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Prevalence, Severity and Treatment Modalities of Retinopathy of Prematurity in Infants Born Before 32 Weeks of Gestation in the Southeastern Region of Türkiye: A 6-Year Retrospective Study

Türkiye'nin Güneydoğu Bölgesinde 32. Gebelik Haftasından Önce Doğan Bebeklerde Prematüre Retinopatisinin Prevalansı, Şiddeti ve Tedavi Yöntemleri: 6 Yıllık Retrospektif Çalışma

Ayşegül ÇÖMEZ[1], Pelin ÇELEMLER[2], Yalçın KARAKÜÇÜK[3], Sadık YURTTUTAN[4], Gizem GÜRBOSTAN SOYSAL[5], Nurten SERİNGEÇ AKKEÇECİ[6]

[1]Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Ophthalmology, Kahramanmaraş, Türkiye
[2]Gaziantep Children's Hospital, Clinic of Ophthalmology, Gaziantep, Türkiye
[3]Selçuk University Faculty of Medicine, Department of Ophthalmology, Konya, Türkiye
[4]Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Pediatrics, Division of Neonatology, Kahramanmaraş, Türkiye
[5]Gaziantep City Hopital, Clinic of Ophthalmology, Gaziantep, Türkiye
[6]Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Physiology, Kahramanmaraş, Türkiye

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ABSTRACT

Objective: To investigate the severity and prevalence of retinopathy of prematurity (ROP) and treatment modalities within the past 6 years among premature infants with gestational age (GA) <32 weeks.

Methods: This dual-center, retrospective study was conducted at two referral centers for the screening and treatment of ROP. For all patients included in the study; GA, birth weight (BW), sex, race, duration of hospitalization, type of ROP, and treatments performed were recorded.

Results: The study included 755 (48.5%) female and 802 male (51.5%) preterm infants with a GA <32 weeks, for a total of 1557 patients. The prevalence rates of any stage of ROP and severe ROP development in all patients were 59.3% and 19.0%, respectively. These rates were 87% and 44.3% in extremely preterm infants (<27 weeks), respectively. A statistically significant negative correlation was determined between GA and BW and the development of any stage ROP and severe ROP (r=-0.299, r=-0.298, p<0.001; r=-0.338, r=-0.309, p<0.001). Treatment was required in 296 (19%) of the infants who underwent ROP screening. Of these patients, 163 (55.1%) underwent LP, and 103 (34.8%) were administered anti-vascular endothelial growth factor (VEGF), while 27 (9.1%) received anti-VEGF followed by LP therapy.

Conclusion: The increased prevalence of ROP among infants in the current study underscores the necessity of taking more severe measures to enhance quality standards of neonatal intensive care units to prevent the occurrence of ROP. Anti-VEGF treatment has provided a safe and effective alternative to LP, particularly in patients with aggressive ROP and posterior location.

Keywords: Retinopathy of prematurity, treatment modalities, prevalence

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Corresponding Author/ Sorumlu Yazar:

Ayşegül ÇÖMEZ, MD,
Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Ophthalmology, Kahramanmaraş, Türkiye
draysegulcomez@gmail.com
ORCID: 0000-0002-2628-9426

ÖZ

Amaç: Gebelik haftası (GH) <32 hafta olan prematüre bebeklerde, prematüre retinopatisinin (PR) şiddetini, görülme sıklığını ve son 6 yıldaki tedavi yöntemlerini araştırmak.

Yöntem: Bu çift merkezli, retrospektif çalışma PR tarama ve tedavisi için iki sevk merkezinde gerçekleştirildi. Çalışmaya dahil edilen tüm hastalar için; GH, doğum ağırlığı (DA), cinsiyet, ırk, hastanede kalış süresi, PR tipi ve uygulanan tedaviler kaydedildi.

Bulgular: Çalışmaya GH <32 hafta olan 755 (%48,5) kız ve 802 (%51,5) erkek erken doğmuş bebek olmak üzere toplam 1557 hasta dahil edildi. Tüm hastalarda herhangi bir evrede PR ve şiddetli PR gelişmesi görülme oranı sırasıyla %59,3 ve %19,0 idi. Bu oranlar aşırı preterm bebeklerde (<27 hafta) sırasıyla %87 ve %44,3 idi. GH ve DA ile herhangi bir evre PR gelişimi ile şiddetli PR arasında istatistiksel olarak anlamlı negatif korelasyon belirlendi (r=-0,299, r=-0,298, p<0,001; r=-0,338, r=-0,309, p<0,001). PR taraması yapılan bebeklerin 296'sında (%19) tedavi gerekti. Bu hastaların 163'üne (%55,1) lazer fotokoagülasyon (LF), 103'üne (%34,8) intravitreal anti-vasküler endotelyal büyüme faktörü (VEBF) tedavisi uygulanırken, 27'sine (%9,1) intravitreal anti-VEBF ve ardından LF tedavisi uygulandı.

Sonuç: Bu çalışmada bebeklerde PR görülme sıklığının artması, PR oluşumunu önlemek için yenidoğan yoğun bakım ünitesinin kalite standartlarının yükseltilmesine yönelik daha ciddi önlemlerin alınması gerekliliğini vurgulamaktadır. Anti-VEBF tedavisi, özellikle Agresif PR ve arka bölge yerleşimli PR'li hastalarda LF'ye kıyasla güvenli ve etkili bir tedavi alternatifi sağlamıştır.

Anahtar Kelimeler: Prematüre retinopatisi, tedavi yöntemleri, prevalans

INTRODUCTION

Retinopathy of prematurity (ROP) is a retinal vascular proliferative disease that can cause blindness and impaired vision. ROP risk has grown as a result of advancements in neonatal intensive care, which have raised the survival rates of extremely low birth weight (BW) newborns.[1] ROP may be mild or regress spontaneously, but may also lead to retinal detachment and blindness in severe cases.[2,3]

ROP prevalence in developed countries is gradually decreasing in parallel with the more stringent monitoring of oxygen administration, an important risk factor for ROP development, as well as blood oxygen saturation and the increase in the quality of neonatal intensive care.[4] In addition, infants with very low gestational age (GA) at birth in developed countries are more prone to severe ROP.[4,5] However, due to insufficient awareness of the risk factors associated with ROP and the lack of experienced professionals in developing countries, ROP develops at higher rates and occurs more commonly in infants that are more mature and heavier at birth.[6]

The mainstay of ROP therapy has historically been the ablation of the avascular peripheral retina with cryotherapy, and more recently, with laser photocoagulation (LP).[7,8] However, recurrences requiring treatment, adverse structural outcomes, refractive errors, and higher rates of insufficient regression have been reported to occur after LP therapy, especially in patients with aggressive-ROP (A-ROP) and ROP located in zone 1.[9-12] Therefore, during the past ten years, the usage of anti-vascular endothelial growth factors (VEGF) in the treatment of ROP has steadily grown.

The current study aimed to determine the severity and prevalence of ROP in premature infants (GA of less than 32 weeks) born at two tertiary centers in Türkiye's southeast region.

METHODS

The current non-randomized retrospective study was conducted in two tertiary centers, that are the reference centers for ROP screening and treatment in the region. The study enrolled patients who were followed up in the neonatal intensive care units (NICU) of these two centers and those who were referred to these institutions from various centers in the region for treatment and diagnosis. The Helsinki Declaration guided the study's execution, and the clinical research ethics committee of Kahramanmaraş Sütçü İmam University Faculty of Medicine approved the study (decision no: 13, date: 22.01.2020). Each patient's parents provided an informed consent form.

Study Population and Dataset

All babies were screened according to the appropriate screening criteria for our country (all babies who were born at GA <34 weeks or with BW ≤1700 grams, or preterm babies who were born at GA ≥34 weeks or with BW >1700 g who were given cardiopulmonary supportive treatment or were deemed at risk by the clinician monitoring the infant).[13] This study included patients born at GA <32 weeks, who were either treated at these two centers or referred to these centers for screening and treatment across the region between March 2013 and January 2019.

All study data were collected from the medical records of retinal examinations of preterm infants who met the screening criteria. Patients who died before completing the ROP scans or before the first ROP scan were excluded from the study, as well as infants with missing data.

For all patients included in the study, length of hospital stay, race, GA, BW, gender, treatments [LP and/or vitreoretinal surgery (VRC), intravitreal bevacizumab (IVB)], and ROP type (A-ROP, type 1 or 2 ROP) were recorded.

Patients with a GA of 27 weeks or less were classified as extremly preterm according to previous studies.[14] Infants were also categorized according to BW as<1000 g, 1000-1250 g, 1251-1500 g and >1500 g.[15] ROP cases that did not require treatment were classified as mild ROP, whereas any stage of ROP development in any zone was defined as ROP development.[16] Cases diagnosed with A-ROP, pretreshold type 1 and treated pretreshold type 2 ROP cases were defined as severe ROP (ROP requiring treatment).[17,18] According to location, cases requiring treatment were classified as infants referred from tertiary centers (training and research hospitals and university hospitals), state hospitals, and private hospitals. In this retrospective cohort study, treatment modalities and the severity and incidence of ROP were evaluated in relation to GA, BW, gender, race, and hospitalization time.

Ophthalmic Examination and Treatment Modalities

Eye examinations were performed at 4 weeks postpartum by experienced ophthalmologists (retinal specialists) using a scleral depressor and an indirect ophthalmoscope according to GA (infants born <27 weeks postnatal 31st week). Ophthalmological examinations were repeated weekly or biweekly using the follow-up program recommended by the American Academy of Pediatrics until complete vascularization of the retina reaches zone 3 (the most peripheral temporal retinal region). If ROP developed, ophtalmic examinations were conducted more frequently, depending on the severity and progression. The findings of plus disease, zone, and ROP stage were classified according to the international classification of ROP criteria.[17] The Early Treatment ROP (ETROP) guidelines were followed for scheduling follow-up exams and treatments.[18] However, not all treated infants met these criteria and were defined as unclassified (zone 3 stage 3 with plus disease group).

Treatment was applied to babies with type 1 ROP and A-ROP. According to ETROP guidelines, children with type 2 ROP were closely monitored (once every three to five days) in our research centers, whereas infants who progressed to type 1 ROP received LP treatment.[18] LP was performed in infants with stage 3 ROP who continued to have vascular tortuosity in zone 2 despite being followed closely for at least 1 month, and in infants with type 2 ROP who showed structural changes such as the extension of the fibrovascular membrane into the vitreous and traction causing flattening of the temporal arcuates, and who developed preretinal hemorrhage and/or intravitreal hemorrhage during follow-up.

Furthermore, infants from different NICUs in southeastern and Eastern Anatolia and our region were referred to our study centers for ROP treatment. Because of these centers' geographic location (due to their border with Syria), a large number of refugee infants were screened and followed up with. Therefore, LP was performed to babies with type 2 ROP (zone 2 stage 3 plus without disease) who could not adapt to close follow-up due to transfer from distant cities after discharge from the NICU, and to refugees who have to return to their countries and to the refugees who have to return to their countries.

In cases where the retina was not fully vascularized, ophthalmologic examinations were continued until complete vascularization ocurred or until the 45th postpartum age. The highest ROP stage detected during the follow-up examinations was recorded for each infant.

In patients with posterior zone involvement (zone 1 and posterior zone 2) and A-ROP, IVB was administered as the primary treatment with the family's consent, in accordance with the results of the Bevacizumab Eliminates the Angiogenic Threat-ROP study.[11] In babies with involvement in the mid zone 2, zone 3, and posterior zone 2 for whom families did not consent to IVB treatment, photocoagulation with diode laser was performed in the avascular retinal areas under general anesthesia. Patients who underwent IVB were monitored until peripheral retinal vascularization was completed. Additional LP therapy was applied in infants with insufficient regression (persistence of plus disease and neovascularization 3 to 5 days after injection) and progression (intravitreal hemorrhage developing after IVB, increase of neovascularizations and tractional components), and recurrence (recurrence of the plus disease requiring treatment and neovascularizations or extraretinal fibrovascular proliferation despite regression of all ROP findings after treatment). Patients whose ROP findings did not regress and showed progression despite all these interventions were referred to a higher center for potential VRC.

Statistical Analyses

The statistical software program "SPSS 16.0 for Windows" was used to analyze the study data. Kolmogorov-Smirnov and Levene's test were used to determine whether the data distribution was normal, the variances were homogeneous. Numerical data with a homogeneous variance and normal distribution were analyzed using the independent samples t-test (Student's t-test) and One-Way analysis of variance; numerical data that did not satisfy the parametric test assumptions were analyzed using the Kruskal-Wallis test and Mann-Whitney U test; and categorical data were analyzed using the chi-square test. Numerical data were displayed as mean±standard deviation, and categorical data as numbers (percentages). The p value was set at 0.05 for statistical significance. For $p<0.05$, test findings were deemed significant.

RESULTS

This study enrolled a total of 1557 preterm infants born at GA <32 weeks, of which 755 (48.5%) were female and 802 (51.5%) were male. The mean GA of the subjects was 29.05±1.72 (range, 23-31) weeks, and the mean BW was 1354±340 (range, 450-2500) grams. One thousand three hundred and sixty (87.3%) patients were Turkish citizens, 197 (12.7%) were refugees, and 339 (21.8%) were from multiple pregnancy.

Table 1 shows the rate of development of any ROP and severe ROP by GA and BW. The overall rates of development of any ROP and severe ROP were 59.3% and 19.0%, respectively. The corresponding rates for extremely preterm infants (GA ≤27) were 87% and 44.3%, respectively.

A statistically significant negative correlation was found between GA and BW and the development of any ROP (r=-0.299, r=-0.298; p<0.001 for both) and severe ROP (r=-0.338, r=-0.309; p<0.001 for both). The mean length of hospitalization was 50.01±25.0 (range, 7-180) days. A statistically significant positive correlation was found between the length of hospitalization and the development of any ROP and severe ROP (r=0.392, r=0.345; p<0.001 for both).

The mean BW and GA were significantly lower in infants who developed any ROP compared to those who did not (p<0.001) (Table 2). The mean BW and GA of patients with severe ROP were found to be significantly lower than those with mild ROP (p<0.001) (Table 3).

The length of hospitalization was significantly longer in cases with any ROP compared to those without (Table 2) and cases with severe ROP compared to cases with mild ROP (Table 3) (for both, p<0.001). No statistically significant differences were observed in terms of gender, race and multiple pregnancy in the development of any stage ROP and severe ROP (p=0.275, p=0.973, p=0.379; p=0.728, p=0.807, p=0.733, respectively) (Tables 2, 3).

Treatment was required for 296 (19%) of all infants who underwent a ROP scan. LP therapy was applied to 163 patients (55.1%) and anti-VEGF to 103 (34.8%) LP was applied to 27 (9.1%) patients due to insufficient regression, progression, or recurrence after anti-VEGF treatment. In addition, 3 (1%) patients with A-ROP developed partial retinal detachment (stage 4 ROP) despite primary LP and required VRC treatment. In addition, 24 (5.1%) infants who required treatment had a body weight above 1500 g. Table 4 shows the types of ROP and treatment modalities in patients requiring treatment.

Among patients treated for severe ROP, 34 (11.5%) were from our tertiary centers and other tertiary centers; 66 (22.6%) patients were referred from state hospitals, and 195 (65.9%) patients from various private hospitals. The mean BW and GA of the patients referred from private hospitals (1325.7±3212 g, 29.0±1.7 weeks, respectively) were significantly higher than those of the patients referred from state hospitals (1227.9±322 g, 28.4±1.6 weeks, respectively) and tertiary centers (1161.3±347 g, 27.8±2.3 weeks, respectively) (p=0.002, p=0.019, respectively).

Table 1. The rates of developing any ROP and severe ROP by gestational age and birth weight

Gestational age (weeks)	**Screened infant n (%)**	**Any ROP n (%)**	**Severe ROP n (%)**
23	2 (0.1)	2 (100)	2 (100)
24	20 (1.3)	19 (95)	13 (65)
25	40 (2.6)	39 (97.5)	23 (57.5)
26	75 (4.8)	68 (88)	31 (41.3)
27	125 (8.0)	102(81.6)	47 (37.6)
≤27 (subtotal)	262 (16.8)	228 (87)	116 (44.3)
28	310 (19.9)	207(66.8)	65 (21.0)
29	195 (12.5)	122 (62.6)	38 (19.5)
30	425 (27.3)	208 (48.9)	55 (12.9)
31	365 (23.4)	158 (43.3)	22 (6.0)
Total	1557	923 (59.3)	296 (19.0)
Birth weight (grams)			
≤1000	306 (19.7)	214 (85.6)	100 (41.8)
1001-1250	310 (19.9)	211 (68.1)	64 (20.6)
1251-1500	466 (29.9)	264 (56.7)	80 (17.2)
>1501	475 (30.5)	186 (39.2)	24 (5.1)
Total	1557	923 (59.3)	296 (19)

ROP: Retinopathy of prematurity

DISCUSSION

ROP is a potentially preventable cause of childhood blindness, and the increase in survival rate of extremly preterm infants with advances in neonatal intensive care technology has increased the incidence of ROP.[19] Therefore, it is estimated that globally, 20,000 infants become severely visually impaired due to ROP each year.[20] Two-thirds of children with vision loss due to ROP live in middle-income and moderately developed countries such as China, Southeast and South Asia, Latin America and Eastern European countries.[20,21] In contrast, in highly developed countries where risk factors such as blood oxygen saturation and oxygen supplementation are carefully monitored, the rate of ROP-induced blindness is lower.[21]

In this study, which spanned 6 years between 2013 and 2019 at two tertiary reference centers -both reference centers for the diagnosis and treatment of ROP in our region- the overall incidence of severe ROP was 19%, and any ROP was 59.3% in infants born at a GA of less than 32 weeks. Additionally, the prevalence and severity of ROP increased as BW and GA decreased. Furthermore, the prevalence of severe ROP was 44.3% in patients born at GA ≤27 weeks (extremely preterm).

Considering the current and large-scale treatment-requiring ROP study data from our country, patients born at GA ≤32 weeks had incidences of severe ROP and any ROP of 8.2% and 32.9%, respectively, while the corresponding rates for infants born at GA ≤28 weeks were 62.9% and 21.6%, respectively.[15] Another research in Türkiye found that among babies with GA ≤27 weeks, type 1 ROP incidence was 16.6% and any ROP incidence was 70.7%.[22] In another study investigating the incidence of ROP and treatment frequency in infants born between 2008 and 2017 in

Table 2. The relationship between GA, BW, length of hospitalization and developing any ROP

	No ROP (Mean±SD)	Any ROP (Mean±SD)	P
GA (weeks)	29.6±1.34	28.6±1.8	<0.001
BW (g)	1493.8±309.9	1258.7±328.1	<0.001
Sex (f/m) (n)	437/486	318/316	0.275
Length of hospital stay (days)	39.4±18.4	57.2±26.3	<0.001
Race (citizen/refugee) (%)	59.3/59.4	40.7/40.6	0.973
Multiple pregnancy, n (%)	208 (20.7)	131 (22.8)	0.379

GA: Gestational age, BW: Birth weight, ROP: Retinopathy of prematurity, g: Grams, SD: Standard deviation, f: Female, m: Male

Table 3. The relationship between GA, BW, length of hospitalization and developing severe ROP

	Mild ROP (n=627)	Severe ROP (n=296)	P
GA (weeks) (Mean±SD)	28.9±1.67	27.9±1.9	<0.001
BW (g) (Mean±SD)	1317.7±323.3	1135.8±301.8	<0.001
Gender (f/m,n)	138/158	300/327	0.728
Length of hospital stay (days) (Mean±SD)	52.3±23.8	67.3±28.2	<0.001
Race (citizen/refugee) (%)	18.9/19.8	40.3/40.2	0.807
Multiple pregnancy, n (%)	65 (22)	144 (23)	0.733

GA: Gestational age, BW: Birth weight, ROP: Retinopathy of prematurity, g: Grams, SD: Standard deviation, f: Female, m: Male

Table 4. Severity of ROP and treatment modalities in infants with severe ROP (requiring treatment)

	Laser	Anti-VEGF	Anti-VEGF+Laser	Laser+VRC	Total number of participants (%)
APROP	5	77	25	3	110 (37.2)
Type 1 ROP	95	26	2	0	123 (41.6)
Type 2 ROP	61	0	0	0	61 (20.6)
Unclassified	2	0	0	0	2 (0.7)
Total	163	103	27	3	296 (100)

ROP: Retinopathy of prematurity, APROP: Aggressive posterior retinopathy of prematurity, VEGF: Vascular endothelial growth factor, n: Number of infants, VRC: Vitreoretinal surgery

Sweden, the incidence of ROP requiring treatment in infants born at GA ≤31 was found to be 6.1%.[23] In the United Kingdom, Adams et al.[4] found ROP requiring treatment in 327 (4%) of 8112 infants born at 31 gestational weeks or less; and a BW of less than 1500 g.

A review of the literature indicates that reported ROP incidences vary between countries, even between rural and urban regions of a given country. Regional differences in ROP rates in high-income countries have been explained by differences in neonatal care such as different oxygen targets and different routines of oxygen level monitoring.[24] We believe that the higher rates of ROP found in our study in comparison to developed countries and other studies conducted in our country stems from the fact that high-risk patients are referred to our centers for diagnosis and treatment of ROP from a wide region and different NICUs. At the time, neonatal mortality rate has decreased significantly in our country in the last two decades. As a result of this development, the number of infants at risk of developing ROP has increased.[25] In Canada, Isaza et al.[26] reported the incidence of severe ROP as 14.3% between 2010 and 2016 in infants born at GA <32 weeks and with BW <1500 g; they also observed that the incidence almost doubled compared with that recorded in the same center between 2006 and 2010. They authors suggested that this increase may have resulted from the number of infants with a GA of 24 weeks or less, which had nearly doubled.

BW and GA have been recognized as important risk factors for the development of ROP, and most screening guidelines use these factors to identify infants in need of an examination. The present study is in line with the literature data; furthermore, the length of hospital stay in the present study was determined to be a predictive factor for the development of both ROP and severe ROP.

In the current study, 63 infants did not meet the ETROP criteria and were treated before reaching the criteria for type 1 ROP. Based on the findings of the ETROP research, current treatment guidelines recommend treating type 1 ROP and closely monitoring type 2 ROP.[18] However, decision-making in real-life ROP treatment applications is complex. Because delay in treating ROP can quickly lead to permanent vision loss, some ROP want to treat this dynamic disease at an earlier stage. This is due to medicolegal (increasing demands for responsibility by physicians providing ROP care and fear of litigation due to increased decisions against the attending ophthalmologist) and logistical reasons (parental non-compliance with repeated long-distance travel and close follow-ups).[27-31] In a survey of pediatric ophthalmologists treating ROP in the United Kingdom, 27% of 654 eyes treated were diagnosed with ROP less severe than type 1.[4] Gupta et al.[30] showed that 13 out of 137 eyes (9.5%) treated for ROP had a clinical diagnosis less severe than type 1 ROP in a study of 1444 eyes of 722 infants from 6 centers in the United States. Rajan et al.[31] found that 33 of 241 eyes (13.7%) treated in India between 2016 and 2019 were treated outside the guidelines. The indications for treatment reported in these studies included the presence of stage 3 ROP persisting for >6 weeks, type 1 ROP in the fellow eye, preretinal and/or intravitreal hemorrhage, ROP persisting despiteadvanced postmenstrual age (>41 weeks), structural changes associated with subsequent anatomic complications (macular ectopia and vitreoretinal traction etc.) and logistical worries.[4,30,31]

Anti-VEGF was applied as the primary treatment to 130 of 296 infants (the patients with the A-ROP) requiring treatment, and no serious complications such as retinal detachment were observed in any of the infants. However, retinal detachment was observed in 3 patients who received laser therapy as the primary treatment for A-ROP. In the literature, rates of favorable outcomes have been reported between 71% and 84% in patients with A-ROP despite early LP.[32,33] For infants with poor general conditions, zone 1 ROP, A-ROP, and reduced retinal vision, some authors suggested anti-VEGF treatments.[11] In our study, anti-VEGF application provided a safe and effective alternative to LP, especially in cases with A-ROP and posterior location.

In this study, 195 (65.9%) of the patients requiring treatment due to severe ROP consisted of patients referred from various private hospitals to our centers, and both GA and BW of these cases were higher than those referred from university hospitals and state hospitals. This reflects the differences in the standard of care units in our country, including non-standard conditions such as non-standardized oxygen supplementation levels, lack of experienced professionals and the nurse-to-baby and physician-to-baby rations.[6,15]

Study Limitations

The most significant limitation of our study was that it lacked any analysis of the risk factors affecting the development of ROP. Another limitation is that in our country, it is recommended to screen babies <34 weeks and ≤1700 grams, but in this article, the screening results of 32-week infants are discussed. In addition, observation of the study results from these two centers, which are among the largest referral centers especially for at-risk infants in the region, as well as the retrospective nature of the study were the other limitations of the current study. Therefore, the results should be interpreted cautiously.

CONCLUSION

In conclusion, in the present study, the improvement in neonatal care and the increase in the survival rates of the new population of extremely preterm infants increases the number of infants developing both ROP and severe ROP. Therefore, the current study emphasized the need to make more serious measures to increase and standardize NICU quality standards to prevent ROP development.

Ethics

Ethics Committee Approval: The clinical research ethics committee of Kahramanmaraş Sütçü İmam University Faculty of Medicine approved the study (decision no: 13, date: 22.01.2020).

Informed Consent: Consent form was filled out by all participants.

Presented in: This study was presented as an oral presentation at the 19th online International Eastern Mediterranean Family Medicine Congress 17th-20th September 2020.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.Ç., P.Ç., Concept: A.Ç., Design: A.Ç., Y.K., S.Y., Data Collection or Processing: A.Ç., P.Ç., Y.K., S.Y., G.G.S., N.S.A., Analysis or Interpretation: A.Ç., S.Y., N.S.A., Literature Search: A.Ç., Writing: A.Ç.

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