Maternal and Infantile Risk Factor Profile of Preterm Infants Screened for Retinopathy of Prematurity in a Tertiary Hospital

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ABSTRACT

Objective: To identify maternal and infantile risk factors for retinopathy of prematurity (ROP) among preterm infants screened in St. Luke's Medical Center, Quezon City (SLMC-QC) from 2014-2017.

Methods: This was a retrospective study that included the ROP databank of the Eye Institute and the Research and Biotechnology Group of St. Luke's Medical Center, Quezon City from 2014 to 2017. This study included medical records of all premature infants screened for ROP and excluded those who had incomplete data or other ocular pathologies other than ROP. Risk factors were analyzed using univariate analysis. Odds ratio (OR) and 95% confidence interval (CI) were also calculated with significant *P* value set at <0.05.

Results: Among the 455 infants screened for ROP, 118 (25.9%) had any stage of ROP while 23 (5.0%) had treatment-warranted ROP (TW-ROP). Univariate regression analysis showed that the top 5 infantile risk factors associated with any stage of ROP and TW-ROP were low birth weight (97.5% and 100%, respectively), prematurity (87.3% and 100%, respectively), history of blood transfusion (21.2% and 13%, respectively), sepsis (21.2% and 17.4%, respectively), and oxygen supplementation (16.1% and 8.7%, respectively). After multivariate analyses, the most important adjusted risk factors associated with any stage of ROP include low birth weight (OR 52, CI 16.20-166.96, *P*=0.001), prematurity (OR 25.73, CI 14.10-46.95, *P*=0.001), and history of blood transfusion (OR 8.79, CI 4.08-18.96, *P*=0.0001).

Conclusion: The most significant infantile risk factors associated with any ROP include low birth weight, prematurity, and history of blood transfusion. There were no significant probable maternal risk factors. Timely ROP screening is recommended especially among infants with any of these risk factors in their profile.

Keywords: retinopathy of prematurity, risk factors, low birth weight, blood transfusion, oxygen supplementation

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Retinopathy of prematurity (ROP) is a preventable cause of blindness among infants and children. It is characterized by an initial hyperoxic state with cessation in the growth of existing retinal vessels, followed by a pathological hypoxia-induced outgrowth of new vessels.[1,2] Established risk factors for ROP include prematurity of 32 weeks gestational age or less at birth and birth weight of 1500 grams or less.[2-11]

Several studies have shown that ROP is a multifactorial disease and many have described a correlation between ROP and several maternal and infantile risk factors. Possible maternal risk factors in literature include multiple gestation, premature rupture of membranes (PROM), pre-eclampsia/eclampsia, placenta previa/accreta, antenatal infection, and antenatal steroid injection. Apart from prematurity and low birth weight, probable infantile risk factors include oxygen supplementation, blood transfusion, sepsis, seizures, respiratory distress syndrome (RDS), hyperbilirubinemia, intraventricular hemorrhage (IVH), apnea, and anemia. Published studies on ROP risk factors, however, have shown variabilities in results.[2-12] At present, there are no local studies that show the association of these risk factors to ROP.

The primary objective of this study was to identify significant probable maternal and infantile risk factors for ROP. Specifically, the following infantile risk factors were investigated: low birth weight, prematurity, use of oxygen supplementation, blood transfusion, sepsis, seizure, respiratory distress syndrome (RDS), hyperbilirubinemia, intraventricular hemorrhage, apnea, and anemia. Additionally, the following maternal risk factors under investigation were multiple gestation, premature rupture of membranes (PROM), pre-eclampsia/eclampsia, placenta previa/accreta, antenatal infection, and antenatal steroid. This study determined possible association of above-mentioned with any ROP and treatment-warranted ROP.

Results of this study can pilot a prospective investigation in the future as well as development of a more advanced risk-based screening model and modification of current ROP screening guidelines. More importantly, prevention of these identified risk factors may reduce ROP incidence and severity and its early identification prompt early diagnosis and treatment.

METHODOLOGY

This was a retrospective cohort study reviewing the maternal and infantile risk factor profiles of infants in the ROP databank of the Eye Institute and the Research and Biotechnology Group of St. Luke's Medical Center, Quezon City from January 2014 to April 2017. The ROP databank is a collection of data kept by the Research and Biotechnology Group (RBG) of St. Luke's Medical Center, Quezon City. It contains electronic information on the routine clinical care (e.g. gestational age, birth weight, and clinical course), and ophthalmologic care (e.g., ROP diagnosis, stage, and treatment) of preterm infants referred for ROP screening. Quality of data was assured as the ROP screening forms were duly accomplished by the attending retina and/or pediatric ophthalmology specialist and their accompanying fellows or residents as they conducted individual ROP screening. Incompletely-filled forms were not entered into the ROP databank and returned to the attending physician for completion. Only data from January 2014 to April 2017 were used since the validated ROP screening forms, containing the listed risk factors pertinent to the study, were only utilized for ROP screening from 2014 to present.

This study included all medical charts of preterm infants screened for ROP and excluded those who had other ocular pathologies other than ROP and those with incomplete data on maternal and neonatal risk factors. Institutional Scientific Review Committee and Institutional Ethics Review Committee approvals were obtained.

Primary outcome was any ROP and secondary outcome was treatment-warranted ROP (TW-ROP).

"Any ROP" pertained to infants with stage 1, 2, 3, 4 or 5 ROP, regardless of zone and extent, in at least one eye. "Treatment-warranted ROP" (TW-ROP) pertained to infants that satisfied the type 1 Early Treatment for ROP (ET-ROP) criteria as well as any ROP which required treatment (i.e., laser indirect ophthalmoscopy, intravitreal injection of anti-vascular endothelial growth factor [anti-VEGF], and/or vitrectomy) in at least one eye. Type 1 ET-ROP or threshold ROP based from the ET-ROP study is characterized by the presence of any of the

following: (1) zone 1, any stage, with plus disease, (2) zone 1, stage 3, without plus disease, (3) zone 2, stage 2 or 3, with plus disease, or (4) stage 4 or higher disease.[13] The worse ROP in either eye of each infant was considered.

Six (6) probable maternal risk factors were identified: antenatal infection, antenatal steroid injection, placenta previa/accreta, pre-eclampsia/eclampsia, multiple gestation, and PROM. Eleven (11) probable infantile risk factors were included in the study: low birth weight, prematurity, anemia, IVH, hyperbilirubinemia, sepsis, seizure, apnea of prematurity, RDS, oxygen supplementation, and blood transfusion were identified in this study. Low birth weight was defined as equal to or less than 1500 grams and prematurity in this study was defined as equal to or less than 32 weeks gestational age.

Medical records from the ROP databank were reviewed and the following data were collected: gestational age, birth weight, presence or absence of the 11 probable maternal and infantile risk factors mentioned above, ROP diagnosis, stage, and treatment, if any.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences Software (SPSS for Windows, Chicago, IL, USA). Assuming that the incidence of ROP mirrors that of Owen et al[5], the computed sample size was 376 with 95% confidence interval and power of 80%. Nominal significance was considered at a *P*-value of <0.05 and estimates were reported as odds ratio (OR) with 95% confidence intervals (CI). Logistic regression with univariate and multivariate analyses were performed to determine risk factors most predictive for any ROP and TW-ROP.

RESULTS

Medical records of 455 preterm infants were included in the study. Among the 455 infants screened for ROP, 118 (25.9%) had any stage of ROP while 23 (5.0%) had TW-ROP.

The top 5 infantile risk factors associated with any ROP and TW-ROP were low birth weight (97.5% and 100%, respectively), prematurity (87.3% and 100%, respectively), history of blood transfusion (21.2% and 13%, respectively), sepsis (21.2% and 17.4%, respectively), and oxygen supplementation (16.1% and 8.7%, respectively). Majority of infants with any ROP and TW-ROP had maternal history of PROM (5.9% and 13%, respectively), multiple gestation (0.8% and 4.3%, respectively) and pre-eclampsia or eclampsia (0.8% and 4.3%, respectively) (Table 1).

Table 1. Frequency of Probable Infantile and Maternal Risk factors for ROP

	No ROP n (%)	Any ROP n (%)	TW- ROP n (%)
Infantile Risk Factors			
Low birth weight	143 (42.4)	115 (97.5)	23 (100)
Prematurity	71 (21.1)	103 (87.3)	23 (100)
Blood transfusion	29 (8.6)	25 (21.2)	3 (13)
Sepsis	10 (3)	25 (21.2)	4 (17.4)
Oxygen supplementation	62 (18.4)	19 (16.1)	2 (8.7)
Apnea of prematurity	4 (1.2)	11 (9.3)	0 (0)
Hyperbilirubinemia	6 (1.8)	4 (3.4)	0 (0)
RDS	52 (15.4)	3 (2.5)	1 (4.3)
Anemia	0 (0)	2 (1.7)	0 (0)
Seizure	20 (5.9)	1 (0.8)	0 (0)
IVH	7 (2.1)	0 (0)	0 (0)
Maternal Risk Factors			
PROM	1 (0.8)	7 (5.9)	3 (13)
Multigestation	7 (5.9)	1 (0.8)	1 (4.3)
Pre-eclampsia/eclampsia	1 (0.8)	1 (0.8)	1 (4.3)
Antenatal infection	0 (0)	1 (0.8)	0 (0)
Antenatal steroid injection	1 (0.8)	1 (0.8)	0 (0)
Placenta previa/accreta	1 (0.8)	0 (0)	0 (0)

*TW-ROP- treatment-warranted retinopathy of prematurity; RDS- respiratory distress syndrome; IVH- intraventricular hemorrhage; PROM- premature rupture of membranes

After univariate analysis, the most important risk factors associated with any ROP include: low birth weight (OR: 52.0, *P*=0.001), prematurity (OR: 25.7, *P*=0.001), history of blood transfusion (OR: 8.79, *P*=0.0001) and oxygen supplementation (OR:

2.04, *P*=0.0247) (**Table 2**). For TW-ROP, the only statistically significant risk factor was PROM (OR: 5.25, *P*=0.0155) (**Table 3**).

Table 2. Univariate Analyses of Probable Risk Factors for ROP

	Any ROP			TW-ROP		
	OR	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Infant Risk Factors						
Low birth weight	52.0	16.20 - 166.96	0.0001	-	-	0.9980
Prematurity	25.73	14.10 - 46.95	0.0001			0.9976
Oxygen supplementation	2.04	1.10 - 3.79	0.0247	0.8	0.18 - 3.52	0.7669
Blood transfusion	8.79	4.08 - 18.96	0.0001	1.88	0.53 - 6.65	0.3304
Sepsis	1.19	0.71 - 2.01	0.5077	0.89	0.29 - 2.67	0.8287
Seizure	0.71	0.08 - 6.43	0.7619			0.9982
RDS	1.44	0.35 - 5.85	0.6108	2.41	0.29 - 20.12	0.4169
Hyper-bilirubinemia	0.19	0.07 - 0.54	0.0019	-	-	0.9975
IVH	-	-	-	-	-	-
Apnea of prematurity	1.63	0.76 - 3.51	0.2126	-	-	0.9981
Anemia	0.81	0.17 - 3.97	0.7978	-	-	0.9984
Maternal Risk Factors						
Multigestation	0.35	0.04 - 2.84	0.3267	2.41	0.29 - 20.12	0.4169
PROM	2.59	0.92 - 7.32	0.0717	5.25	1.37 - 20.10	0.0155
Pre-eclampsia/ eclampsia	0.18	0.02 - 1.40	0.1025	1.26	0.16 - 10.01	0.8246
Placenta previa/ accreta	-	-	0.9980	-	-	0.9978
Antenatal infection	0.07	0.01 - 0.54	0.0106	-	-	0.998
Antenatal steroid injection	0.11	0.01 - 0.80	0.0291	-	-	0.998

*OR -odds ratio; CI- confidence interval; TW-ROP-treatment-warranted retinopathy of prematurity; RDS- respiratory distress syndrome; IVH- intraventricular hemorrhage; PROM-premature rupture of membranes

Table 3. Multivariate Analyses of Probable Risk factors for Any ROP

	Any ROP		
	OR	95% Confidence Interval	P-value
Low birth weight	10.2	2.8 to 37.4	0.0005
Prematurity	8.1	4.1 to 16.3	0.0001
Oxygen supplementation	0.5	0.2 to 1.3	0.1612
Blood transfusion	4	1.5 to 11.1	0.0006
	TW-ROP		
PROM	3.6	0.8 to 17.5	0.1071

*OR- odds ratio; TW-ROP -treatment-warranted retinopathy of prematurity; PROM- premature rupture of membranes

Table 3 shows the results of the multivariate analysis. The most important risk factors associated with any stage of ROP are low birth weight (OR: 10.02, *P*=0.0005), prematurity (OR: 8.1, *P*=0.0001) and history of blood transfusion (OR: 4, *P*=0.006). Oxygen supplementation and PROM are not significantly associated with any ROP or TW-ROP after multivariate analysis.

DISCUSSION

The incidence of any stage of ROP among infants screened in St. Luke's Medical Center, Quezon City in 2014-2017 was 25.9%. This is similar to the 25% ROP incidence rate among infants in SLMC-QC reported by Corpus and colleagues in 2013.[14] This is less than the 47.53% ROP incidence rate in Philippine General Hospital reported by Arroyo et al[15] and the 35% incidence rate in University of Santo Tomas Hospital described by Ladores and co-authors.[16]

Our study demonstrated that factors historically known to influence ROP risk, namely low birth weight and prematurity, remain to be leading risk factors. This was consistent with previous reports.[4-11] Shah et al. explained that the immaturity of retinal vascularization has an increased susceptibility to retinal oxidative damage. Furthermore, lower birth weight was significantly associated with ROP because of physical susceptibility for oxygen therapy, prolonged ventilation, sepsis, and other perinatal events.[4-6]

History of blood transfusion among preterm infants was found to be strongly associated with development in any stage of ROP consistent with other studies.[7-11] Furthermore, Slidsborg et al. also cited that blood transfusion was also a significant risk factor to TW-ROP. Seiberth and Hakeem suggested various mechanisms including that (1) blood transfusion rapidly replacing fetal hemoglobin with adult hemoglobin lowered oxygen affinity and increased oxidative vessel damage and that (2) blood transfusion increased insulin growth factor levels thereby promoting retinal neovascularization.[4,7-11]

Although maternal PROM was seldom included in the risk factor analysis of similar studies, it was found not to be statistically significant after multivariate analysis in this investigation. This finding was consistent in the report of Owen et al.[5]

Several studies have shown that oxygen supplementation, in varying forms such as mechanical ventilation, continuous positive airway pressure, oxygen mask, or nasal cannula, to be significantly associated with ROP.[4,6,-7,9,11] Shah and Seiberth explained that intensive exposure to high-pressure oxygen and fluctuating oxygen levels may be the

actual problem and not the specific form of oxygen supplementaiton.[6,11] However, after multivariate analysis, oxygen supplementation was no longer a strong risk factor in this investigation. No explanations yet can be given for this inconsistency but further studies are highly recommended, specifically, conducting a larger retrospective study or a prospective cohort study with a larger sample size and more proposed risk factors to show a stronger correlation with any stage of ROP and TW-ROP.

While these findings reiterate the accepted importance of low birth weight and prematurity to ROP risk, it is found that additional consideration of blood transfusion may create a potential predictive model for ROP development and possible modification of current ROP screening guidelines in the future.

In conclusion, among the infants screened for ROP in St. Luke's Medical Center, Quezon City from 2014-2017, any stage of ROP and TW-ROP were seen in 25.9% and 5.0% respectively. The most significant risk factors associated with any ROP include low birth weight, prematurity, and history of blood transfusion. These are significant probable risk factors in the development of ROP which necessitates further investigation. Timely ROP screening is recommended especially among infants with these risk factors in their profile.

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