The Turkish Journal of Pediatrics 2025; 67: 808-817
https://doi.org/10.24953/turkjpediatr.2025.6685

**Original Article**

# Reflections of the 2021 update of the retinopathy of prematurity (ROP) guideline: a single-center retrospective comparative cohort analysis

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## ABSTRACT

**Background.** We aimed to determine the risk factors for retinopathy of prematurity (ROP) and investigate the effects of the expanded screening criteria according to the 2021 update of the Turkish Neonatology Society guidelines on the clinical outcomes of premature infants and the incidence of severe ROP.

**Materials and Method.** Patient records of infants treated in the neonatal intensive care unit (NICU) between January-December 2020 and January-December 2023, who were identified as at-risk for ROP were retrospectively analyzed. Infants with severe ROP were compared with those without ROP or with mild ROP not requiring treatment in terms of risk factors.

**Results.** Among the cohort of 169 patients at risk of ROP, the median gestational age was 30.2 (interquartile range [IQR]: 27.4-32.1) weeks and the median birth weight was 1354 g (IQR: 920-1760). Severe ROP was detected in 2.9% (n=5) of the premature infants included in the study. When comparing the periods before and after the 2021 guideline update, the incidence of severe ROP was found to be 3.7% vs. 2.2%, respectively (p=0.085). After the 2021 update, the number of infants examined at ≥33 weeks increased approximately 2.5-fold, but no severe ROP was detected in this group. Small gestational age, low birth weight, multiple erythrocyte suspension transfusions, patent ductus arteriosus, prolonged oxygen duration, and prolonged invasive mechanical ventilation were found to be statistically significant risk factors for severe ROP ($p<0.05$).

**Conclusion.** ROP is a significant cause of disability in extremely premature infants. Early diagnosis and treatment with optimum screening criteria can reduce permanent visual damage. As the premature population at risk for ROP evolves, screening criteria must also adapt. The 2021 ROP guideline states that, due to variations in quality of care and patient populations, each center may define its own optimal screening criteria based on local data. However, it is essential to use the expanded 2021 criteria within national ROP screening programs.

**Key words:** prematurity, retinopathy of prematurity, permanent visual damage.

Retinopathy of prematurity (ROP) occurs due to abnormal development of retinal vessels in premature and low birth weight infants and is the leading cause of childhood blindness.[1,2] Technological developments in neonatal intensive care units and improvements in neonatal care have increased the survivorship of extremely premature infants, making it

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Received 22nd Jul 2025, revised 9th Oct 2025, 19th Nov 2025, accepted 20th Nov 2025.

possible to keep much smaller premature infants alive. As a result, the incidence of ROP is rising worldwide.[3-7] The most well-known risk factors for ROP are low birth weight and small for gestational age (SGA).[8] Many other factors including ethnicity and a country's level of development also influence the incidence of ROP. Therefore, different guidelines are used for the screening, diagnosis, and treatment of ROP around the world. Studies conducted in high-income countries have shown that infants born at ≥ 32 weeks are not at risk for ROP, and most infants born at >28 weeks who develop ROP have mild disease that spontaneously regresses without treatment.[9] On the contrary, countries with lower development indices tend to use broader screening criteria that more accurately reflect the population at risk of ROP.[10] Studies conducted in developing countries, including Türkiye, have reported cases of severe ROP requiring treatment in infants with birth weight (BW) between 1500-2500 grams.[11-14] Consequently, countries need to implement national ROP guidelines tailored to their own sociodemographic characteristics. In a multicenter study conducted by the Turkish Neonatology Society (TR-ROP study), the incidence of ROP in infants with a gestational age (GA) of 33-35 weeks was found to be 6.1% and the incidence of advanced stage ROP was 6 per thousand in this group.[15] The Turkish consensus guidelines on retinopathy of prematurity, created in 2016 by the Turkish Neonatal Society (TNS) in collaboration with the Turkish Ophthalmology Society, were updated in 2021 after evaluation of current literature as well as the TR-ROP study results, and the screening criteria were expanded.[16,17]

In this study, we aimed to investigate the effects of the expanded screening criteria according to the 2021 guideline update on the clinical outcomes of premature infants and the incidence of severe ROP.

## Materials and Methods

### *Study design and setting*

This was a single-center, cross-sectional, retrospective comparative study. The study was conducted in the neonatal intensive care unit (NICU) of a tertiary university hospital in İstanbul, Türkiye, with admits approximately 1000 patients per year. Patient records of infants treated in the NICU between January-December 2020 and January-December 2023, who were identified as at-risk for ROP and underwent ROP examination were analyzed. The study was approved by the Clinical Research Ethics Committee of Göztepe Prof. Dr. Süleyman Yalçın City Hospital (Registration no: 2023/0960).

### *Participants and definitions*

Searching of the data was performed using the hospital's software system for the following International Classification of Diseases 10th Revision (ICD-10) codes: H35.1 for ROP, P07.2 and P07.3 for prematurity.

Demographic and clinical characteristics, diagnostic information, and consultation notes of premature infants who were screened for ROP risk and whose records were fully accessible were retrospectively obtained from electronic patient files. Premature infants treated in the NICU in 2020 were treated and screened for ROP according to the 2016 TNS guidelines. According to this guideline, all infants with a gestational age of ≤ 32 weeks or a birth weight of ≤ 1500 grams as well as infants with BW > 1500 grams or GA > 32 weeks and an unstable clinical course (e.g. those who received cardiopulmonary support or were considered to be at risk by any means) were screened for retinopathy of prematurity.[16] Premature infants hospitalized in the NICU in 2023 were treated and followed for ROP according to the 2021 guideline update. According to this updated

guideline, all infants with a GA of < 34 weeks or a BW of ≤ 1700 grams were determined as at risk for retinopathy of prematurity. Preterm infants with a gestational age of ≥ 34 weeks or a BW of > 1700 grams who received cardiopulmonary support therapy or who were considered at risk for ROP by the clinician following them were also screened.[17]

Demographic characteristics of premature infants screened according to the 2016 and 2021 ROP guidelines as well as antenatal, natal and postnatal risk factors for ROP were reported. These risk factors were antenatal corticosteroid use, preeclampsia/eclampsia, infants of diabetic mothers, clinical chorioamnionitis, multiple pregnancy, mode of delivery, male gender, early gestational age, low birth weight, respiratory distress syndrome (RDS), prolonged duration of invasive mechanical ventilation, total duration of oxygen requirement, bronchopulmonary dysplasia (BPD) defined by oxygen requirement at a postmenstrual age of 36 gestational weeks (GW), intraventricular hemorrhage (IVH) > grade II according to Volpe staging[18], hemodynamically significant patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC) ≥ stage II according to modified Bell's criteria [19] and the number of red blood cell (RBC) transfusions (20 mL/kg per transfusion).

Infants who died before the first ROP examination were excluded from the study. These infants were included only in the cohort mortality rate. After pupil dilation with 2.5% phenylephrine (Mydfirin, Alcon, USA) and 0.5% cyclopentolate (Sikloplejin, Abdi İbrahim, Turkey), anterior segment examination with a light source was performed, followed by fundus examination using an indirect ophthalmoscope and a 20-diopter lens. Infants with premature retinopathy were monitored at a frequency deemed appropriate by the ophthalmologist, while those without ROP findings were monitored every 1 to 2 weeks until retinal vascularization was complete. Findings were recorded in accordance with the International Classification of Premature Retinopathy.

### *Statistical analysis*

SPSS (Statistical Packages for Social Sciences: SPSS Inc, Chicago, IL, USA) software version 20.0 was used for all statistical calculations and analyses. Demographic data and diagnosis distributions were analyzed using descriptive analysis methods. In descriptive analyses, mean ± standard deviation was used for variables that conformed to normal distribution and median (interquartile range [IQR]) was used for variables that did not conform to normal distribution.

When comparing the incidence of severe ROP and clinical data before and after the 2021 ROP guideline update, an independent samples t-test was used for continuous variables with a normal distribution, while the Mann–Whitney U test was applied for variables without a normal distribution. Categorical variables were compared using the chi-square test, and Fisher's exact test was applied when appropriate. A p-value < 0.05 was considered statistically significant.

## Results

During the study period, 18.3% (n=195) of the 1061 newborns treated in the level 3 neonatal intensive care unit were identified as at risk for ROP. Of these infants 13.3% (n=26) died before their first ROP examination could be performed. Among those who died, 23% (n=6) had major congenital anomalies, and 65.3% (n=17) were extremely premature infants born between 22-24 weeks of gestation. The data of these infants were excluded from the analysis. The demographic and clinical characteristics of premature infants who were followed and treated due to the risk of ROP according to the criteria before and after the 2021 guideline update are compared in Table I. Severe ROP rates in infants evaluated according to screening criteria before and after the 2021 guideline update were 3.7% and 2.2%, respectively; this difference was not statistically significant. (p= 0.085) (Table II). When newborns at risk for ROP were grouped according to gestational

**Table I.** Comparison of demographic and clinical characteristics of newborns screened before and after the 2021 ROP guideline update

| Patients features | Before 2021 update, n=81 | After 2021 update, n=88 | p |
|---|---|---|---|
| Demographic features | | | |
| Gestational age,† weeks+days, median (IQR) | 29+5 (26+2-31+2) | 31+4 (28+5-33+1) | <0.001 |
| Birth weight,† g, median (IQR) | 1235 (833-1528) | 1497 (110-2022) | <0.001 |
| Male sex, n (%) | 46 (56.8%) | 37 (42%) | 0.306 |
| Vaginal delivery, n (%) | 14 (17.3%) | 8 (9%) | 0.262 |
| Multıple pregnancy n (%) | 11 (13.6%) | 8 (9%) | 0.82 |
| Twin | 9 (11.1%) | 7 (7.9%) | |
| Triplet | 2 (2.4%) | 1 (1.1%) | |
| Clinical features | | | |
| RDS, n (%) | 60 (74%) | 52 (59%) | 0.154 |
| PDA requiring treatment, n (%) | 19 (23.4%) | 18 (20.4%) | 0.808 |
| IVH > grade II, n (%) | 12 (14.8%) | 8 (9%) | 0.170 |
| NEC ≥ grade II, n (%) | 10 (12.3%) | 4 (4.5%) | 0.063 |
| BPD, n (%) | 29 (35.8%) | 24 (27.2%) | 0.249 |
| Mild | 10 (12.3%) | 14(15.9%) | |
| Moderate | 14 (17.2%) | 7 (7.9%) | |
| Severe | 5 (6.2%) | 3 (3.4%) | |
| Frequency of ET, n (%) | | | |
| Once | 19 (23.4%) | 14 (15.9%) | 0.185 |
| More than once | 16 (19.7%) | 11(12.5%) | |
| Severe ROP, n (%) | 3 (3.7%) | 2 (2.3%) | 0.837 |
| Duration IMV,† days, median (IQR) | 2 (0-11) | 1 (0-3) | 0.040 |
| Total days on oxygen,† median (IQR) | 13 (3-36) | 2 (0-15) | <0.001 |
| Duration of hospital stay,† days, median (IQR) | 40 (25-78) | 29 (12-55) | 0.019 |

BPD: Bronchopulmonary dysplasia; ET: Erythrocyte suspension transfusion; IMV: Invasive mechanical ventilation; IQR: Interquartile range (25th to 75th percentiles); IVH: Intraventricular hemorrhage; NEC: Necrotizing enterocolitis; PDA: Patent ductus arteriosus; RDS: Respiratory distress syndrome; ROP: Retinopathy of prematurity.
†Fisher's exact test p-value < 0.05.

age, severe ROP was observed only in babies born at 22-27 GW. Although the number of infants who underwent ROP examination at ≥ 33 gestational weeks increased approximately 2.5-fold after the 2021 update, no severe ROP cases were detected in this group (Table II).

Infants diagnosed with severe ROP requiring treatment were compared with those without ROP or with self-resolving ROP at any stage in terms of associated risk factors (Table III). Small gestational age, low birth weight, prolonged invasive mechanical ventilation, and duration of oxygen requirement significantly increased the risk of severe ROP (p< 0.001).

## Discussion

Improvements in neonatal care globally have increased the survival of extremely premature infants and the incidence of ROP is rising accordingly. In the light of rapidly evolving literature, the national ROP diagnosis and treatment guideline, originally created in 2016, was updated in 2021. In this study, we found that the changes in screening criteria with the

**Table II.** Severe ROP incidence by gestational age (before vs after 2021 update)

| Patient groups | | | Any ROP or no ROP n (%) | Severe ROP n (%) | P |
|---|---|---|---|---|---|
| Before 2021 update n=81 | GA groups | 22-27 wk | 20 (24.7%) | 3 (3.7%) | |
| | | 28-32 wk | 46 (56.7%) | 0 | |
| | | ≥ 33 wk | 12 (14.8%) | 0 | 0.085 |
| After 2021 update n=88 | GA groups | 22-27 wk | 13 (14.7%) | 2 (2.3%) | |
| | | 28-32 wk | 41 (46.5%) | 0 | |
| | | ≥ 33 wk | 32 (36.3%) | 0 | |

GA: gestational age; ROP: Retinopathy of prematurity.
Fisher's exact test p-value < 0.05.

**Table III.** Maternal and neonatal risk factors associated with severe retinopathy of prematurity

| | Any ROP or no ROP (n=164) | Severe ROP (n=5) | p |
|---|---|---|---|
| Antenatal features | | | |
| Antenatal steroid, two doses, n (%) | 79 (48.1%) | 3 (60%) | 0.68 |
| Preeclampsia, n (%) | 53 (21.3%) | 3 (60%) | 0.33 |
| Gestational diabetes, n (%) | 12 (7.3%) | 1 (20%) | 0.33 |
| Chorioamnionitis, n (%) | 10 (6%) | 0 (0) | 0.73 |
| Vaginal delivery, n (%) | 15 (9.1%) | 0 (0) | 0.61 |
| Clinical features | | | |
| Gestastional age,† weeks, median (IQR) | 31 (23-24) | 24 (24-25) | <0.001 |
| Male sex, n (%) | 91 (55.4%) | 0 (0%) | 0.018* |
| Birth weight,† g, , median (IQR) | 1440 (550-3590) | 560 (430-690) | <0.001 |
| IMV duration,† days, median (IQR) | 1 (0-85) | 70 (43-101) | <0.001 |
| Total days on oxygen,† median (IQR) | 6 (0-104) | 98 (70-156) | <0.001 |
| Hospital stay,† days, median (IQR) | 33 (3-180) | 125 (103-213) | <0.001 |
| IVH, n (%) | 19 (11.5%) | 1 (20%) | 0.48 |
| PDA, n (%) | 33 (20.1%) | 4 (80%) | 0.001* |
| NEC, n (%) | 11 (6.7%) | 3 (60%) | 0.004* |
| BPD, n ( %) | 48 (29.2%) | 5 (100%) | 0.003* |
| ET more than once, n (%) | 22 (13.4%) | 5 (100%) | <0.001* |

BPD: Bronchopulmonary dysplasia; ET: Erythrocyte suspension transfusion; IMV: Invasive mechanical ventilation; IQR: Interquartile range (25th to 75th percentiles); IVH: Intraventricular hemorrhage; NEC: Necrotizing enterocolitis; PDA: Patent ductus arteriosus; ROP: Retinopathy of prematurity.
†Fisher's exact test p-value < 0.05.

2021 update did not change the incidence of severe ROP or clinical outcomes in our cohort.

Severe ROP is a multifactorial disorder that can lead to blindness in premature infants. Its incidence is associated with well-known clinical risk factors such as younger gestational age and lower birth weight, the duration and concentration of oxygen therapy, hyperoxia/hypoxia, as well as sociodemographic risk factors related to countries and families. Due to the diversity of the cohort at risk for ROP, the incidence of severe ROP has been reported in a very wide range of 3-44% in the literature.[5-7,9,14,20] In Türkiye, two large multicenter studies conducted in 2015 and 2018 reported the rate of severe ROP as 5% and 6.7%, respectively.[11,15]In a 2012 study by the department of ophthalmology

of our hospital, examining premature infants at risk of ROP in our unit, the incidence of severe ROP was as high as 22.6%.[21]

In the current study, incidence of severe ROP was 2.9%, which is lower than both national multicenter studies and our unit's rate reported in 2012. The 85% reduction in severe ROP incidence in our unit in the last 13 years is likely associated with increased clinical experience of the healthcare team, improved access to advanced technical equipment, and strengthened multidisciplinary collaborations. As reported in the BIG-ROP study, the incidence of severe ROP is associated with the level of hospitals providing NICU services.[22] With the optimal quality of care of premature infants in NICU, risk factors that increase ROP such as NEC, BPD, IVH, and prolonged oxygen exposure and mechanical ventilation can be minimized.

Studies from developing countries including our own, have reported severe ROP cases requiring treatment in infants with a BW of 1500-2500 grams.[11,14,15,20] In line with these findings, the 2021 guideline update aims to detect ROP cases that may develop in more mature infants during screening and to enable their early treatment. An increase in the rate of severe ROP can be anticipated in programs conducted with expanded screening criteria. However, in a study by Kaya Guner and Inci Bozbıyık, the guideline was compared before and after the update and it was reported that although the rate of ROP at any stage increased after the update, the rate of severe ROP decreased.[23]

In the current study, the rates of severe ROP were similar between the cohorts before and after the 2021 guideline update. However, some important points should be taken into consideration when interpreting these results. In this comparative cross-sectional study, the number of premature babies between 22-27 GW- the group in which severe ROP was most frequently seen- was coincidentally higher in the pre-update group than in the post-update group. This may falsely create the impression that the rate of severe ROP decreased in the post-update period. As expected, median gestational age and birth weight were higher in this group because expanded screening criteria were used after the update. The duration of invasive mechanical ventilation, total oxygen use time, and hospital stay were longer in the pre-update group, which we believe is a reflection of this. In conclusion, the two retrospective cohorts compared in this study were not homogeneously distributed. Therefore, comparing the ROP rate before and after the update may be misleading. However, what is striking in our study is that there were no cases of severe ROP observed above 27 GW in either cohort. This result is parallel to the results of developed countries.[9,24]

Although the number of infants who underwent ROP examination at ≥33 GW increased by approximately 2.5 times following the expansion of screening criteria after the 2021 update, no severe ROP cases were detected. On the other hand, given that only a small number of patients require treatment and since ophthalmologic examination of these very premature infants may result in adverse conditions such as tachycardia, apnea and pain, some authors have proposed risk calculators such as DIGIROP (develop a prediction tool) calculator, in order to determine which infants most need ophthalmologic examination.[25] However, use of these calculators has not yet gained widespread acceptance.

Given the wide variation in healthcare systems, healthcare financing across countries and the socioeconomic status of families of premature infants, ROP screening should be tailored to local settings. The population of premature infants at risk for ROP may change as the quality of care in neonatal intensive care units improves and technical infrastructure becomes standardized. Therefore, the most appropriate screening criteria may also change in the future. Emerging technologies such as ROP video cameras and new biomarkers for the prevention, early diagnosis, and treatment of ROP will bring new opportunities for ROP screening.[10,26]

The 2021 ROP guideline also emphasizes that the quality of care in neonatal intensive care units may vary from unit to unit and that centers should determine the upper limits of birth weight and gestational age for ROP screening based on their own patient populations and epidemiological data. However, the National ROP Guideline updated in 2021 is based on the results of a large-scale study involving numerous centers across the country.[15] Considering the differences in quality of care among centers and the demographic characteristics of patients in our country, the use of the updated and expanded screening criteria is essential. This ensures that all infants at risk for severe ROP can be safely and effectively identified and monitored.

The most important risk factors for retinopathy of prematurity are small gestational age and low birth weight.[8] The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP), which demonstrated that these risk factors are inversely proportional to the risk of developing ROP, reported that each 100 g increase in BW reduced the probability of reaching threshold (severe) ROP by 27% and each weekly increase in GA reduced the probability of reaching the threshold disease by 19%.[27] There are many other studies showing similar results.[24,28-32] The results of the current study are consistent with the literature and confirm that small gestational age and low birth weight are important risk factors for severe ROP.

Mechanical ventilation treatment and oxygen delivery according to the infant's needs are vital for the survival of premature infants. However, it has also been reported that oxygen treatment is an important risk factor for ROP.[33] The increase in ROP due to high oxygen concentration can be explained by several mechanisms: An increase in free oxygen radicals and oxidant damage causes apoptosis and vasoobliteration in vascular endothelial cells.[34,35] BPD, which is associated with prolonged oxygen therapy, has been reported to contribute to the development of ROP. [28,36-38] In this study the increase in the duration of mechanical ventilation and oxygen treatment evidently increases the incidence of severe ROP. Great care should be taken when applying noninvasive ventilation methods in neonatal intensive care units, and it should not be forgotten that oxygen is a drug and that its dose must be adjusted precisely.

Studies have shown that repeated transfusions with adult blood increase the risk for ROP.[32,39,40] This is associated with the fact that 2.3 diphosphoglycerate in adult red blood cell suspensions causes lower oxygen binding to hemoglobin, thus increasing the amount of oxygen delivered to the tissues. Similar to the literature, we also observed that ≥ 2 RBC transfusions significantly increased the incidence of severe ROP. Strategies that reduce anemia in premature infants including late cord clamping after birth may reduce the incidence of ROP by enabling less frequent RBC transfusions.

Problems associated with advanced prematurity, including advanced NEC (stage ≥2), BPD, hemodynamically significant PDA, and IVH are known to increase the risk of ROP.[32,41-43] In this study due to the limited sample size, independent risk factors could not be analyzed using logistic regression. In the univariate analysis, hemodynamically significant PDA, advanced necrotizing enterocolitis, and bronchopulmonary dysplasia were found to significantly increase the incidence of severe ROP. These findings were consistent with the literature. However, advanced IVH, which is among the known risk factors, was not found to be associated with severe ROP in our study. This finding may be related to the low number of advanced IVH cases in our cohort. Awareness of the risk factors that contribute to ROP and implementing neonatal intensive care strategies that will reduce these factors may decrease the development of ROP.

### *Study strengths and limitations*

In this study, we reported the data before and after the 2021 TNS ROP guideline update with a comparative cohort analysis. This is one of the few studies investigating the results of the expanded screening criteria. Further guideline updates will likely be required as more data from similar studies accumulate and as the premature population at risk of ROP continues to evolve in the future.

This study has several limitations. First, the pre- and post-update cohorts compared retrospectively were not homogeneously distributed. Second, not all risk factors associated with ROP (such as genetic predisposition, postnatal growth restriction, and episodes of sepsis) were evaluated. The third limitation of the study is that, due to the small sample size, logistic regression analysis could not be performed to identify independent risk factors contributing to the development of ROP. Therefore, univariate analysis was used to evaluate the risk factors.

### *Conclusion*

Retinopathy of prematurity is an important cause of disability that is influenced by several risk factors and can result in permanent visual damage without screening and early treatment. Optimum ROP screening criteria and early treatment algorithms aim to ensure the survival of premature infants without sequelae. As the premature population at risk for ROP continues to change, it is likely that screening criteria will also need to adapt accordingly.

## Ethical approval

The study was approved by Istanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee (date: December 20, 2023, number: 2023/0960).

## Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: SSÖ, EYİ, FO; data collection: SSÖ, SK, BK; analysis and interpretation of results: SSÖ, FO, SA, EYİ, SK, BK; draft manuscript preparation: SSÖ, SA, FO, EYİ. All authors reviewed the results and approved the final version of the manuscript.

## Source of funding

The authors declare the study received no funding.

## Conflict of interest

The authors declare that there is no conflict of interest.

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