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Myopia Incidence Among Premature Infants with Type-2 ROP and Without ROP: A Single Center Retrospective Cohort Study

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ABSTRACT

Introduction: Retinopathy of prematurity (ROP) arises from the atypical development of retinal blood vessels in infants born prematurely. These infants face an increased likelihood of developing myopia, particularly those diagnosed with ROP. The occurrence and intensity of myopia in this population are associated with various factors, including low birth weight, the degree of prematurity, the severity of ROP, and the treatments administered for the condition. Purpose: This study aims to compare the incidence of myopia and examine the relationship between risk factors (birth weight, gestational age, oxygen use) and myopia in premature infants with Type 2 ROP and those without ROP at Dr. Soetomo General Hospital, Surabaya. Methods: This analytical observational study used a retrospective cohort design. All premature infants meeting the inclusion criteria from medical records between January 2017 and December 2022 were included. Visual acuity was assessed using Grating Acuity and Cycloplegic Examinations, and myopia was evaluated at 12 months using streak retinoscopy. Results: Among 67 preterm infants, 34 (50.7%) did not develop ROP, while 33 (49.3%) had Type 2 ROP. Most infants had a birth weight between 1500-2000 grams (43.3%) and a gestational age over 32 weeks (55.2%). Oxygen use was recorded in 39 infants (58.2%). Most infants did not develop myopia, with 62.7% in the left eye and 67.2% in the right eye. A notable difference in the incidence of myopia was observed between infants with Type 2 ROP and those without, with statistical significance ($p = 0.002$). In contrast, factors such as birth weight, gestational age, and oxygen therapy showed no significant association with myopia in either group. Conclusion: Preterm infants without ROP exhibited a lower rate of myopia compared to those with Type 2 ROP. The lack of correlation with common risk factors implies that impaired anterior segment development may contribute to the onset of myopia.

Keywords: *Retinopathy of Prematurity type 2, Premature Baby, Myopia, Birth weight, Gestational Age, Oxygen Supplementation.*

1. INTRODUCTION

Improvements in neonatal care have significantly increased the survival rates of premature infants. Consequently, medical attention has shifted from merely ensuring survival to enhancing their overall quality of life. Due to the incomplete development of the eyeball at birth, the incidence of ocular disorders has risen. Conditions such as Retinopathy of Prematurity (ROP), ametropia, amblyopia, and strabismus are commonly associated with prematurity (Chen & Zhang, 2013); (Xie et al., 2022); (Wilkinson et al., 2008). OP, specifically, is an ischemic retinal condition resulting from the abnormal formation of retinal blood vessels in premature babies (Harder, 2003). The quality of life of premature babies is significantly affected by ROP. Visual impairment and blindness caused by ROP account for 6-8% of childhood blindness. (Courtright et al., 2011).

The emmetropization process and the stages of eye development in premature infants are influenced by prematurity. (Achiron et al., 2000) Full-term infants usually have hyperopia. However, premature infants, even without ROP, are prone to myopia (Ruan et al., 2015), astigmatism (Quinn et al., 2013), anisometropia (Ouyang et al., 2015), and strabismus (Gursoy et al., 2014). Myopia is among the most frequently observed long-term effects of ROP. [11] A study by O'Connor et al., as cited by (Stephenson et al., 2007), found that both premature children with and without ROP exhibited elevated rates of myopia.

The study by (Al Oum et al., 2014) reported a significantly higher prevalence of myopia in premature children with severe ROP (40.6%) compared to without ROP (7%), with both groups evaluated at one year of age. These findings are consistent with those of Baker and Tasman, who observed that over 80% of children with cicatricial ROP develop high myopia (greater than 6 diopters). According to (NABABAN et al., 2023), the prevalence and severity of myopia in premature infants are influenced by factors such as low birth weight, the degree of prematurity, ROP severity, and the treatment administered for ROP.

A previous study conducted at RSUD Dr. Soetomo Surabaya aimed to assess the differences in objective refractive status in children aged 6 months to 3 years (corrected age) with a history of prematurity. The rate of myopia was found to be 14.5%, emmetropia 18.8%, and hypermetropia 66.7%. In contrast, in the full-term group, the rate of myopia was 3% and hypermetropia was 97%. Currently, in Indonesia, there is no information on the incidence of myopia in premature infants with untreated ROP or premature infants without ROP. Therefore, this is the first study to do research in that population.

2. METHODS

This study employed an analytical observational approach using a retrospective cohort design, conducted at Dr. Soetomo General Hospital in Surabaya between January and March 2024. The research utilized secondary data obtained from medical records of all premature infants treated at the hospital's ophthalmology clinic from January 1, 2017, to December 31, 2022. Ethical approval for the study was granted by the Health Research Ethics Committee of Dr. Soetomo General Hospital, with clearance number: 1524/LOE/301.4.2/XI/2023.

The sampling was carried out using the total sample approach that fits the following criteria: 1) Premature infants recorded at the ophthalmology clinic who are not diagnosed with ROP; 2) Premature infants recorded at the ophthalmology clinic with ROP but have not received therapy; 3) Patients with complete data regarding gestational age, birth weight, and history of oxygen usage; 4) Patients with complete fixation or grating acuity examination and cycloplegic refraction data during follow-up at 3 months, 6 months, and 12 months of age. Premature infants with eye disorders other than ROP, such as refractive media opacities or other congenital eye abnormalities, and patients with incomplete medical records were excluded from this study. The research sample was taken from the search for ICD-10 medical records with the diagnosis of ROP, coded H35.1, resulting in 4,571 diagnoses, and among these, a total of 1,586 babies were identified. Premature infants who met the inclusion and exclusion criteria amounted to 67 patients, including 34 (50.7%) premature infants without ROP and 33 (49.3%) premature infants with Type 2 ROP.

The chi-square test was used for inferential statistical analysis to assess variations in the incidence of myopia. A comparative analysis employing the contingency coefficient was utilized to assess the association between birth weight, gestational age, and history of oxygen use with the incidence of myopia in premature infants, both with and without a history of type 2 ROP. All statistical tests were conducted at a 5% significance level (p-value < 0.05) using SPSS version 27.0 (IBM Corporation).

3. RESULTS

The characteristics of the study subjects are shown in Table 1. Of the total 67 premature infants, 61.76% were male in the group without ROP and 45.45% in the group with Type 2 ROP, with the remainder being female. The gestational age range in the group without ROP was 28–36 weeks, with an average of 33 weeks and a standard deviation (SD) of ±2.21. The ROP group's gestational age ranged from 26 to 37 weeks, with an average of 31 weeks ±3.28. According to the gestational age sub-classification, 26.47% of the newborns in the group without ROP were under 28 weeks along, 47.05% were between 28 and 32 weeks along, and 26.47% were over 32 weeks along. In the ROP group, 33.33% of the infants were born before 28 weeks, 42.40% between 28 and 32 weeks, and 24.24% after more than 32 weeks. This indicates that the majority of premature infants had a gestational age of 28-32 weeks.

The average birth weight of premature infants in the group without ROP was 1,817.12 grams with an SD of ±490.90, and in the group with Type 2 ROP, it was 1,716.82 grams with an SD of ±482.09. The range of birth weights in the group without ROP was 900-2,500 grams, while in the Type 2 ROP group, it was 800-2,500 grams. According to the sub-classification, 5.90% of the infants in the group without ROP were born weighing less than 1,500 grams, 23.50% were born weighing between 1,500 and 2,000 grams, and 70.60% were born weighing more than 2,000 grams. Of the babies in the ROP group, 33.30% were born weighing less than 1,500 grams, 42.40% were born weighing between 1,500 and 2,000 grams, and 24.20% were born weighing more than 2,000 grams. The history of oxygen use was predominantly absent in both groups, with only 35.29% of infants in the group without ROP having a history of oxygen use, compared to 48.48% in the group with Type 2 ROP.

Table 1. Analysis of various characteristics of premature babies

			Premature without ROP (n=34)			ROP Type 2 (n=33)		
			Mean ± SD	**Total (%)**	**Range**	**Mean ± SD**	**Total (%)**	**Range**
Gender	Male			21 (61.76%)			15 (45.45%)	
	Female			13 (38.24%)			18 (54.54%)	
Gestational age (week)			33 ± 2.21		28-36	31 ± 3.28		26-37
	≤ 28			9(26.47%)			11(33.33%)	
	28-32			16(47.05%)			14 (42.42%)	
	> 32			9(26.47%)			8(24.24%)	
Birth weight (grams)	Total		1817.12 ±490.90		900-2500	1716.82 ± 482.09		800-2500
	≤ 1500			2(5.90%)			11(33.30%)	
	1500-2000			8(23.50%)			14(42.40%)	
	> 2000			24(70.60%)			8(24.20%)	
Oxygen supplementation	Yes			12 (35.29%)			16 (48.48%)	
Myopia (babies)	Unilateral			1 (14.2%)			3 (15.79%)	
	Bilateral			6 (85.71%)			16 (84.21%)	
Not Myopia (babies)				27(79.4%)			14(42.4%)	
Myopia (eyes)	Low Myopia	RE	S -2.25 ± 1.46	6	S-1.00- to S-5.00	S -1.79 ± 1.51	7	S -0.50 to S -5.00
		LE	S -1.75 ± 1.15	6	S -1.00 to S-4.00	S -1.95 ± 1.65	9	S -0.50 to S -5.00
	High Myopia	RE	S-6.00 ± 0	1	S-6.00	S -8.44 ± 2.31	10	S -6.00 to S -12.00
		LE		0		S -8.67 ± 3.02	9	S -6.00 to S -14.00

The number of babies and the number of afflicted eyes were used to calculate the incidence of myopia. In the ROP group, the incidence of myopia was 42.4%, while in the group without ROP, 79.4% of the newborns did not have myopia. Unilateral myopia was found in 14.2% of the infants in the group without ROP and 15.79% in the group with Type 2 ROP. Bilateral myopia occurred in 85.71% of the infants in the group without ROP and 84.21% in the group with Type 2 ROP.

The degree of myopia, which was divided into mild and high myopia, was also explained for the affected eyes (right and left). In the group without ROP, there was only one case of high myopia, which was unilateral myopia, with a magnitude of -6.00 diopters. In contrast, myopia was more frequently found in the group with Type 2 ROP, where 9 infants had high myopia in the right eye and 9 infants in the left eye, with the highest value being -14.00 diopters.

Table 2 The incidence of myopia in premature infants with a history of Type 2 ROP and premature infants without ROP

	Incidence (n%)		**Total n(%)**	**Chi Square**
	Myopia	**Not Myopia**		**P value**
without ROP	7 (20.6%)	27 (79.4%)	34(100%)	**0.002**
ROP Tipe 2	19 (57.6%)	14 (42.4%)	33 (100%)	
Total	**26**	**41**	**67**	

Out of 67 newborns in this study, 26 had myopia: 57.6% in the group with Type 2 ROP and 20.6% in the group without ROP. The p-value obtained from the Chi-Square test was 0.002, which is less than the significance level of 0.05. This suggests that premature infants with Type 2 ROP and those without ROP have a statistically significant difference in the incidence of myopia.

Table 3. Correlation between birth weight and incidence of myopia

		Incidence n (%)		**Total n (%)**	**Contingency coefficient**
		Myopia	**Not Myopia**		
Premature Infants without a History of ROP					**P Value**
Birth weight	≤ 1500 gram	2(22.2%)	7(77.8%)	9(26.5%)	0.595
	1500-2000 gram	4(26.7%)	11(73.3%)	15(44.1%)	
	>2000 gram	1(10.0%)	9(90.0%)	10(29.4%)	
Total		7(20.6%)	27(79.4%)	34(100%)	
Premature Infants with Type 2 ROP					**P Value**
Birth weight	≤ 1500 gram	4(36.4%)	7(63.60%)	11(33.30%)	0.084
	1500-2000 gram	8(57.10%)	6 (42.90%)	14(42.40%)	
	>2000 gram	7(87.50%)	1 (12.50%)	8(24.20%)	
Total		19(57.6%)	14 (42.4%)	33(100%)	

The relationship between risk factors for myopia and the incidence of myopia in premature infants with a history of Type 2 ROP and premature infants without ROP will be tested based on the researched risk factors, namely birth weight, history of oxygen use, and gestational age. The first analysis showed that most premature infants without a history of ROP did not develop myopia, regardless of their birth weight (Table 3). For infants with a birth weight of ≤1500 grams, 77.8% did not develop myopia, for those between 1500-2000 grams, 73.3% did not, and for those over 2000 grams, 90.0% did not develop myopia. With a p-value of 0.595 (greater than $\alpha = 0.05$), indicates that there is no statistically significant association between

birth weight and the incidence of myopia in premature infants without ROP.

In premature infants with Type 2 ROP, those weighing ≤1500 grams had a 63.6% likelihood of not developing myopia, while 36.4% did (see Table 3). In the 1500–2000 gram birth weight group, 57.1% developed myopia and 42.9% did not, suggesting a higher incidence in this category. Among infants with a birth weight over 2000 grams, 87.5% developed myopia, and only 12.5% remained unaffected. Despite these trends, the p-value of 0.084 exceeds the 0.05 significance level, indicating that the association between birth weight and myopia incidence in this group is not statistically significant.

Table 4. Correlation between gestational age and incidence of myopia

		Incidence n (%)		Total n (%)	Contingency coefficient
		Myopia	Not Myopia		
Premature Infants without a History of ROP					**P Value**
Gestational age	**≤ 28 weeks**	0(0.0%)	2 (100%)	2(5.90%)	0.342
	28-32 weeks	3(37.50%)	5 (62.50%)	8(23.50%)	
	> 32 weeks	4(16.70%)	20 (83.3%)	24(70.60%)	
Total		**7(20.60%)**	**27 (79.40%)**	**34(100%)**	
Premature Infants with Type 2 ROP					**P Value**
Gestational age	**≤ 28 weeks**	3(37.50%)	5(62.50%)	8(24.20%)	0.236
	28-32 weeks	9(75.00%)	3(25.00%)	12(36.40%)	
	> 32 weeks	7(53.80%)	6(46.20%)	13(39.40%)	
Total		**14(42.40%)**	**19(57.60%)**	**33(100%)**	

As presented in Table 4, none of the premature children with a gestational age of ≤28 weeks and no history of ROP acquired myopia. Among those born between 28–32 weeks, 62.5% did not develop myopia, while 37.5% did. For infants with a gestational age over 32 weeks, 83.3% were free of myopia, and 16.7% were affected. Overall, the majority of infants without ROP did not develop myopia across all gestational age ranges. However, with a p-value of 0.342 > 0.05 significance level, there is no statistically significant association between gestational age and the incidence of myopia in this group.

Table 5. Correlation between oxygen supplementation and the incidence of myopia

Correlation between oxygen supplementation and the incidence of myopia					
		Incidence n (%)		Total n (%)	Contingency coefficient
		Myopia	Not Myopia		
Premature Infants without a History of ROP					**P Value**
Oxygen Supplementation	**No**	3(13.60%)	19(86.40%)	22(64.71%)	0.175
	Yes	4(33.30%)	8(66.70%)	12(35.29%)	
Total		**27(79.40%)**	**7(20.60%)**	**34(100%)**	
Premature Infants with Type 2 ROP					**P Value**
Oxygen Supplementation	**No**	12(70.60%)	5(29.40%)	17(51.52%)	0.119
	Yes	7(43.80%)	9(56.30%)	16(48.48%)	
Total		**19(57.60%)**	**14(42.40%)**	**33(100%)**	

The analysis of the relationship between oxygen use history and myopia incidence in premature infants with and without Type 2 ROP shows that among 22 premature infants without ROP who did not use oxygen, 86.4% did not develop myopia, while 13.6% did. In contrast, of the 12 infants who had used oxygen, 66.7% did not develop myopia, indicating that most infants in both groups remained free of myopia. The p-value of 0.175 suggests no significant relationship between oxygen use and myopia in this cohort ($p > 0.05$). In the group of 17 infants with Type 2 ROP who did not use oxygen, 29.4% did not develop myopia, while 70.6% did, indicating a higher incidence of myopia among these infants. Among 16 infants with Type 2 ROP who had used oxygen, 56.3% did not develop myopia, suggesting a different outcome. The p-value of 0.119 indicates no significant relationship between oxygen use history and myopia incidence in infants with Type 2 ROP ($p > 0.05$).

4. DISCUSSION

This study consist of 67 premature infants, with 34 (50.7%) classified as infants without ROP and 33 (49.3%) as those with Type 2 ROP. The incidence of myopia was assessed using streak retinoscopy examinations conducted at 12 months of age. Out of the 67 premature infants, 41 did not develop myopia. The highest incidence of myopia, at 57.6%, was observed in the Type 2 ROP group, while the non-ROP group showed a lower incidence of 20.6%. These results align with findings from Wang *et al*, which reported the highest myopia incidence in the ROP group (9 out of 50) compared to the non-ROP group (11 out of 110) and the non-premature control group (6 out of 92) at the age of 7 years. (Ouyang et al., 2015).

Among the 67 premature infants studied, the majority had a birth weight between 1500 and 2000 grams (43.3%), and most had a gestational age of over 32 weeks (55.2%). Additionally, 39 infants (58.2%) did not have a history of oxygen use. The distribution of the study sample revealed that 50.7% were infants without a history of ROP, while 49.3% had Type 2 ROP. This distribution is consistent with findings from prior studies, which noted that the group of non-ROP premature infants was larger than that of ROP infants.

Early postnatal and late embryonic phases are critical for the development of the eye, particularly its refractive components. The majority of fetal retinal blood vessels develop during the third trimester. When birth occurs prematurely, it can disrupt this process, resulting in retinal vascular ischemia, hypoxia, and underdevelopment factors that contribute to the onset of ROP (Dikopf et al., 2019). ROP can vary in severity and negatively impact the development of the eye's optical components, frequently resulting in long-term refractive anomalies like elevated rates of astigmatism and myopia in children who are affected.[18],[19] Research has consistently shown a correlation between the severity of ROP and the prevalence of myopia.

In this study, data were presented for each eye, analyzing the incidence of myopia across all infants. For the left eye, 82.4% of the 34 premature infants without a history of ROP did not develop myopia, while 17.6% experienced mild myopia, and none had high myopia. In the right eye, 79.4% were free from myopia, 21.2% had mild myopia, and 2.9% had high myopia. In the group of premature infants with Type 2 ROP, among the 33 infants, 42.4% of the left eyes did not develop myopia, 30.3% had mild myopia, and 27.3% had high myopia. For the right eye, 51.5% did not develop myopia, 21.2% had mild myopia, and 27.3% had high myopia. Premature babies without ROP and those with a history of Type 2 ROP had significantly different incidences of myopia ($p=0.002$).

These results align with previous studies, such as that by Ouyang et al., which assessed the refractive status and ocular components of premature children aged 3–4 years with pre-threshold or milder ROP. Their findings indicated that myopia occurred exclusively in the ROP group, with a 5.08% incidence, while no cases were observed among premature infants without ROP or among full-term children. Similarly, Chang et al. reported premature newborns without ROP had a higher prevalence of myopia than their full-term counterparts.

In another study by Xie et al., involving children aged 3–8 years with mild ROP, both prematurity and mild ROP were found to influence refractive development. The ROP group demonstrated significantly higher rates of myopia and high astigmatism ($P<0.05$). Even in the non-ROP group, myopia was more prevalent than in full-term controls, suggesting that prematurity alone increases the risk of refractive errors, particularly when accompanied by ROP. The study also identified thicker crystalline lenses as a contributing factor to the elevated myopia rates in both ROP and non-ROP premature groups. Consistent with these findings, our research found that premature newborns without ROP had a decreased incidence of myopia, while those with Type 2 ROP exhibited a higher risk of developing both mild and high myopia.

A study by Al Oum *et al* involving 217 premature infants without ROP, 28 with mild ROP (stages 1 and 2), and 16 with severe ROP found that the former two groups were more likely to develop astigmatism by one year of age (54% and 53%, respectively). Myopia was most common in the severe ROP group, with an incidence rate of 41% at one year. The study revealed that premature newborns with ROP had a significantly greater prevalence of myopia ($P<0.05$) than those without, and the chance of acquiring myopia increased significantly ($P<0.05$) as the severity of ROP increased.

The primary risk factors for myopia in premature infants are ROP, low birth weight, and low gestational age. Myopia was predominantly found in the ROP group.[15] Pawar *et al* found that factors such as lower gestational age, neonatal respiratory distress, and oxygen therapy were linked to a higher prevalence of myopia. This study aims not only to compare the incidence of myopia among premature infants but also to explore the associated risk factors within the same cohort.

Yang *et al* highlighted the correlation between low birth weight and increased myopia incidence [2], a finding that aligns with Ouyang *et al,* who suggested that the lower incidence of myopia in their study could be due to relatively higher birth weights. O'Connor *et al* noted that refractive status tends to remain stable in the first decade of life, but low-birth-weight children may experience a shift toward myopia. Observations in premature children have revealed changes such as increased corneal curvature and lens thickness, along with decreased axial length, which are linked to myopia development.[3] A New Zealand cohort study by Darlow *et al* found that untreated ROP in very low birth weight infants was associated with a higher likelihood of developing significant myopia. However, there was no discernible link between the incidence of myopia and birth weight in our study.

The research found no significant correlation between birth weight and the incidence of myopia in the group of premature infants without ROP ($p = 0.595$). Similarly, there was no discernible relationship between the incidence of myopia and birth weight in the Type 2 ROP group ($p = 0.084$). These findings are consistent with the Pawar et al. study, which likewise revealed no evidence of a significant correlation between the development of refractive defects and birth weight. Premature babies are typically more likely to develop myopia, regardless of their ROP status. These results emphasize the value of routine eye exams to detect refractive problems in low-birth-weight babies throughout their formative years.

According to a number of studies, the prevalence of myopia in babies born before 37 weeks of pregnancy is inversely correlated with both birth weight and gestational age. Moreover, various parts of the visual system, such as the brain's white matter, are especially vulnerable to damage when gestational duration is reduced by up to 40%. However, our study did not find a significant correlation between gestational age and myopia incidence, either in premature infants with Type 2 ROP ($p = 0.236$) or those without ROP ($p = 0.342$).

Research on the effects of oxygen supplementation on myopia incidence is still very limited. Pawar *et al* noted that the prevalence of mild to moderate myopia was more common in children who required oxygen therapy during the neonatal period. (Korkmaz et al., 2018) It is known that oxygen supplementation is a risk factor that plays a role in the severity of ROP. High oxygen levels cause avascular retinas to become hypoxic when oxygen supplementation is withdrawn, leading to the release of angiogenic factors and intravitreal blood vessel growth. Since then, vascular endothelial growth factors have been recognized as critical for vascular activity in severe ROP (Kaya et al., 2018). However, the pathophysiology of myopia related to oxygen supplementation has not yet been clearly supported by clinical studies. Oxygen supplementation can influence the severity of ROP, and ROP itself can lead to myopia. A supporting theory was proposed by Cook *et al*, suggesting that sudden oxygen withdrawal may cause a vascular crisis affecting choroidal vascularity, potentially contributing to myopia development.[35] Our study found no significant relationship between oxygen use history and myopia in both groups: premature infants without ROP ($p=0.175$) and those with Type 2 ROP ($p=0.119$).

A limitation of this study was incomplete medical records during the study period due to changes in the hospital's medical record storage system, particularly regarding the results of streak retinoscopy eye examinations and patient hospitalization data.

5. CONCLUSIONS

The results of this study indicate a significant difference in the incidence of myopia between preterm infants with and without a history of Type 2 ROP. However, no correlation was observed between birth weight, gestational age, or a history of oxygen use and the occurrence of myopia in either group of preterm infants, whether they had a history of Type 2 ROP or not.

To enhance future research, it would be beneficial to conduct similar studies using a prospective design, allowing for more comprehensive data collection. This could include the addition of measurable parameters in eye clinics, such as keratometry and biometry. Furthermore, exploring other risk factors that may contribute to the development of myopia in preterm infants could provide valuable insights for understanding and addressing this condition.

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