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Incidence and Risk Factors of Retinopathy of Prematurity (ROP): A Single Center Study in a Tertiary Center in Indonesia

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Abstract

Background: Retinopathy of prematurity (ROP) is an abnormal proliferative retinal blood vessel in premature infants. ROP is known as one of the causes of blindness in children in developed countries.

Objectives: We conducted this study to report the incidence and identify the potential risk factors associated with ROP.

Methods: This study was a hospital-based retrospective cohort study of preterm infants in the tertiary neonatal intensive care unit from May 2009 to April 2011. The ROP was identified by an ophthalmologist with binocular indirect ophthalmoscope (BIO). Potential risk factors such as gestational age, birth weight, oxygen therapy, sepsis, small for gestational age, blood transfusion, asphyxia, and respiratory distress syndrome were analyzed using the bivariate and multivariate analysis.

Results: There were 248 preterm infants enrolled in this study. Thirty-two (12.9%) patients were diagnosed with various ROP stages, and 43.7% patients suffer from severe ROP requiring treatment for severe ROP. Gestational age and birth weight were not independent risk factors of ROP. In contrast, oxygen therapy (OR 36.93, CI 4.73-288.02), sepsis (OR 4.86, CI 1.85-12.82), and small for gestational age (OR 3.99, CI 1.47-10.82) include as independent risk factors.

Conclusions: Incidence of ROP were 12.9%, while the independent risk factors were oxygen therapy, sepsis, and small for gestational age.

Keywords: binocular indirect opthalmoscope; blindess; premature; risk factors; retinopathy of prematurity

1. Introduction

Retinopathy of prematurity (ROP) is a retinal disorder resulting from the disruption of normal retinal vascular development. Vasoconstriction and obliteration of the capillary bed followed by neovascularization towards the vitreous causes retinal edema, retinal hemorrhages, fibrosis, and traction, eventually resulting in retinal detachment.[1] The disease has been extensively studied worldwide due to increased survival rates among very low birth weight preterm newborns (NBs) (birth weight (BW) ≤1500 g) who are at the highest risk for developing ROP. The high rates lead to a significant rise of other comorbidities related to preterm birth that have a significant social impact, i.e., blindness secondary to ROP.[2]

Globally, in 2010, an estimated 184,700 of 14.9 million preterm babies suffer from the various stage of ROP, of whom 20,000 were blind. While in high-income countries, approximately 6,300 of 32,700 babies with ROP require treatment, and 1,700 babies were blind or severely visually impaired from ROP.[3] The World Health Organization's VISION 2020 program has identified ROP as an essential cause of blindness in both high- and middle-income countries.[4]

ROP incidence and severity are inversely related to gestational age (GA) or BW of the infant. Approximately 65% of the infant with BW <1250 g and 80% of those with BW <1000 g will develop ROP.[5] Approximately 2% of the infant with BW 1000-1250 g and 16% with BW <750 will suffer threshold stage 3+ disease which eligible for treatment.[1] ROP is a multifactorial disease.[5] ROP has been related to hyperoxemia, although the exact mechanism of ROP with high oxygenation alone was not well known. Other various risk factors that have been identified including extreme prematurity, sepsis, blood transfusion, anemia, intraventricular hemorrhage, small for gestational age (SMG), respiratory distress syndrome (RDS), postnatal weight gain, and insulin-like growth factor 1 (IGF-1).[1,5,6] Identification of the risk factors and determine the etiology may help neonatologists and ophthalmologists to establish an accurate diagnosis and prevent the disease progression.[7]

2. Subjects and Methods

This cohort retrospective study was conducted in the Neonatal Intensive Unit (NICU) from May 2009 to April 2011. This study's inclusion criteria were premature infants born at gestational age <37 weeks and birth weight <2500 grams. The exclusion criteria including: 1) infant who passed away before sufficient eye examinations for diagnosis of ROP, 2) infants who were not referred for eye examination although they met the inclusion criteria, 3) infant who was loss to follow-up before sufficient eye examination for either rule out ROP or identify the progression/regression of established ROP.

The premature infants who met the criteria underwent the initial eye examinations on their 4th-7th week of life. All eye examination was performed by the ophthalmologist who has certification for ROP examination with BIO. The stages of ROP were classified according to the International Classification of Retinopathy. The opthalmologist would repeat the tests every two weeks if the ROP were not found in the initial assessment. The

screening intervals were dependent on the disease's severity until the retina was fully vascularised or the infant developed threshold ROP. All infants who develop threshold ROP were treated with laser therapy.

The data was analyzed using Statistical Package for the Social Science (SPSS) version 17.0. Categorical variables were reported as counts and percentages. Univariate logistic regression was used to identify potential risk factors of ROP. The results present as frequencies, means ± standard deviation (SD), and *pvalues*. *P-value* <0.25 was considered statistically significant. Multiple logistic regression analyses were performed to determine the independent predictors of the development of ROP. Unadjusted, as well as adjusted odds ratios were recorded with a 95% confidence interval. *P-value* <0,05 was considered statistically significant.

3. Results

Of 430 preterm infants enrolled in this study, 253 (58.8%) infants met the inclusion criteria. Meanwhile, the 177 (41.2%) infants were excluded: 56 (13.0%) infants died before the ROP examination, 51 (11.9%) infants discharged on request, 50 (11.6%) infants absent for outpatient ophthalmologist control schedule, and 20 (4.7%) infants were suffering from severe congenital abnormalities. The 253 infants underwent a BIO eye examination at the Department of Ophthalmology. However, four preterm infants lost to follow-up during the observation, and one infant died before the observation period was completed (42 weeks). During the two years of the study, the total sample was 248 premature infants. From the BIO examination results, 32 infants (12.9%) had ROP, and the remaining 216 (87.1%) infants had no signs of ROP. The incidence of ROP in this study was 12.9%. The flowcharts of the study participants were shown in Figure 1.

Most of the patients with ROP were level 1 and 2 (75%), level 3 was 6 (18.7%), and only 2 (6.3%) were levels 4 and 5. Plus disease, which associates with severe ROP, was found in 14 cases (43.7%) and absent in the remaining 18 cases (56.3%). In this study, most patients (56.3%) experienced spontaneous regression, while the remaining 14 patients (43.7%) require laser treatment. None of the patients with ROP required surgery during the study period.

Table 1 shows results of mean GA of the study subjects was 32.2±2.5 weeks (range 24-36) weeks. The mean GA of preterm infants with ROP was 30.8±2.9 weeks (range 24-36) weeks, while the group of preterm infants who did not suffer ROP was 32.5±2.3 weeks (range 25-36) weeks. In the 36 weeks GA group, there was a 10.0% incidence of ROP, while two preterm infants in the 24 weeks GA group did not suffer from ROP. ROP incidence in the GA <32 weeks group was 19 (25.3%), while those without ROP were 56 (74.7%). On the other hand, in the GA above or equal to 32 weeks group, there were 13 (7.5%) suffered from ROP while the remaining 160 (92.5%) did not suffer from ROP. The mean BW of preterm infants in this study was 1670.1±344.2 g (range 760-2450) g. The mean BW of ROP patients was 1376.9±341.6 g (range 760-2300) g, and the mean BW without ROP was 1713.6±323.4 g (range 1000-2400) g. A total of four preterm infants under 1000 g and one preterm infant with BW 2300 g were suffered from ROP.

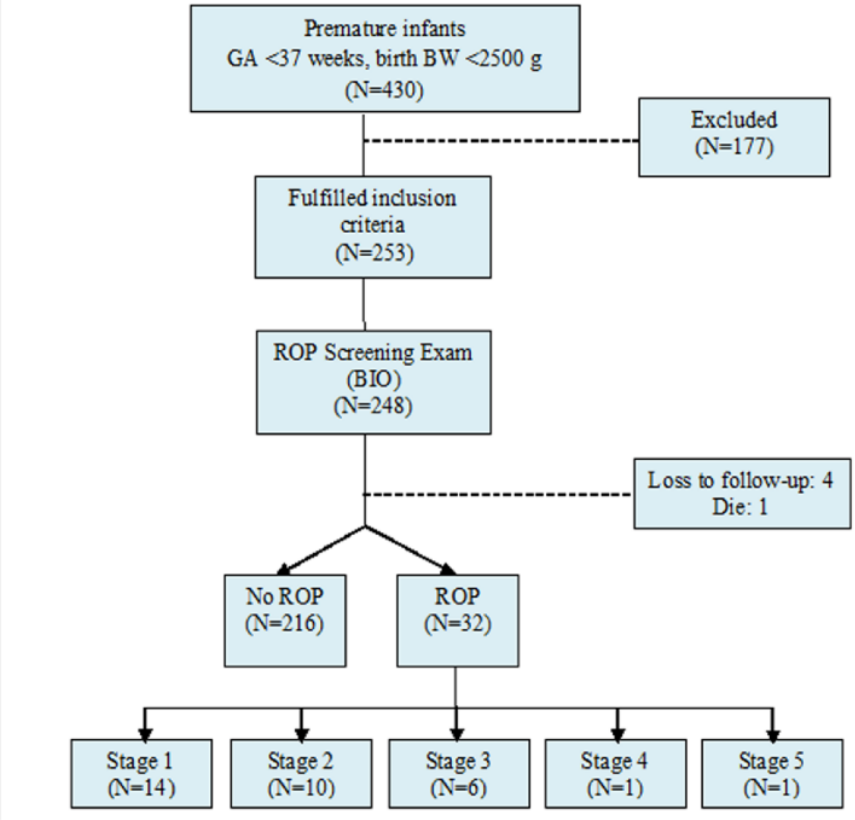

Fig. 1. Schematic diagram of the study

Table 1. Subject characteristics

Characteristics	ROP		Total
	n(%)	n(%)	N

Sex			
Male	12(9.1)	120(90.9)	132
Female	20(17.2)	96(82.8)	116
GA (weeks)			
<28	6(28,6)	15(71,4)	21
29	2(20,0)	8(80,0)	10
30	7(30,4)	16(69,6)	23
31	4(19,0)	17(81,0)	21
32	6(11,5)	46(88,5)	52
33	0(0,0)	28(100,0)	28
34	4(8,7)	42(91,3)	46
35	1(3,7)	26(96,3)	27
36	2(10,0)	18(90,0)	20
BW (grams)			
750-999	4(100,0)	0 (0,0%)	4
1000-1249	8(36,4)	14(63,6)	22
1250-1499	4(8,9)	41(91,1)	45
1500-1749	12(16,9)	59(83,1)	71
1750-2000	3(4,5)	63(95,5)	66
^{3}2000	1(2,5)	39(97,5)	40

Table 2 shows that GA less than 32 weeks, BW less than 1501 g, oxygen therapy, sepsis, SGA, history of transfusion, and RDS were statistically significant ($p<0.25$), considered ROP incidence's potential factors. Meanwhile, asphyxia was not statistically significant ($p>0.25$) and was not considered to have a potential effect on the ROP incidence. In the multiple logistic regression analysis, only three factors were statistically significant, i.e., oxygen therapy ($p=0.001$; OR=36.93; CI 95% 4.73 to 288.02), sepsis ($p=0.001$; OR=4.86; CI 95% 1.84 to 12.82), and SGA ($p=0.007$; OR=3.99; CI 95% 1.47 to 10.82). Meanwhile, gestational age, birth weight, blood transfusion, and RDS were not statistically significant ($p>0.05$) (Table 3).

Table 2. Univariate analysis of ROP potential risk factors

Risk Factors	ROP		*p*
	Yes n(%)	No n(%)	

GA<32 weeks			
Yes	19(25,3)	56(74,7)	<0,001
No	13(7,5)	160(92,5)	
BW< 1501 g			
Yes	22(23,4)	72(76,6)	<0,001
No	10(6,5)	144(93,5)	
Oxygen therapy			
Yes	31(32,0)	66(68,0)	<0,001
No	1(0,7)	150(99,3)	
Sepsis			
Yes	18(43,9)	23(56,1)	<0,001
No	14(6,8)	193(93,2)	
SGA			
Yes	15(25,4)	44(74,6)	0,002
No	17(9,0)	171(90,9)	
Blood transfusion			
Yes	13(40,6)	19(59,4)	<0,001
No	19(8,8)	197(91,2)	
Asphyxia			
Yes	3(15,8)	16(84,2)	0,697
No	29(12,7)	200(87,3)	
RDS			
Yes	21(30,9)	47(69,1)	<0,001
No	11(6,1)	169(93,9)	

Table 3. Independent risk factors of ROP based on multiple logistic regression analysis

Risk Factors	β	*p*	OR	CI 95%
GA < 32 weeks	0,872	0,06	2,39	0,94-6,07
BW< 1500 g	0,108	0,842	1,11	0,39-3,21
Oxygen therapy	3,609	0,001	36,93	4,73-288,02
Sepsis	1,582	0,001	4,86	1,85-12,82
SGA	1,384	0,007	3,99	1,47-10,82
Blood transfusion	0,165	0,776	1,18	0,38-3,66
RDS	0,482	0,328	1,62	0,62-4,25

4. Results

This study showed that the incidence of ROP in premature infants was 12.9%. The incidence rate was lower compared to previous studies. The Vermont Oxford Network database, which collects data from >1000 NICUs

worldwide, estimated the incidence of ROP was 33.2% in neonates with BW <1500 g.[8] Akkawi MT et al. reported that the ROP incidence and severe stage 1 ROP requiring treatment were 23.5% and 11.3%, respectively.[9] In India, a comparable country to Indonesia in terms of socioeconomic aspects, Patel SS et al. reported that the ROP efficacy rate was 24.1%.[10] ROP incidence were varied depending on the inclusion criteria, neonatal care quality, and population heterogeneity. Some risk factors were well established (GA, BW). However, another risk is not well-known.[11] These variations may be due to a lack of access to advanced neonatal care units in many parts of developed and underdeveloped countries.[12] Read the study carefully while comparing the reports due to differences in methodologies and selection criteria.[13] The variety of ROP incidence showed in Table 4.

Numerous ROP studies only include <32 weeks of gestation infants or BW <1500 g.[14] Current screening criteria in the United States and many developed countries are base on GA and BW at delivery.[15,16] According to the most recent American Academy of Pediatrics (AAP) guidelines, screening examinations for ROP are recommended for all infants born at a GA ≤30 weeks or with a BW ≤ 1500 g, as well as for those who born at GA >30 weeks with BW between 1500 g and 2000 g with an unstable clinical course.[15] In middle-income countries, this scenario is significantly varies depending on the birth conditions and survival rates of premature infants. ROP can occur in much older and bigger infants in middle-income than in high-income countries due to various neonatal care standards.[17] In this study, we included infants with BW >1500 g or >32 weeks of gestation. Our inclusion criteria were preterm infants <37 weeks' gestation and BW <2500 g.

Gilbert et al. suggested that the ROP in highly developed countries differs from ROP in less developed countries. However, notice that: 1) most published data of ROP are from selected NICU series, and 2) due to the intensive care setting, these types of series are rarely valid in population and epidemiology.[18] In this study, the low incidence of ROP was related to the inclusion criteria (GA <37 weeks and BW <2500g), and data were taken from all newborn care rooms. Besides, the number of preterm infants (177 infants) who met the inclusion criteria should be excluded from the study for various reasons, possibly affect the ROP incidence. The wide range of ROP incidence from various existing studies was probably due to differences in neonatal facilities standards in different countries. In theory, the increase in ROP incidence causes by the higher life expectancy of preterm infants. Besides, the decrease in the ROP incidence is due to a higher knowledge of neonatal pathophysiology, the presence of surfactants proven to improve lung maturity, pulse oximetry uses for control oxygen and antenatal steroids use.[19]

Tabel 4. Studies of ROP incidence and risk factors

Author	Country	Year of Publication	GA (week)	BW (gram)	ROP (%)	Independent risk factors
[20]	Kuwait	2000	<34	>1500	19.1	None

[21]	India	2004	≤35	≤1500	21.7	oxygen therapy, apnea, sepsis
[22]	Indonesia	2005	<37	<2500	26.0	asphyxia, multiple, sepsis, blood transfusions, and oxygen therapy
[13]	Pakistan	2008	≤32	≤1500	32.4	GA, sepsis, RDS
[12]	Iran	2010	<37	≤1500	19.0	GA, blood transpusion
[23]	China	2011	<30	<1501	47.0	sepsis, oxygen ex-posure, and low GA
[24]	India	2016	≤30	≤1500	28.57	sepsis, prematurity, RDS, apnea, BW, GA, red blood cell transfusions
[25]	Turkey	2018	≤32	≤2500	27.0	BW, GA, oxygen therapy, sepsis, red blood cell transfusions
[26]	Ghana	2020	≤32	≤1500	13.7	sepsis, nasogastric tube feeding, poor pupil dilation, oxygen therapy
[27]	Saudi Arabia	2020	<34	<1500	33.3	None

Some studies identified oxygen therapy, anemia, double volume exchange, packed cell volume transfusion, septicemia, apnea, and sepsis as important risk factors. Parekh et al. found that oxygen therapy, ventilation, RDS, blood transfusion, apnea, surfactant, low birth weight, low gestational age were significant ROP risk factors. However, in multivariate analysis, only RDS, blood transfusion, apnea, low BW, and low GA (prematurity) are independent and significant.[24] Besides, Al Essa et al. and AlBalawi HB et al. reported no independent and significant ROP risk factors found in their study.[20,27] Summary of independent risk factors that can affect ROP presented in Table 4. In this study, the univariate analysis showed a significant relationship between GA, BW, oxygen therapy, blood transfusion, RDS, sepsis, and SGA (Table 2) on ROP incidence, in line with previous studies. However, in multiple logistic regression analysis, only oxygen therapy, sepsis, and SGA were independent predictors of ROP development. Although prematurity is wellestablish as the most significant risk factor in ROP development, this study showed that both GA and BW were not independent

predictors of ROP.[13] These findings explained the critical role of the environment affect the progression of ROP.

The differences of independent risk factors in the various studies mentioned above depend on the inclusion criteria, neonatal care facilities, and the ability to control risk factors.[21] Besides, with the low life expectancy of preterm infants with very low birth weight, the ROP may not be identified because the patient died before the examination.[22] Similar situation happened in this study, where the mortality rate of preterm infants with very low BW was still high. Taqui et al. reported that ROP could occur in preterm infants with higher BW and GA in developing and underdeveloped countries, which probably causes by uncontrolled infection, oxygen consumption, and other risk factors.[13] The ability to identify post-natal risk factors as predictors of ROP is beneficial for screening programs.[27] In this study, we found that independent risk factors as predictors of ROP were oxygen therapy, sepsis, and small gestational age.

Gestational age, BW, and post-natal oxygen supplementation are major independent risk factors of ROP.[28] The use of supplemental oxygen, oxygen concentration, duration, and prolonged mechanical ventilation were the most frequent risk factors of severe and treatment-requiring ROP.[7] This study is similar to previous studies regarding oxygen therapy's role in ROP, although the oxygen saturation was not controlled and documented. The altered regulation of vascular endothelial growth factor from repeated episodes of hyperoxemia and hypoxia is an important factor in the pathogenesis of ROP.[29] Ebrahim M et al. reported that there was no relationship between oxygen therapy and ROP. However, their study overemphasized the oxygen roles, and no excessive oxygen administration was identified in their neonatal services.[12]

Multiple studies have reported that neonatal sepsis plays a role in the development of ROP.[30,31] Sepsis is an independent predictor of ROP development in many Asian studies, including in Indonesian studies.[22] Patel SS et al. stated that sepsis was a highly significant risk factor. Linear regression analysis showed that septicemia alone was an independent risk factor in the etiology of ROP.[10] Our study also found that sepsis was an independent risk factor in the development of ROP. Sepsis plays a role through cytokines and endotoxins, which directly affect retinal angiogenesis. This process is frequently accompanied by hypotension, which causes impairment of tissue perfusion and retinal ischemia.[3] Sepsis is a risk factor of ROP, especially severe sepsis due to the pro-inflammatory mediators that affect the vessels' endothelium (it may occur in the retinal vessels that interrupt the normal growth of the retina).[32]

Some previous studies have reported that ROP prevalence was higher in SGA infants than appropriate for GA preterm, while SGA was not a risk factor for ROP in other reports.[33,34] SGA have greater risks of any ROP (90% vs 58%, p<0,01). In a multivariate regression model, both SGA and BW <35th percentile for GA (growth restriction) was associated with increased risks of threshold ROP (relative risk: 3.7 and 4.5, respectively).[35] Factors that are considered an increased risk for severe ROP in SGA infants were chronic uterine hypoxia, abnormal growth factor levels, nutrient restriction, and antioxidant deficiency.[36] Bas et al. reported SGA was associated with a decreased incidence of severe ROP in VLBW infants.[25] However, in our study, SGA was associated with an increased incidence of ROP in preterm infants.

We also found ROP among infants with a higher range of GA and BW. Since the range of GA and BW of ROP patients in developing countries are higher than those in underdeveloped countries, we suggest performing ROP screening in the infant with <37 weeks GA and <2500 g BW with consideration of some risk factors such as oxygen therapy, sepsis, and SGA.[18] These facts require nationwide attempts to improve public awareness and collaborate with the referral hospital for premature infants screening programs. Our study had several limitations, i.e., a small sample size and the limitation to identify other risk factors in premature infants.

5. Conclusion

The incidence of ROP is 12.9%. The independent predictor of ROP are oxygen therapy, sepsis, and SGA. Current study suggests that screening criteria for ROP particularly in this institution are GA <37 weeks and BW <2500 g.

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Ethical Standard: This study obtained permission from the Institutional Ethical Committee of Dr. Soetomo General Academic Hospital (No. 48/Panke.KKE/III/2011).

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