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Original Article

Prevalence and risk factors of retinopathy of prematurity

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Abstract

Background Retinopathy of prematurity (ROP) is the main cause of visual impairment in premature infants. Due to advances in neonatal care, the increased survival of extremely low birth weight (ELBW) infants in recent years has produced a population of infants at very high risk of ROP.

Objective The aims of this study were to determine the prevalence and potential risk factors for ROP.

Methods This retrospective study was conducted at the Neonatalogy Ward, Cipto Mangunkusumo Hospital, from January 2005 to August 2010. We included all premature infants of gestational age (GA) < 37 weeks, body weight (BW) not exceeding 2000 grams, as well as those who had eye examinations and complete medical records. Risk factors such as GA, BW, duration of oxygen (O_2) therapy, sepsis, and red blood cell (RBC) transfusion were analyzed using the Chi-square and logistic regression tests. Pediatric ophthalmologists had performed eye examinations on all infants. ROP was graded according to the International Classification of ROP.

Results The prevalence of ROP and of stage 3 or greater ROP was 11.9% and 4.8% of all subjects, respectively. Body weight, GA, duration of O_2 therapy, and sepsis were found to be associated with the development of ROP. However, stepwise logistic regression analysis revealed that only BW of ≤ 1000 g [odds ratio (OR) 10.88; 95% CI 3.09 to 38.31; P < 0.000], O2 therapy ≥ 7 days (OR 5.56; 95% CI 1.86 to 16.58; P < 0.0001), and GA of ≤ 28 weeks (OR 4.26; 95% CI 1.15 to 15.81; P = 0.030) were statistically significant risk factors for ROP. The equation obtained was y = -4.092 + 2.388 (BW) + 1.451 (GA) + 1.716 (duration of O2 therapy). The model showed good calibration (a non-significant Hosmer-Lemeshow test; P = 0.816) and discriminative ability. The area under the curve (AUC) value was 92.2% (95% CI 0.867 to 0.976; P < 0.0001).

Conclusion Prevalence of ROP in this study (11.9%) was lower than that of previous studies. By regression logistic analysis, the main risk factors for development of ROP were BW of ≤ 1000 g, O_2 therapy ≥ 7 days, and GA ≤ 28 weeks. The probability of ROP occurrence increased with greater number of risk factors. **[Paediatr Indones. 2012;52:138-44]**.

Keywords: *retinopathy of prematurity, risk factors*

ROP is a proliferative retinopathy in premature infants.[1] Recent advances in neonatal care have improved the survival rates for premature infants, and as such, have been accompanied by an increase in the incidence of ROP. ROP is a leading cause of childhood blindness and has multifactorial etiologies.[2-4] The objectives of this study were to determine the prevalence of ROP and to evaluate possible risk factors associated with the development of ROP in premature infants.

Methods

This study was a retrospective, observational analysis on premature infants who met the criteria

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for ROP screening. All infants with GA < 37 weeks, BW not exceeding 2000 grams, admitted to the NICU between January 2005 and August 2010, who underwent eye examinations for ROP and had complete medical records were eligible for the study.

We included 269 infants (92.1% of eligible subjects) in our study who had eye examinations by pediatric ophthalmologists to detect ROP. We excluded infants with major congenital malformations, incomplete records, and those without eye examinations. Eye examinations were performed on infants with a BW < 1500 g or a GA of ≤ 32 weeks, and on selected infants with a BW of 1500 - 2000 g or GA > 32 weeks with an unstable clinical course, including those requiring cardiorespiratory support and those believed to be at high risk by their attending pediatrician or neonatologist.

Infants were examined at 6 weeks chronological age or 34 weeks corrected age, whichever was earlier. Infants underwent fundus examination by indirect ophthalmoscopy with a +28 D condensing lens. Pupils were dilated with 0.5% tropicamide eyedrops. An infant eyelid speculum was used during examinations, after administration of topical anesthesia with 0.5% tetracain hydrochloride. Scleral indentation was done only if necessary, to view the retina periphery.

If no ROP was noted, eye examinations were repeated every 2 weeks until vascularization had reached zone 3. Stages of ROP were classified according to the International Classification of Retinopathy of Prematurity. Threshold severity of ROP was defined as 5 or more contiguous or 8 cumulative clock hours of stage 3 in zone 1 or 2 and the presence of Plus disease. Plus disease was defined by dilatation and tortuosity of blood vessels in the posterior pole. Pre-threshold ROP was considered to be zone 1 ROP of any stage less than threshold, zone 2 stage 2 ROP with Plus disease, zone 2 stage 3 without Plus disease, and zone 2 stage 3 ROP with Plus disease, but fewer than 5 continuous or cumulative clock hours. Subjects were observed

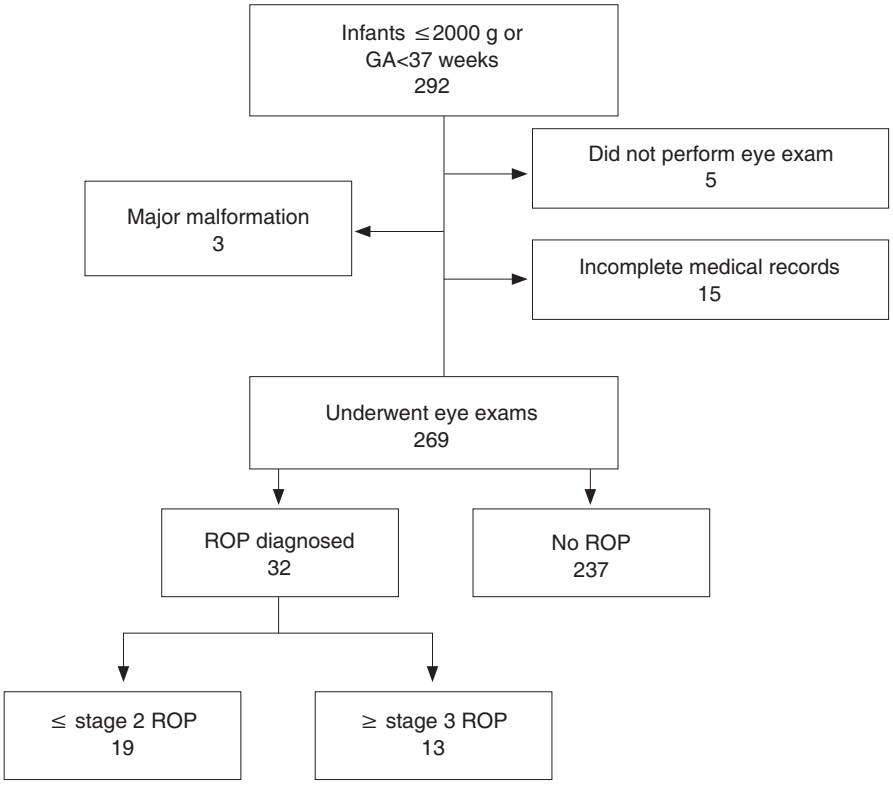

Figure 1. Schematic diagram of the subject distribution

closely until ROP was resolved or until it progressed to threshold ROP.

Data were recorded retrospectively and the presence of retinopathy was graded according to the International Classification of ROP. Subjects' demographic data included GA, BW, gender, as well as maternal age and employment. Clinical data included duration of O_2 treatment, sepsis, and RBC transfusion. Prematurity was defined as infants with GA < 37 weeks, as ascertained by obstetric records. Sepsis was diagnosed by blood cultures positive for bacteria and/or *Candida*.

Univariate comparison of risk factors between groups with and without ROP was evaluated by Student's t-test and Chi-square test with significance set at $P < 0.05$. Stepwise multivariate logistic regression was used to evaluate factors predictive of ROP development. Odds ratios and 95% confidence intervals for possible risk factors were also calculated. The fit of the models was checked with the Hosmer-Lemeshow goodness-of statistic,[5] with additional verification that the models were not overfitted (indicated by very high P values). The discriminatory ability of the models was assessed by the area under the curve-receiver operator curves (AUC-ROC).

This study protocol was approved by the Ethics Committee of the University of Indonesia Medical School.

Table 1. Subjects' characteristics

Characteristics	n = 269
Gender, n (%)	
Male	139 (51.7)
Female	130 (48.3)
Birth status, n (%)	
Multiple	30 (11.2)
Single	239 (88.8)
Method of birth, n (%)	
Caesarean section	145 (53.9)
Forceps	1 (0.4)
Vacuum extraction	0 (0)
Spontaneous	123 (45.7)
Median birth weight, g (range)	1450 (585-2000)
≤ 1000 g, n (%)	37 (13.8)
1001-1500 g, n (%)	124 (46.1)
1501-2000 g, n (%)	108 (40.1)
Median gestational age, weeks (range)	32 (25-36)
≤28 weeks, n (%)	30 (11.2)
29-32 weeks, n (%)	144 (53.5)
33-34 weeks, n (%)	67 (24.9)
35-36 weeks, n (%)	28 (10.4)
Duration of O2 therapy	
≥ 7 days, n (%)	91 (33.8)
< 7 days, n (%)	178 (66.2)
Sepsis, n (%)	
Yes	68 (25.3)
No	201 (74.7)
Red blood cell transfusion, n (%)	
Yes	73 (27.1)
No	196 (72.9)

Results

Between January 1, 2005 and August 30, 2010, there were 292 infants with BW ≤ 2000 grams or GA < 37 weeks. Of these infants, 269 (92.1%) underwent eye examinations (**Figure 1**). ROP was diagnosed in 32 (11.9%) infants. Thirteen (4.8%) of these infants had severity of stage 3 ROP or greater. ROP prevalence was higher in infants with BW ≤ 1000 grams (62.2%) and GA ≤ 28 weeks (66.6%).

The demographic and perinatal factors of subjects who underwent eye exams are summarized in **Table 1**. There were 139 (51.7%) male infants and 130 (48.3%) female infants. The number of male and female subjects was similar (male/female ratio 1.07:1). The median GA of all enrolled subjects was 32 weeks, with a range of 25–36 weeks. Median BW was 1450 g, with a range of 585–2000 g. Ninety-two (34.2%) subjects received O_2 therapy for 7 days or more. There were 68 (25.3%) subjects with sepsis and 73 (27.1%) who received RBC transfusions.

The following variables were not significantly related to ROP in univariate analyses: gender, birth status, method of birth, and RBC transfusion (**Table 2**). Unadjusted risk for ROP was significantly associated with lower BW (unadjusted OR 40.7; 95% CI 15.88 to 104.31), younger GA (unadjusted OR 37.8; 95% CI 14.54 to 98.38), O_2 therapy for ≥ 7 days (unadjusted OR 11.5; 95% CI 4.51 to 29.13), and sepsis (unadjusted OR 3.06; 95% CI 1.43 to 6.54).

Multiple logistic regression model was used to further analyze the variables of GA ≤ 28 weeks, BW ≤1000 grams, O_2 therapy ≥ 7 days, and sepsis (bacterial and *Candida* infections). Sepsis was not significantly associated with ROP in this analysis. However, BW ≤ 1000 grams (adjusted OR 10.88; 95% CI 3.09 to 38.31), GA ≤ 28 weeks (adjusted OR 4.26; 95% CI 1.15 to 15.81), and O_2 therapy ≥ 7 days (adjusted OR 5.56; 95% CI 1.86 to 16.58) were identified to be factors predictive of ROP (**Table 3**).

Table 2. Variables associated with ROP

Variable	ROP				P value*	Unadjusted OR (95% CI)
	Yes		No			
	n	%	n	%		
Gender						
Male	15	10.8	124	89.2	0.563	0.8 (0.39 to 1.68)
Female	17	13.0	113	87.0		
Birth status*						
Multiple	3	10.0	27	90.0	1.000	0.8 (0.23 to 2.82)
Single	29	12.1	210	87.9		
Method of birth						
Caesarean section	18	12.4	127	87.6	0.851	1.1 (0.51 to 2.34)
Spontaneous	14	11.3	110	88.7		
Birth weight, grams**						
≤1000	23	62.2	14	37.8	<0.000	40.7 (15.88 to 104.31)
>1000	9	3.9	223	96.1		
Gestational age, weeks**						
≤28	20	66.6	10	33.3	<0.000	37.8 (14.54 to 98.38)
>28	12	5.0	227	95.0		
Duration of O2 therapy, days						
≥7	26	28.6	65	71.4	<0.000	11.5 (4.51 to 29.13)
<7	6	3.4	172	96.6		
Sepsis						
Yes	15	22.1	53	77.9	0.003	3.06 (1.43 to 6.54)
No	17	2.8	184	97.2		
Red blood cell transfusion						
Yes	11	15.1	62	84.9	0.327	1.48 (0.67 to 3.24)
No	21	10.7	175	89.3		

*Chi square test; ** Fisher test

Table 3. Multiple logistic regression of risk factors for ROP

Predictor variable	Coefficient	P value*	Adjusted OR (95% CI)
Step 1			
Birth weight ≤1000 g	2.745	<0.000	15.56 (3.88 to 62.30)
Gestational age ≤28 weeks	2.326	0.009	10.24 (1.77 to 59.09)
O_2 therapy ≥7 days	1.711	0.002	5.53 (1.848 to 16.57)
Sepsis	-1.626	0.070	0.197 (0.03 to 1.14)
Constant	-3.899	<0.000	0.020
Step 2			
Birth weight ≤1000 g	2.388	0.000	10.88 (3.09 to 38.31)
Gestational age ≤28 weeks	1.451	0.030	4.26 (1.15 to 15.81)
O_2 therapy ≥7 days	1.716	0.002	5.56 (1.86 to 16.58)
Constant	-4.092	<0.000	0.017

*Logistic regression; OR=odds ratio; CI= confidence interval
The equation obtained from this study was:
y = -4.092 + 2.388 (BW) + 1.451 (GA) + 1.716 (duration of O_2 therapy).

The Hosmer-Lemeshow statistical analysis indicated a good model fit (P value 0.816). The AUC value from the ROC curve was 92.2%, (95% CI 0.867 to 0.976; P < 0.000), indicating excellent discrimination (**Figure 2**).

Figure 3 shows the probability of a subject having ROP, with BW, GA, and duration of O2 therapy as variables. A body weight of ≤1000 g, O2 therapy for ≥ 7 days, and GA < 28 weeks increased the probability (81.2%) of having ROP

Discussion

This study included data from infants of GA < 37 weeks in Cipto Mangunkusumo Hospital, Indonesia,

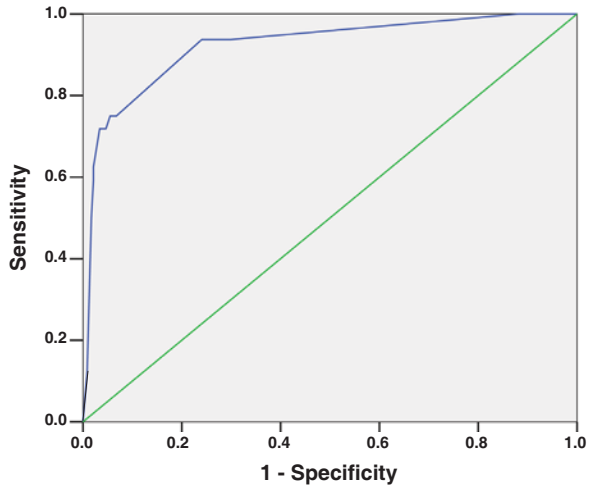

Figure 2. ROC curve

previous Indonesian reports,[7,8] but similar to a report by Madden *et al.*[9] It is possible that this decrease in ROP prevalence is due to improved understanding of the pathophysiology of premature infants and various means of supportive care.

In this study, we also report demographic factors that may be important in the development of ROP. We observed nearly equal numbers of male and female infants with ROP similar to previous reports by the ROP Cooperative Group.[10,11] However, Darlow *et al* reported that male infants were more vulnerable to ROP (OR 1.67; 95% CI 1.34 to 2.09; P = 0.001).[12] We also observed no significant birth status differences (singles vs. multiples) in the prevalence of ROP, similar to previous reports.[13,14] The lower number of vaginal deliveries in the ROP group probably reflects the high-risk perinatal status of these immature infants at delivery and the perinatologist's decision not to

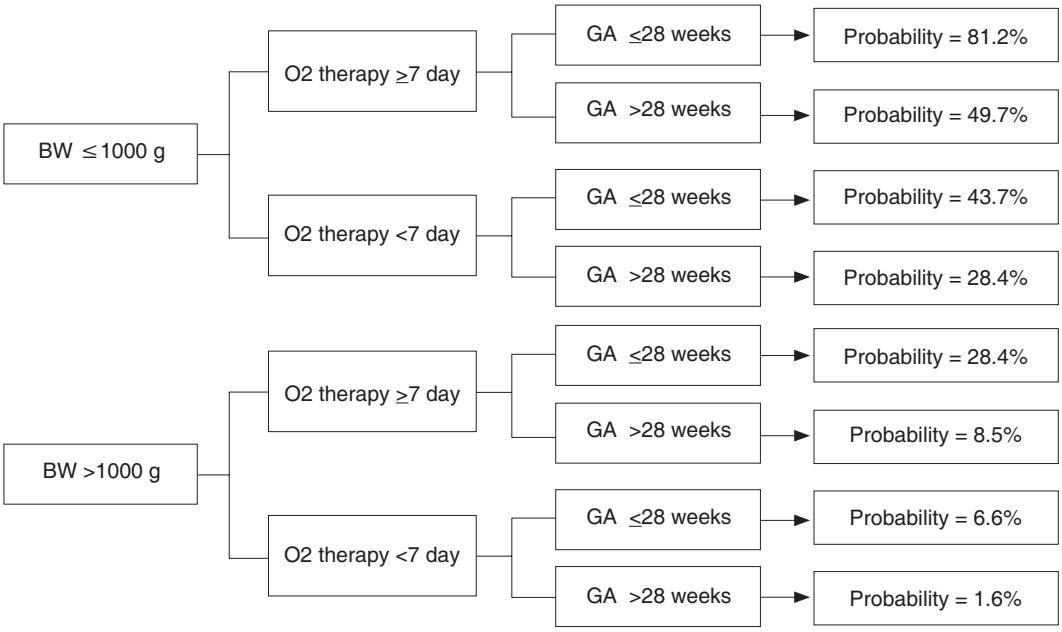

Figure 3. Probability of developing ROP in extremely low birth weight infants

January 1, 2005 and August 30, 2010, who underwent eye examinations. We report the prevalence and risk factors in ROP.

The impact of ROP on vision in premature infants has been well documented since an early report by Terry.[6] ROP prevalence has decreased in relation to changes in clinical practice. We report here a significant decrease in the prevalence of ROP from

deliver by this route.

There have been varied results reported on the use of RBC transfusions and ROP prevalence. Brooks *et al*[15] reported that RBC transfusion was not associated with development of ROP, but a previous report by Sacks *et al*[16] stated there was an association between RBC transfusion with ROP. They found that ROP incidence in infants receiving ≥ 130 ml

of packed RBC per kg BW was significantly higher (42.9%) than that in infants receiving 61 to 131 ml of packed RBC per kg BW (15.4%) and in infants receiving ≤ 60 ml of packed RBC per kg BW (0%) ($P < 0.001$). This finding was not confirmed by our study, but the difference may be due to the small quantities (≤ 60 ml per kg BW) of RBC received in our subjects.

Previous reports have linked increased ROP incidence to sepsis.[17,18,19] Bivariate analysis of our data showed that culture-positive sepsis of any etiology was significantly associated with ROP. However, multiple logistic regression analysis on BW, GA, and days of supplemental O_2 treatment did not show independent or additional contributions by sepsis to the risk of ROP (adjusted OR 0.197; 95% CI 0.03 to1.14 $P = 0.070$). This difference may be caused by the fact that while sepsis may be present in infants with any deterioration in weight status, we defined sepsis to only be in those with positive blood culture growth. The association between sepsis and ROP needs to be studied in the greater detail to determine any independent influence of infection.

Multivariate analyses revealed that the variables GA, BW, and days of O_2 treatment were significant after simultaneous adjustment. Immaturity, reflected by lower BW and GA at birth, was a significant factor in infants who developed ROP. Birth weight of ≤ 1000 g was the greatest risk factor for ROP (adjusted OR 10.88), followed by prolonged use of O_2 therapy ≥ 7 days (adjusted OR 5.56), and GA ≤ 28 weeks (adjusted OR 4.26).

Infants with birth weight ≤ 1000 g had a 10.88 times greater risk to develop ROP compared to infants with BW > 1000 g, similar to previous research.[7,21,22] Infants with GA ≤ 28 weeks had a 4.26 times greater chance to develop ROP compared to those with GA > 28 weeks. This finding was supported by Darlow *et al* who reported that infants with GA < 25 weeks had a 20 times greater risk to develop ROP compared to those with GA >28 weeks.[22] The increased incidence of ROP in smaller BW and lower GA infants, has been attributed to the wide avascular retinal area, resulting in a high vascular endothelial growth factor (VEGF) value. In addition, premature infants do not have adequate defenses against free radicals, making them more vulnerable to ROP. In our study, infants with BW ≤ 1000 g had a 91.6% probability to develop ROP, whereas infants with GA ≤ 28 weeks had 80.9% probability.

Infants with O_2 administration for ≥ 7 days had a 5.56 times higher chance to develop ROP, similar to previous studies.[7,8,20,23] Long periods of O_2 administration may increase the risk of ROP because O_2 produces more free radicals, inducing abnormal retinal neovascularisation. The probability of infants receiving O_2 administration for ≥ 7 days to develop ROP was 84.7%.

The quality of equation from this research had a good calibration ($P > 0.005$ in Hosmer-Lemeshow test) and the discrimination value was very strong (AUC value 92.2%, 95% CI 0.867 to 0.976, $P < 0.0001$). Such an equation may be used to augment clinical practice.[5,24]

In conclusion, we found a significantly increased risk of ROP in premature infants with shorter GA, lower BW, and prolonged use of O_2. These data suggest that factors related to the degree of infant immaturity and O_2 therapy contribute to the development of ROP.

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