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Original Article

Risk factors of immature retina on the first screening for retinopathy of prematurity

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Abstract

Background ***Immature retina is characterized by peripheral retinal*** avascularity. Retinal development is influenced by risk factors that affect retinal maturity.

Objective To identify risk factors for immature retina on the first retinopathy of prematurity (ROP) screening at the Neonatology Care Unit, Al-Islam Hospital, Bandung, in 2013-2021.

Methods This case-control, retrospective, observational study was performed by evaluating medical records of preterm infants screened for ROP. The subjects were divided into two groups, immature retina and mature retina. We recorded potential risk factors including gestational age (GA), birth weight (BW), birth weight for gestational age, respiratory distress syndrome (RDS), oxygen therapy >7 days, asphyxia, sepsis, multiple transfusion, apnea of prematurity (AOP), patent ductus arteriosus (PDA), and bronchopulmonary dysplasia (BPD) and analyzed them for potential associations with retinal development.

Results On the first ROP screening of 203 premature infants, 5 (2.5%) had ROP, 90 (44.6%) had immature retinas, and 107 (53.0%) had mature retinas. Bivariate logistic regression analysis showed significant relationships between immature retina (P<0.05), GA (OR=0.575; P=0.000), BW (OR=0.997; P=<0.001), gestational age maturity (OR=2.639; P=0.006), RDS (OR=1.809; P=0.042), oxygen therapy of >7 days (OR=4.494; P=0.002), sepsis (OR=2.028; P=0.034), multiple transfusions (OR=4.656; P=0.000), AOP (OR=2.553; P=0.002), PDA (OR=2.119; P=0.030). Multivariate regression analysis revealed a significant simultaneous relationship between all the risk factors and immature retina, with a Nägelkerke R2 value of 0.421.

Conclusion GA, BW, gestational age maturity, oxygen therapy of >7 days, sepsis, multiple transfusions, AOP, and PDA are significant risk factors of immature retina, be it independently or simultaneously. **[Paediatr Indones. 2023;63:189-94; DOI: https://doi.org/10.14238/pi63.3.2023.189-94]**.

Keywords: *: risk factor; immature retina; retinopathy of prematurity (ROP)*

Retinopathy of prematurity (ROP) is characterized by the abnormal development of retinal vessels in premature infants due to incomplete vascularization of the retinal tissue.[1-3] ROP is one of the leading causes of visual impairment in premature infants, accounting for 10% of blindness in preschool children worldwide.[3] Blencowe *et al.*[4] estimated that ROP blinds or impairs the vision of 32,000 infants annually. According to a WHO report, 1.4 million children globally are blind, of which, ROP was responsible for 50,000 cases.[5] There is limited information regarding ROP-related blindness in Indonesia, but a study by Badriah et al. reporting that the incidence of ROP at Dr. Cipto Mangunkusumo Hospital Jakarta, was 11.9% from 2005 to 2010.[6]

Recent advances in neonatal care have increased the survival rate of premature infants, but this has been accompanied by an increased incidence of ROP.[7,8] However, ophthalmologists and neonatologists can conduct screening, provide a precise diagnosis, and prevent disease progression by identifying risk

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factors in an effort to prevent to ROP development.[9] Premature infants are born before blood vessel growth reaches the edge of the retina; therefore, the part of the retina not covered by blood vessels receives insufficient oxygen and nutrients. To fulfill the oxygen and nutrient requirements, the edge of the retina transmits signals to other regions of the retina, causing the blood vessels to become exceedingly fragile and rupture easily. Several risk factors that affect retinal maturity impact retinal development in premature infants ("immature retina"). This retina either develops into ROP, matures, or remains immature, thus, early detection is useful not just for diagnosis, but also for monitoring the development of retinal blood vessels.[10,11]

The International Classification of Retinopathy of Prematurity (ICROP) provides an objective approach to diagnosing ROP.[12] A more comprehensive and technical definition was considered when this classification was reviewed more than ten years ago.[13] However, there has been a lack of discussion on the precursor of ROP, namely, the degree of retinal immaturity. The immature retina is characterized by peripheral retinal avascularity and vasoconstriction, which can be observed during ophthalmoscopic examination.[12] This study was conducted to identify possible risk factors for the development of an immature retina on the first ROP screening of preterm infants treated at the Neonatology Care Unit of Al-Islam Hospital, Bandung, between 2013 and 2021.

Methods

This retrospective observational case-control study was performed by reviewing the medical records of premature infants who were screened for ROP at Al Islam Hospital, Bandung, from January 1, 2013, to December 31, 2021. We included all infants born during the study period who had birth weight (BW) of <1,500 g or gestational age (GA) of <32 weeks. As controls, we selected infants with a BW of >1,500 g or GA > 32 weeks, with unstable clinical conditions, including those requiring cardiorespiratory support and classified as high-risk by pediatricians. The exclusion criteria were infants who failed to survive more than 28 days for the first retinal maturity screening and infants diagnosed with ROP.

The first retinal examination was performed by an ophthalmologist at the age of 4-6 weeks. If the retina was classified as immature, follow-up examination was performed four weeks later. Before the examination, both pupils were dilated using topical eye drops (2.5% phenylephrine and 0.5% tropicamide) until fully dilated, and local anesthesia of 0.5% tetracaine hydrochloride was applied during indirect ophthalmoscopy to identify the peripheral retina. Research subjects who met the inclusion criteria were divided into two groups, those with immature retina (case group) and those with mature retina (control group) on the first examination.

The independent variables evaluated included GA, BW, birth weight for gestational age, RDS, oxygen therapy >7 days, asphyxia, sepsis, multiple transfusions, AOP, PDA, and BPD. Bivariate and multivariate binary logistic regression tests were conducted. We also calculated exp(B)/odds ratios and Nägelkerke R square values. A P value of <0.05 was considered significant. The model fit was analyzed by the Hosmer Lemeshow test. All statistical analyses were conducted using *SPSS version 25* (*IBM*, Armonk, New York).

Results

During the study period, 202 premature infants met the inclusion criteria. There were 111 (55%) male and 91 (45%) female infants; 112 (55.4%) infants were delivered vaginally, and 87 (43.1%) Caesarean section. Subjects' mean birth weight was 1,492.77 (SD 360.35) g and mean gestational age was 31.65 (SD 2.29) weeks. There were 153 (75.7%) small for gestational age (SGA) and 49 (24.3%) appropriate for gestational age (AGA) infants; there was no large for gestational age (LGA) infant. At the first ROP screening examination, there were 5 (2.5%) infants with ROP, 90 (44.6%) with immature retinas, and 107 (53.0%) with mature retinas. The incidence of ROP at Al Islam Hospital Bandung was relatively low at 2.5% (**Table 1**).

At the first ROP screening examination, there were 5 infants with ROP, 90 with immature retinas, and 107 with mature retinas. Four weeks after the first retinal examination, there were 7 infants with an immature retina that required further follow-up until

Table 1. Characteristics of research subjects

Variables	(N=202)
Delivery type, n(%)	
Normal vaginal	112 (55.4)
Vacuum	3 (1.5)
Caesarean section	87 (43.1)
Sex, n (%)	
Male	111 (55.0)
Female	91 (45.0)
Birth weight, n(%)	
ELBW	17 (8.4)
VLBW	87 (42.9)
LBW	78 (38.4)
LBW	21 (10.3)
Mean (SD), g	1,492.77 (360.35)
Gestational age, n(%)	
<28 weeks (very early preterm)	10 (4.9)
28-31+6 weeks (very early preterm)	87 (42.9)
32-34+6 weeks (early preterm)	87 (42.9)
35-36+6 weeks (late preterm)	19 (9.4)
Mean (SD), weeks	31.65 (2.29)
Birth weight based on gestational age, n(%)	
SGA	153 (75.7)
AGA	49 (24.3)
LGA	0
First retinal screening, n(%)	
ROP	5 (2.5)
Immature retina	90 (44.6)
Mature retina	107 (53.0)
ROP, n (%)	
Yes	5 (2.5)
No	197 (97.5)

ELBW=extremely low birth weight (< 1,000g), VLBW=very low birth weight (1,000-1,499g), LBW= low birth weight (1,500-1,999g), LBW=low birth weight (2,000-2,499), SGA=small for gestational Age, AGA=appropriate for gestational Age, LGA=large for gestational age

the retina became mature. The retina matured in 38 infants, but statistical tests could not be conducted due to the small number of samples (**Figure 1**).

Binary logistic regression analysis revealed a significant association between immature retina and GA (OR=0.575; P<0.0001), BW (OR=0.997; P<0.0001), gestational maturity (OR=2.639; P=0.006), RDS (OR=1.809; P=0.042), oxygen therapy >7 days (OR=4.494; P=0.002), sepsis (OR=2.028; P=0.034), multiple transfusions (OR=4.656; P<0.0001), apnea of prematurity (OR=2.553; P=0.002), as well as PDA (OR=2.119; P=0.030) (**Table 2**). Asphyxia (P=0.408) and BPD (P=0.054) were not associated with immature retina. In the regression equation, the B values for oxygen therapy >7 days and multiple transfusions were positive and >1, indicating that these variables were positively associated with immature retina (**Table 2**).

For the multivariate logistic regression, we included independent variables that had a P value of <0.05 in bivariate analysis; there were no confounding factors. The Hosmer Lemeshow test indicated that the model matched the observational data (P=0.131), so the logistic regression model was feasible for use at an advanced stage. The Omnibus tests of coefficients showed a regression significance of P<0.0001, meaning that risk factors (independent variable) simultaneously had a significant association on the occurrence of an immature retina (dependent variable). Multivariate analysis revealed that the independent variables simultaneously had a significant association on the occurrence of an immature retina, with a magnitude of influence of 42.1% (**Table 3**).

Discussion

Immature retina is a precursor to ROP in premature infants, and several risk factors that affect retinal maturity impact retinal development. The definition of immature retina according to the ICROP classification has been limited to the absence of disease characterized by progressive tapering of retinal vessels that terminate in the ora serrata.[13,15] The clinical relevance of retinal immaturity is summarized as follows: (1) the degree of immaturity may extend from the posterior pole to a small residual area in zone 3; (2) the degree of retinal immaturity correlates with gestational and postnatal age. Vasculogenesis begins at the optic nerve center at about 10-12 weeks of gestation and reaches the ora serrata at 38-40 weeks of gestation; (3) the larger the retinal avascular area, the larger the potential ischemic area and the increased risk of abnormal vascularization influenced by proangiogenic factors such as vascular endothelial growth factor.[16]

The degree of retinal immaturity can be affected by the level of postnatal care even before the disease occurs. This is especially true in developing countries, where variable levels of neonatal care can lead to more severe immaturity that develops into aggressive posterior retinopathy of prematurity (APROP).[17,18] Studies conducted in Indonesia found similar risk factors for ROP compared to studies in developed countries including low birth weight, preterm

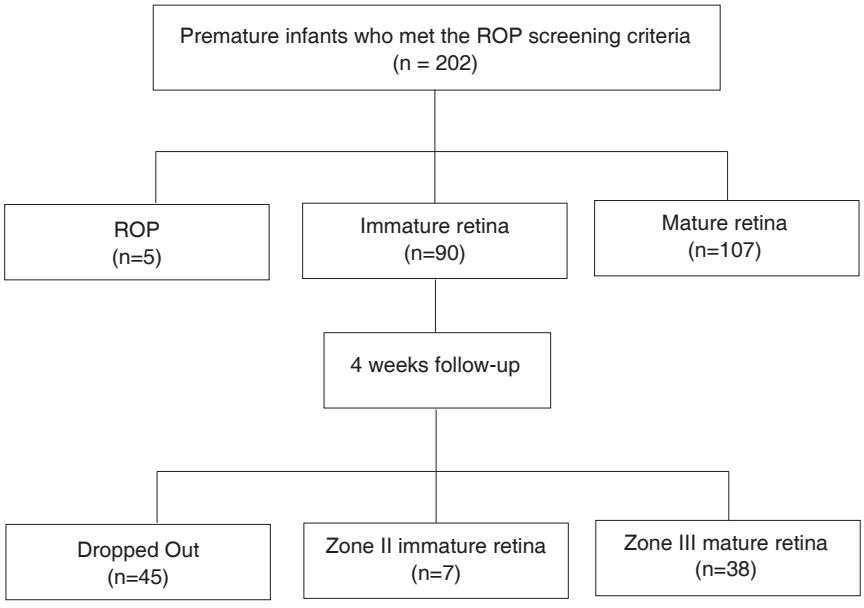

Figure 1. Research subject distribution scheme

Table 2 . Risk factors for immature retina (bivariate test)

Variables	Mature retina (n=107)	Immature retina (n=90)	B	Sig	Exp(B)	Nagelkerke R square
Gestational age, weeks			- 0.553	0.000	0.575	0.326
Birth weight, grams			- 0.003	0.000	0.997	0.262
Birth weight based on gestational age, n(%)						
AGA/LGA	35 (32.7)	14 (15.6)	0.970	0.006	2.639	0.053
SGA	72 (67.3)	76 (84.4)				
RDS						
No	56 (52.3)	34 (37.8)	0.593	0.042	1.809	0.028
Yes	51 (47.7)	56 (62.2)				
Oxygen therapy >7 days, n(%)						
No	26 (24.3)	6 (6.7)	1.503	0.002	4.494	0.079
Yes	81 (75.7)	84 (93.3)				
Asphyxia, n(%)						
No	61 (57.0)	46 (51.1)	0.238	0.408	1.268	0.005
Yes	46 (43.0)	44 (48.9)				
Sepsis, n(%)						
No	36 (33.6)	18 (20.0)	0.707	0.034	2.028	0.031
Yes	71 (66.4)	72 (80.0)				
Multiple transfusion, n(%)						
No	80 (74.8)	35 (38.9)	1.538	0.000	4.656	0.167
Yes	27 (25.2)	55 (61.1)				
Apnea of prematurity, n(%)						
No	60 (56.1)	30 (33.3)	0.937	0.002	2.553	0.068
Yes	47 (43.9)	60 (66.7)				
BPD, n(%)						
No	103 (96.3)	80 (88.9)	1.169	0.055	3.219	0.027
Yes	4 (3.7)	10 (11.1)				
PDA, n(%)						
No	89 (83.2)	63 (70.0)	0.751	0.030	2.119	0.032
Yes	18 (16.8)	27 (30.0)				

Table 3. Multivariate analysis of risk factors for immature retina

Variables	B	Sig	Exp(B)	Nagelkerke R square
Gestational age	- 0.410	0.000	0.664	0.421
Birth weight	- 0.001	0.067	0.999	
SGA	0.521	0.199	1.343	
Septic	- 0.003	0.994	1.003	
Oxygen therapy > 7 days	0.864	0.134	2.371	
Multiple transfusion	1.104	0.007	3.016	
RDS	- 0.228	0.580	0.796	
Apnea of prematurity	- 0.259	0.536	0.772	
PDA	- 0.123	0.796	0.796	
Constant	13.516	0.000		

gestation, asphyxia, multiple blood transfusions, oxygen administration for more than 7 days, oxygen concentration in inspired air, ventilator use, PDA, and sepsis/septicemia. These factors indicate that premature and sick infants had the highest risk of developing ROP.[19] In addition, human resources, limited facilities, and inadequate neonatal care may be the main contributors to the development of ROP.[20]

Bivariate analysis revealed significant associations between immature retina and GA, BW, gestational maturity, RDS, oxygen therapy of >7 days, sepsis, multiple transfusions, AOP, and PDA. Multivariate analysis showed a simultaneous significant relationship between risk factors for immature retina. A study conducted in Iran reported that the significant risk factors for ROP were SGA (P<0.001), low birth weight (P<0.001), sepsis (P=0.021), respiratory distress syndrome (P=0.036), intraventricular bleeding (P=0.005), continuous positive pressure ventilation (P=0.023), oxygen saturation of >50% (P=0.023), apnea (P=0.002), frequency and duration of blood transfusion, oxygen therapy and phototherapy (P<0.005), whereas preeclampsia decreased the prevalence risk of ROP (P=0.014).[21]

Evaluation of the degree of retinal immaturity, especially before ROP develops, is a useful approach for predicting the development of ROP. Therefore, theretinal appearance at the first retinal examination can be used as a surrogate marker to predict which infants are more likely to develop disease or would require treatment. These retinal screening units must make clinical decisions and recommendations to parents before discharge.[18] Validated retinal immaturity nomenclature will assist in decision-making and short-term monitoring of infants with severe immaturity can be provided. In addition, more detailed counseling, as well as warnings and reminders, are needed if patients miss the scheduled follow-up. Meanwhile, infants who initially experienced milder immaturity should undergo further follow-up approximately 3-4 weeks later to ensure and document a fully vascularized retina. Although the risk of the disease developing and requiring treatment is small, the immature retina must be certified as a mature retina before being excluded from ROP screening.[19]

In conclusion, there is a significant bivariate relationship between immature retina in this cohort and GA, BW, gestational maturity, RDS, oxygen therapy of >7 days, sepsis, multiple transfusions, AOP, and PDA. The incidence of ROP was relatively low at 2.5%. Simultaneously, there were significant relationships between all the risk factors for immature retina. Further studies are required to compare risk factors and progression rates at follow-up 4 weeks after screening with a larger sample size.

Conflict of interest

None declared.

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