409	<.001	1.719	0.995-2.968	.048
IVH	4.899	2.529-9.490	<.001	1.574	0.689-3.596	.28
Steroid therapy	3.319	2.112-5.215	<.001			
Surfactant therapy	3.710	2.217-6.210	<.001			

OR: Odds ratio. CI: Confidence interval. GA: Gestational age. BW: Birth weight. RDS: Respiratory distress syndrome. IVH: Intraventricular hemorrhage.

Table V. Univariate and Multivariate Analyses of the Risk Factors for Treatment-Requiring Severe ROP

Risk Factors	Crude OR	95% CI	P	Adjusted OR	95% CI	P
GA (weeks)						
≤28	10.078	5.463-18.592	<.001	6.248	3.090-12.630	<.001
29-32	1.0			1.0		
>32	None*			None*		
BW (g)						
<1000	28.124	11.037-71.665	<.001	2.011	0.545-7.412	.294
1000-1249	8.678	3.242-23.228	<.001	2.543	0.773-8.369	.125
1250-1499	4.355	1.517-12.504	.006	1.588	0.478-5.275	.450
≥1500	1.0			1.0		
Gender	1.178	0.677-2.050	.561			
Multiple births	0.671	0.386-1.167	.158			
Oxygen therapy	8.413	2.024-34.963	.003	0.640	0.107-3.830	.625
Mechanical ventilation	16.333	6.877-38.794	<.001	5.926	2.351-14.937	<.001
RDS	5.629	3.158-10.033	.016	1.229	0.556-2.718	.610
Blood transfusion	7.590	4.246-13.570	<.001	1.617	0.773-3.386	.202
Sepsis	5.049	2.852-8.939	<.001	1.090	0.474-2.509	.839
IVH	13.184	6.738-25.798	<.001	5.828	2.568-13.225	<.001
Different center	16.028	6.028-42.617	<.001	8.133	2.447-27.031	.001
Steroid therapy	2.143	0.981-4.683	.056			
Surfactant therapy	3.103	1.384-6.959	.006			

OR: Odds ratio. CI: Confidence interval. GA: Gestational age. BW: Birth weight. RDS: Respiratory distress syndrome. IVH: Intraventricular hemorrhage.
* No infant treated over 32 weeks' gestation.

Results

A total of 650 neonates who met the screening criteria were planned to be included in the present study. Eight neonates died before the initial examination and two with a major abnormality were excluded from the study. Of the remaining 640 representing the original cohort, 18 were born at different centers and referred to our institution for further follow-up; 326 (50.9%) were male and 314 (49.1%) were female. There were 377 single births (58.9%), 202 twin births (31.6%) and 61 triplet births (9.5%). Across the entire cohort, BW ranged from 500 g to 2800 g, with a mean of 1521.43±423.2 g, and GA ranged from 25 to 36 weeks, with a mean of 30.84±2.20 weeks. Any stage of ROP was detected in 240 neonates (37.5%), and 55 (8.6%) needed treatment. Mean BW and GA for the treated neonates were 1079.18±312.6 g and 27.85±2.013 weeks, respectively. Treatment criterion was threshold ROP in 19 neonates (34.6%) and pre-threshold ROP in 36 neonates (65.4%). Table I displays the baseline characteristics of the study cohort.

The frequencies of any stage of ROP and treatment-requiring severe ROP were inversely correlated with GA and BW ($p<0.001$). Tables II and III list the distribution of ROP and treatment rates according to BW and GA. Of the 240 neonates (380 eyes) developing ROP, 185 (77%) showed spontaneous regression, while 55 (23%) (90 eyes) needed treatment. The shorter the GA and the lower the BW, the greater the neonate's chance of having a higher stage of ROP and higher possibility of undergoing treatment. While a higher regression rate was observed in lower stages (stage 1-2), only one-fourth of the neonates with stage 3 showed regression. One patient who already had stage 4 at the initial examination was

referred from a different center and required retinal surgery. With the addition of 8 neonates, indicated as superscripts in Tables II and III, who showed progression to stage 4-5 despite first-line ablative therapy, a total of 9 neonates (16 eyes) needed retinal surgery. Fourteen eyes of these 9 neonates (1.4%) ended up blind (<6/60). There was no neonate who needed treatment beyond 32 weeks' gestation, and 5 with a higher BW (≥1500 g) needed treatment, but none progressed to stage 4-5.

Two logistic regression analyses were performed to evaluate risk factors for any stage of ROP and treatment-requiring severe ROP. Univariate analysis showed several risk factors as potential risk markers. However, the independent risk factors identified by the multivariate analysis were GA (≤32 weeks, p=0.046), BW (<1500 g, p<0.001), oxygen therapy (p=0.012), RDS (p=0.001) and sepsis (p=0.048) for any stage of ROP (Table IV) and GA (≤28 weeks, p<0.001), mechanical ventilation (p<0.001), IVH (p<0.001), and outborn status (p=0.001) for treatment-requiring severe ROP (Table V).

The last statistical evaluation was performed to compare the two periods of ROP screening to monitor the population characteristics and incidence of ROP during the time course of the study: Group 1 consisted of neonates followed up before October 2005, when treatment criteria were changed from threshold to pre-threshold disease, and Group 2 consisted of neonates followed thereafter. The frequency of ROP was slightly different (Group 1: 37.1%, 118 of 318; Group 2: 37.8%, 122 of 322), but it was not statistically significant (p=0.56). However, the mean GA (p=0.028) and mean BW (p=0.009) of Group 2 were significantly lower than those of Group 1. Furthermore, there were statistically significant differences between the two groups regarding the presence of oxygen therapy, mechanical ventilation, RDS, blood transfusion, multiple births, and sepsis, which were more prevalent in Group 2 (Table VI).

Discussion

The present study reports a 37.5% frequency of ROP. This figure falls in the middle of a wide range between frequencies reported from high and low-middle income countries[18-20]. It is evident that basically the socioeconomic status of the population and its reflections in perinatal care determine the epidemiological indices of ROP. Additionally, differences such as the study design (prospective vs. retrospective, hospital-based vs. population-based), characteristics of the study cohort, inclusion criteria, and the study period may contribute to the global diversity in the frequency of ROP. Similarly, such a wide range (23%-56.2%) was also observed in Turkey[9,21-24]. Table VII summarizes the present and recent studies reported from Turkey. Sarikabadayi et al.[21] reported lower frequencies for any stage of ROP (32.7%) and treatment-requiring severe ROP (3.1%) in their recent study conducted in a tertiary neonatal intensive care unit in Turkey. That study had

Table VI. Comparison of the Groups for Frequency of ROP and Related Risk Factors

	Group 1 (Retrospective) n=318	Group 2 (Prospective) n=322	P
ROP (%)	37.1	37.8	.81
GA (mean, weeks)	31.04±2.3	30.65±2.01	.028
BW (mean, g)	1567.23±439.5	1480.53±397.2	.009
Oxygen Therapy (n)	218	276	<.001
RDS (n)	63	96	.001
Mechanical Ventilation (n)	95	144	<.001
Multiple Births (n)	115	148	.013
Blood Transfusion (n)	35	90	<.001
Sepsis (n)	50	74	.020
IVH (n)	18	28	.298

ROP: Any degree of retinopathy of prematurity. GA: Gestational age. BW: Birth weight. RDS: Respiratory distress syndrome. IVH: Intraventricular hemorrhage.

Table VII. Summary of Various Published Reports Comparing Frequencies of ROP in Turkey

Study	n	Criteria	ROP		BW (g)	GA (weeks)	Percentage of older neonates
			Any (%)	Treated (%)			
Akçakaya et al.	517	< 37 wks	34.2	5.2	1886.3	32.5	≥ 33 wks; 53%
Sarikabadayi et al.	700	< 34 wks; < 2000 g	32.7	3.1	1571.4	31.1	>32 wks; 47%
Uğurbas et al.	260	≤ 34 wks	23	11.5	1416	30.3	> 32 wks; 9.6%
Akman et al.	801	< 37 wks	33.4	6.4	1572.9ǂ	31.5ǂ	≥ 32 wks; 56.5%
Basmak et al.	96	32-35 wks	56.2	9.3	1857.9	33.2	≥ 32 wks; 100%
Present study	640	≤ 34 wks; ≤ 1500 g	37.5	8.6	1521.4	30.8	≥ 32 wks; 10.6%

ROP: Retinopathy of prematurity. BW: Birth weight. GA: Gestational age.
ǂ Arithmetic mean of the three groups defined in the original study.

a large sample size; however, the study period was relatively shorter. Additionally, mean BW, mean GA and the number of neonates with higher GA were considerably higher than those in the present study. They also did not include the neonates who were referred from different centers. The ratio of treatment-requiring severe ROP decreased from 8.6% to 7% when the neonates born at different centers (10 neonates) were excluded in the present study. Despite these differences between the two studies, both revealed that no infant treated was over 32 weeks' gestation. Other studies from Turkey reported similar lower frequencies; however, with more severe cases of ROP requiring treatment over 32 weeks' gestation. Akçakaya et al.[22] reported a ratio of 34.2% for any stage of ROP and of 5.2% for treatment-requiring severe ROP. They chose higher cutoffs for GA and BW for ROP screening and included a significantly high number of heavier (>2000 g, 39.8%) and more mature neonates. Mean BW and mean GA for the original cohort and for neonates requiring treatment (1143.5±337.4 g; 28.6±2.3 weeks) were significantly higher than those in the present study. They had two neonates who developed treatment-requiring severe ROP with GA of ≥32 weeks. Akman et al.[23] reported ratios of 33.4% for any stage of ROP and 6.4% for treatment-requiring severe ROP; however, if they had included the neonates with a GA ≤34 weeks, the figures would then have been 36.3% and 7.2%, respectively. They reported 11 neonates who developed treatment-requiring severe ROP with a GA of 32-34 weeks. Basmak et al.[9] evaluated a more mature group of neonates (32-35 weeks) in a separate analysis and reported ratios of 56.2% and 9.3% for any stage of ROP and treatment-requiring severe ROP, respectively. This is the only study reporting such high frequencies for more mature neonates. Ugurbas et al.[24] reported a lower frequency for any stage of ROP with lower mean BW and mean GA. However, the frequency of treatment-requiring severe ROP (11.5%) was relatively higher, not correlating well with the reported lower frequency of ROP. This supports the importance of management of ROP-related risk factors other than BW and GA. We can comfortably deduce that picking a higher cutoff for ROP screening may contribute to relatively lower frequencies of ROP and treatment in a given population. In the present study, we experienced a high applicability of the American guidelines, but this does not obviate the need for developing a national guideline.

Current literature suggests that severe ROP is more or less constant in extreme prematurity (<1000 g, <28 weeks) in all nations whether they have high or low income. Researchers from high-income countries have mainly focused and reported on such neonates, whereas those from low-middle income countries have reported more mature neonates developing severe and treatment-requiring ROP[9,10,25]. We had five neonates with a BW of 1500 g or more who required treatment. Two of them were born at a different center and did not show progression to a higher stage. If we had

used a screening protocol of British origin (BW <1501 g, GA <32 weeks), two neonates with severe ROP would have been missed[26]. However, the American guidelines that we used did not miss any severe ROP[15]. We also previously reported that neonates with a GA of ≤32 weeks seem to have a greater risk of developing ROP[11]. However, two other studies from Turkey reported that more mature infants may require treatment for ROP[9,23]. Akman et al.[23] reported that 28.8% of the treated neonates had a GA between 32-34 weeks. All these observations clearly indicate a need for nationwide awareness and establishment of a multi-center population-based study to produce a more applicable guideline.

Retinopathy of prematurity (ROP) incidence was slightly higher in Group 2. A concise comparison of the two groups revealed a significantly lower mean BW and GA in Group 2, and percentages of presence of risk factors such as oxygen therapy, mechanical ventilation, RDS, blood transfusion, multiple births, and sepsis were significantly higher in Group 2. This could have led to the development of ROP in heavier neonates. However, as some researchers have emphasized, a definite explanation can only be made by taking into account the interaction between these risk factors[27]. Contrary to some studies reporting either a declining trend in the incidence of ROP or proposing a suspicion of excessive screening examinations, a higher frequency of ROP in Group 2 also indicates that we are facing more immature and sicker neonates probably due to the evolving neonatal nursing care[28,29].

Furthermore, multivariate analysis for treatment-requiring severe ROP revealed GA ≤28 weeks, mechanical ventilation, IVH, and being born at a different center as independent risk factors. Different from multivariate analysis for any stage of ROP, short GA in particular seemed to determine the risk for treatment-requiring severe ROP. Similarly Austeng et al.[25] found a log-linear relationship between severe ROP and GA, rather than BW. The statistical significance of outborn infant status may be due to referral of more unstable neonates from different centers. Mechanical ventilation is solely an indicator of overall health of the neonate. Mechanical ventilation and IVH can cause fluctuations in oxygen, which is considered to have a tight correlation with development of ROP. Oxygen delivery with high pressure by mechanical ventilation creates a hyperoxic environment, which could be detrimental to sprouting retinal vessels[30]. On the other hand, IVH and hypoxia have a bilateral cause-effect relationship in which cerebral hypoperfusion associated with an ischemic/hypoxic environment leads to rupture of immature thin-walled subependymal vessels, which in turn aggravates this hypoxic environment[31].

We are aware that this long-term study has some limitations, such as its hybrid nature, small sample size and being single-center based. Furthermore, the statistically proven effect of each of these factors may not have a direct influence on development of ROP, and the risk factor profile may differ from lower to higher stages of ROP. Therefore, the changeable nature of these factors and interactions between them should be addressed when trying to understand the multi-factorial basis of ROP.

The results of this study suggest that in spite of the evolving neonatal nursing care, frequency of ROP did not seem to follow a decreasing trend, probably due to survival of more immature or sicker neonates. In contrast to recent reports from Turkey, we found higher frequencies of ROP and treatment due to adopting lower cutoffs for screening. Various reported studies from Turkey have interestingly described considerable numbers of neonates developing ROP with higher BWs. Thus, we need to establish a national screening guideline to obtain more reliable data. Close monitoring of the risk factors such as oxygen therapy, RDS and sepsis seems to be crucial in the management of ROP. Examiners should also be alert when the neonates have GA ≤28 weeks, mechanical ventilation, IVH, and birth at a different center, since these neonates are at a greater risk for developing severe and treatment-requiring ROP.

Screening and management of ROP using the current guidelines have offered promising results in the last decade. However, frequent check-backs seem to be necessary to follow the dynamic nature of ROP in a population and to develop national guidelines that meet the needs of any nursing care center in Turkey.

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