Incidence and Risk Factors of Retinopathy of Prematurity, a 10-year Experience of a Single-center, Referral, Hospital

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ABSTRACT

Objective: To explore the incidence and trend of ROP over the past 10 years. The secondary objective was to identify any association between clinical variables and threshold ROP.

Materials and Methods: A cross-sectional, retrospective study of infants with <33 weeks' gestational age (GA) or birth weight (BW) ≤1,500g were screened for ROP between January 2010 and December 2019 Infants who had threshold ROP, labelled as the T-group, were compared against non-threshold infants (either normal or prethreshold ROP), or the NT-group.

Results: Of the 1,247 infants who were screened for ROP, 174 (14%) tested positive for ROP while 26 (2.1%) had threshold ROP. Infants who had ROP had a mean ±standard deviation (SD) GA 27.2 ± 2.2 weeks and 115 (66.1%) were <1000g at birth. Advanced GA was independently associated with lower risk of threshold ROP [adjusted odds ratio (95% confidence interval, CI); 0.71 (0.52, 0.98), p=0.04]. There was no difference in respiratory and hemodynamic outcomes between the T and NT-group, except for longer hospitalization (median [P25, P75]; 121[106.3, 160.5] and 93.5[72.3, 129] days, p=0.003]. Culture-positive septicemia was independently associated with threshold ROP [adjusted odds ratio (95% CI); 4.48 (1.72, 11.68), p=0.002].

Conclusion: The incidence of different stages of ROP in infants was 14% and 2.1% for severe ROP which required treatment. Lower GA and positive-culture septicemia was associated with a higher incidence of severe ROP.

Keywords: Incidence; preterm infants; retinopathy of prematurity; screening; threshold disease (Siriraj Med J 2021; 73: 777-785)

INTRODUCTION

Retinopathy of prematurity (ROP) is the most common cause of avoidable severe visual impairment or blindness regardless of socioeconomic status.[1-3] This condition has been well-documented in affecting not only visual outcomes but also neurodevelopmental outcomes.[4,5] Multifactorial factors have been proposed as both risk factors and preventative measures of severe ROP such as oxygen management, transfusion practices, nutritional and postnatal growth status, and infections. Hence, ROP is inevitably associated with premature birth as postnatal retinal vessel development is hastened due to postnatal oxygen exposure and lack of placental factors to promote normal growth of vessels, leading to an abnormal pattern of vessels. Therefore, despite improvements in perinatal and neonatal care in a bid to minimize the amount and duration of oxygen supplementation, retinal examinations for ROP screening remains a mandatory strategy to prevent severe ROP.

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While the incidence of very preterm infant birth has increased this century, advancements in perinatal care has provided hope in improving their associated morbidities, including severe ROP. Eye examinations screening for ROP require an interdisciplinary approach of pediatricians, ophthalmologists, and caregivers. International guidelines provide a strategy on how to screen for ROP in at-risk preterm infants at a certain postnatal age (PNA).[6,7] Incidences of ROP vary among countries depending on socioeconomic status and accessibility to ophthalmologic examinations.[1] Interestingly, genetic factors have also been proven to have an effect on ROP rates in different racial groups.[8,9] Therefore, understanding the local incidence rate of ROP is important in order to guide strategic planning to minimize or eliminate the disease. Unfortunately, problems related to awareness of ROP in caregivers and a lack of experienced ophthalmologists leads to inadequate coverage of a screening program[10], particularly in middle and low-income countries where preterm infants are more likely to exposed to risk factors, especially inadequate oxygen monitoring and oxygen titration devices or availability of experienced caregivers to monitor and control oxygenation throughout their postnatal period.

We, therefore, wanted to explore incidence of ROP from 2010 until 2019 and identify risk factors associated with severe ROP cases.

MATERIALS AND METHODS

This was a retrospective, cross-sectional, comparative study at the Division of Neonatology, Department of Pediatrics, Faculty of Medicine at Siriraj Hospital, Mahidol University, Bangkok, Thailand. As a teaching and regional tertiary referral hospital, patients in the study were both inborn and outborn infants who ranged between low-risk to high-risk. Preterm infants born <28 days before due date were admitted into a one of several neonatal wards, i.e; a neonatal intensive care unit (NICU), intermediate care unit, or high-risk nursery, depending on birth weight (BW) and respiratory or hemodynamic status, regardless of primary diagnosis.An ACOG guidance for antenatal corticosteroids administrations and intrapartum antibiotics[11] was used throughout the study period. We followed the International Liaison Committee of Resuscitation (ILCOR) guideline for birth resuscitation.[12,13] Respiratory management included encouraging the use of non-invasive ventilation (NIV) and oxygen titration and oxygen monitoring devices were available at delivery suites and neonatal wards. Surfactant replacement therapy was used in infants with a clinical diagnosis of surfactant deficiency and requiring FiO_2 >0.6 (between 2013 to 2015) or >0.4 (from 2016 onwards) under NIV. Oxygen management for preterm infants was targeted between 88%-93% until mid-2013 at which point it was changed to 90%-95%. Nutritional management included early parenteral nutrition within the first few hours of life and encouraging early trophic feeding. Human-milk fortification was added once infants could tolerate 100 mL/kg/day feeds. Vitamin E 25 IU/day was also prescribed after infants were fully-fed until the 40-week PMA.

According to institutional guidelines for screening of ROP, infants born prior to <33 weeks' gestation or with a birth weight ≤1,500g are required to be screened. All eye examinations were performed under indirect ophthalmoscopy at the bedside by- or under the direct supervision of the pediatric ophthalmologist. The first examination was scheduled during the 4th week of chronological age. Subsequent examinations were scheduled over the next 1-4 weeks depending on previous findings and a plan of management was manually recorded following each examination as part of a quality improvement policy. The cases in which infants who had abnormal eye examination reached threshold levels between January 2010 to December 2019 (the threshold, T-group) were explored along with their associated risk factors. Each case was selectively matched with 4 controls of normal or pre-threshold ROP (the non-threshold, NT- group) using the same GA strata (≤27 or >27 weeks-GA) and admitted next to the corresponding case to minimize selective bias from level of prematurity and variation of general care practices over time. Infants who had normal eye examinations were prioritized in the NT group. However, in case there were not enough normal controls, which occurred in the ≤27 weeks-strata, infants who had abnormal examinations but did not meet the criteria for threshold (pre-threshold ROP) were selected. Therefore, the NT-group consisted of both normal and pre-threshold ROP disease. Clinical variables of eligible infants were extracted using pre-specified outcomes by an individual chart review for analysis.

Incidence and demographic characters were presented as a number and percentage for categorical variables and as mean ± standard deviation (SD) or median [percentile 25th (P25), percentile 75th (P75)]. Comparisons of infants' clinical and ophthalmologic outcomes between groups of gestational age (GA) ≤27 weeks and >27- weeks' groups was done using the Chi-square test, Fisher's exact test, paired *t*-test, and Mann-Whitney U test depending on the type and distribution of each variable. A univariate logistic regression analysis evaluated factors associated with occurrence of threshold ROP using the crude odds ratio (OR) with 95% confidence interval (CI) and adjusted

OR for significantly different demographic variables with multivariate logistic regression analysis. All statistical analyses were performed using SPSS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). A *p*-value of <0.05 was considered statistically significant.

RESULTS

The study protocol was approved by the institutional IRB. From January 2010 to December 2019, there were 1247 infants screened for ROP. Of these, 174 (14%) had ROP at various stages. Our annual incidence rate ranged from 9.2% to 24.4% (Fig 1). The mean ± standard deviation (SD) GA of 174 infants who had abnormal eye examinations was 27.2 ± 2.2 weeks and their mean ± SD birth weight was 923.0 ± 257.4 g. One-hundred and fifteen (66.1%) infants had BW <1,000 g. One-hundred and sixty-six (95.4%) were inborn infants, 32 (18.4%) were small-for-gestational age and 34 (19.5%) were born from multifetal pregnancies. Threshold ROP occurred in 26 infants (2.1%) and 14.9% of infants were in the T-group (those with ROP at different stages). Twenty-five infants had laser surgery performed, 5 received both laser surgery and intravitreal anti-VEGF therapy, and one infant received only anti-VEGF therapy. Of the 104 infants in the NT-group, 31 had normal eye examinations (11 infants with GA ≤27 weeks and 20 infants with GA >27 weeks) and 73 with prethreshold ROP (all GA ≤27 weeks). Table 1 compares baseline demographic characteristics between the T and NT-group. Although attempts were made to match GA, the median [P25, P75] GA of the T-group was significantly lower than the NT-group, 25.5 [25, 26] versus 26 [25, 27], p=0.02, and their corresponding BW was marginally different (775 [707.5, 932.5] and 870 [770, 1115], respectively; p=0.05). The other baseline characteristics were not significantly different. Table 2 demonstrates clinical outcomes during hospitalization at birth between the groups. There were no differences in respiratory and hemodynamic outcomes between the groups. However, infants in the T-group had a higher rate of culture-positive septicemia (46.2% versus 17.3%, p=0.004) and a longer median hospitalization stay, 121 days [106.3, 160.5] and 93.5 days [72.3, 129], p=0.003].

Among infants who had ROP at various stages, the median [P25, P75] postnatal age (PNA) of initial eye examination was 30 days [28, 32] at 31 [30, 33] weeks' postmenstrual age (PMA). The PNA of the first abnormal examination was 50 days [40, 58] at PMA at 34 weeks [32, 36]. Table 3 compares the characteristics of eye examinations between the groups. PNA and PMA of initial examinations and the first abnormal detection were not different between the groups. The T-group had a significantly higher number of eye examinations during birth hospitalization (12[9, 13.3] versus 8 [5, 11.8], respectively, p<0.001). Table 4 identifies the potential risk factors of developing threshold ROP. Culture-positive septicemia was independently associated with threshold ROP [adjusted OR (95%CI) 4.48 (1.72, 11.68), p =0.002] while advanced GA was associated with lower risk of threshold ROP [adjusted OR (95%CI) 0.71 (0.52, 0.98) for each week, p <0.001].

Fig 2 demonstrates the proportion of ROP screening results based on GA. The incidence trend of ROP at any stage or at threshold were inversely high with lower GA. (Table 5) compares characteristics of eye examinations and the outcomes of ROP in 174 infants based on GA strata. Infants ≤27 weeks GA had earlier both PMA for initial eye examination and first abnormal detection (30 [29, 31] versus 33 [32, 34] and 33 [31, 34] versus 35 [34, 37] weeks, respectively, both p<0.001). Infants ≤27 weeks GA had a higher rate of threshold ROP (19.8% versus 7.4%, p=0.03) and borderline different rates of laser therapy (18.9% versus 7.4%, p=0.05].

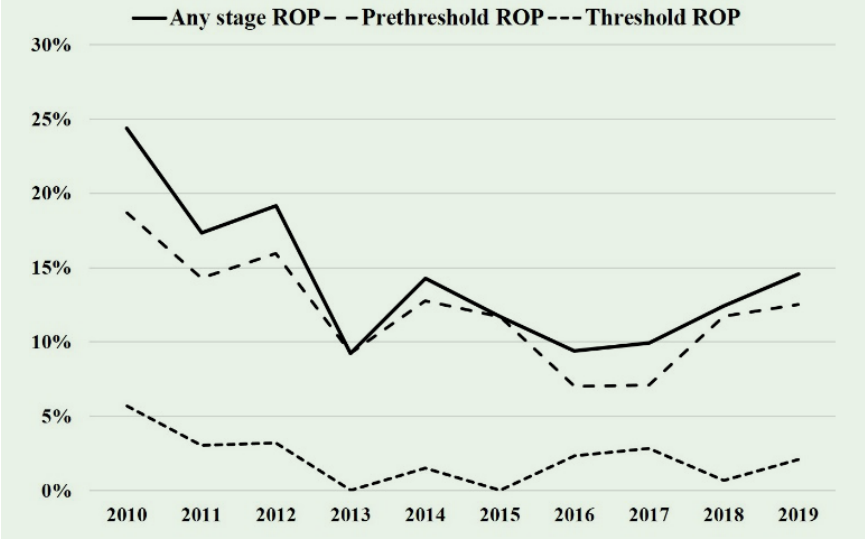

Fig 1. Trend in the incidences of retinopathy of prematurity from 2010 to 2019 (N=1,247)

TABLE 1. Baseline demographic characteristics.

Variable	Threshold disease (n = 26)	Normal or prethreshold disease (n = 104)	*p*-value
Gestational age (week)	25.5 [25, 26]	26 [25, 27]	0.02*
Birth weight (g)	775 [707.5, 932.5]	870 [770, 1115]	0.05
Small-for-gestational age	4 (15.4)	12 (11.5)	0.59
Large-for-gestational age	0	2 (1.9)	0.48
Inborn	25 (96.2)	102 (98.1)	0.56
Multiples	4 (15.4)	19 (18.3)	0.73
Cesarean section	10 (38.5)	67 (64.4)	0.03
Maternal complications (n =128)	(n = 26)	(n = 102)	
Hypertension	2 (7.7)	18 (17.6)	0.36
Diabetes	3 (11.5)	12 (11.8)	1.00
Antepartum hemorrhage	3 (11.5)	4 (3.9)	0.15
Chorioamnionitis / infection	6 (23.1)	20 (19.6)	0.79

Data presented as number (percentage) or median [P25, P75].
*A *p*-value<0.05 indicates statistical significance.

TABLE 2. Clinical characteristics during hospitalization at birth.

Variable	Threshold disease (n = 26)	Normal or prethreshold disease (n = 104)	*p*-value
Respiratory support			
Non-invasive ventilation	25 (96.2)	100 (96.2)	1.00
Mechanical ventilation	25 (96.2)	88 (84.6)	0.19
Received theophylline	21 (80.8)	90 (86.5)	0.54
Surfactant administration	11 (42.3)	34 (32.7)	0.49
Pneumothorax	2 (7.7)	6 (5.8)	0.66
Bronchopulmonary dysplasia	23 (88.5)	75 (72.1)	0.13
Cardiovascular			
Inotropic agent (s)	17 (65.4)	50 (48.1)	0.13
Medical ligation	15 (57.7)	58 (55.8)	1.00
Surgical ligation	7 (26.9)	31 (29.8)	0.82
Infection			
Positive blood culture	12 (46.2)	18 (17.3)	0.004*
Parenteral antibiotics	26 (100)	104 (100)	
GI & Nutrition			
Breast milk	25 (96.2)	100 (96.2)	1.00
Pasteurized donor milk	2 (7.7)	6 (5.8)	0.66
Formula	23 (88.5)	90 (86.50	1.00
Diagnosis of NEC	8 (30.8)	40 (38.5)	0.51
Surgical NEC	0	7 (6.7)	0.34
Days of mechanical ventilation	41 [21.0 , 61.0]	30 [10.8 , 56.5]	0.21
Days of hospitalization	121 [106.3, 160.5]	93.5 [72.3, 129]	0.003*
Death during birth hospitalization	1 (3.8)	5 (4.8)	0.28

Data presented as number (percentage) or median [P25, P75].
*A *p*-value<0.05 indicates statistical significance.
(Abbreviations: CPAP, continuous positive-airway pressure; CSF, cerebrospinal fluid; HFNC, high-flow nasal cannula; NEC, necrotizing enterocolitis; NIPPV, nasal intermittent positive-airway pressure)

TABLE 3. Characteristics of eye examinations (N=130).

Variable	Threshold disease (n = 26)	Normal or prethreshold disease (n = 104)	*p*-value
Postnatal age of first eye examination, day	30 [28, 32.5]	29 [27.3, 32]	0.43
Postmenstrual age of first eye examination, week	29.5 [28.8, 32]	30 [29, 31]	0.09
Postnatal age of first abnormal detection, day (n = 99)	50 [44, 53]	52 [44.5, 61]	0.11
Postmenstrual age of first abnormal detection, week (n = 99)	32 [31, 34]	33 [31.5, 34]	0.16
Number of examinations during birth hospitalization	12 [9, 13.3]	8 [5, 11.8]	<0.001*

Data presents as median [P25, P75].
*A *p*-value<0.05 indicates statistical significance.

TABLE 4. Risk factors of threshold ROP.

Variables	OR (95%CI)	P-value	AOR (95%CI)	*p*-value
Gestational age (every week increment)	0.75 (0.56, 0.99)	0.05	0.71 (0.52, 0.98)	0.04*
Birth weight (every 100-g increment)	0.84 (0.69, 1.02)	0.07	0.95 (0.72, 1.28)	0.75
Mechanical ventilation	4.55 (0.57, 35.97)	0.15	2.42 (0.28, 21.28)	0.43
Surfactant administration	1.51 (0.63, 3.64)	0.36	1.03 (0.39, 2.72)	0.95
Days of mechanical ventilation	1.00 (0.99, 1.01)	0.33	0.99 (0.98, 1.01)	0.78
Did not receive breast milk	1.00 (0.11, 9.34)	1.00	0.68 (0.07, 6.89)	0.75
Culture-positive septicemia	4.10 (1.63, 10.31)	0.003	4.48 (1.72, 11.68)	0.002*
Medical ligation for PDA	1.08 (0.45, 2.58)	0.86	0.64 (0.24, 1.70)	0.37
Surgical ligation for PDA	0.87 (0.33, 2.27)	0.77	0.54 (0.19, 1.54)	0.25
Inotropic agents	2.04 (0.83, 4.99)	0.12	1.11 (0.41, 3.01)	0.84

AOR, adjusted odds ratio, were adjusted by gestational age and positive blood culture.
*A *p*-value<0.05 indicates statistical significance.

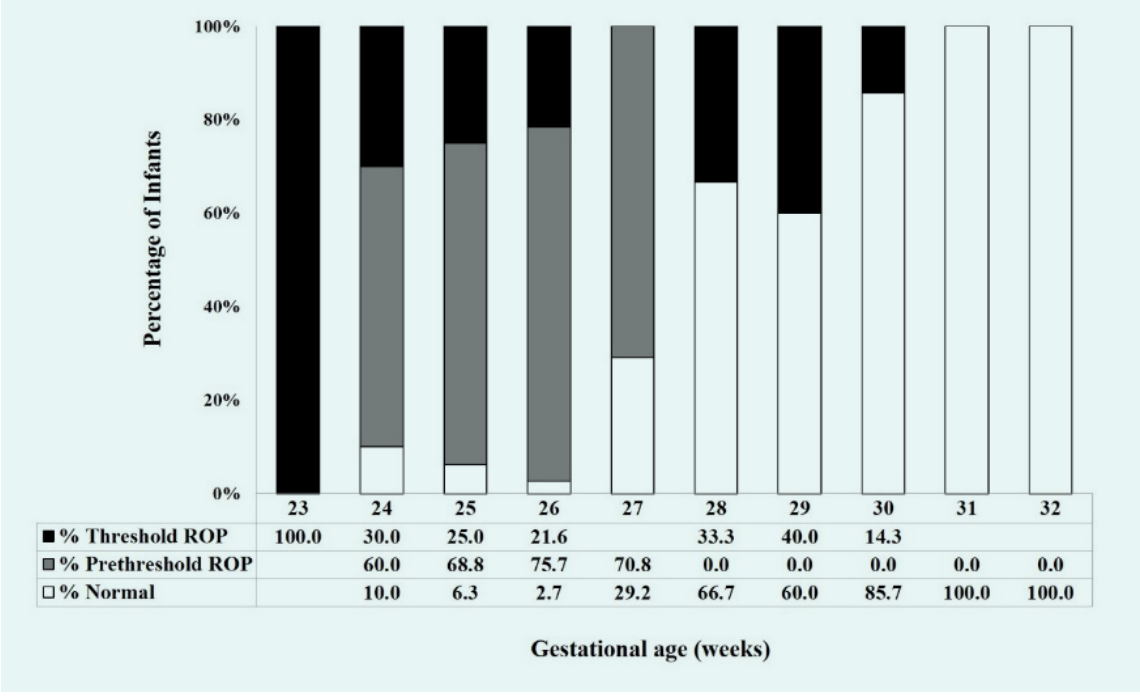

Fig 2. Incidences of retinopathy of prematurity by gestational age (N=1,247)

TABLE 5. Characteristics of abnormal eye examinations (N=174).

	GA ≤27 weeks (n = 106)	GA >27 weeks (n = 68)	*p*-value
PNA of first eye examination (days)	30 [28, 33]	30 [28 ,32]	0.88
PMA of first eye examination (weeks)	30 [29, 31]	33 [32, 34]	<0.001*
PNA of first abnormal detection (days) (n = 99)	51 [44, 59.3]	42.5 [32.3, 53.8]	<0.001*
PMA age of first abnormal detection (weeks) (n = 99)	33 [31, 34]	35 [34, 37]	<0.001*
Number of examinations during hospitalization	10 [8, 13]	6 [4, 9]	<0.001*
Threshold disease	21 (19.8)	5 (7.4)	0.03*
Laser therapy	20 (18.9)	5 (7.4)	0.05*
PNA of LASER therapy (days)	75.5 [66.8, 85.8]	68 [38, 88]	0.37
Intravitreous anti-VEGF therapy	5 (4.7)	1 (1.5)	0.41
PNA of anti-VEGF therapy (days)	69 [61, 108]	43 [43, 43]	0.33

Data presents as median [P25, P75] or number (percentage). *A *p*-value<0.05 indicates statistical significance.
Abbreviations: PMA, postmenstrual age; PNA, postnatal age; VEGF, vascular endothelial growth factor

DISCUSSION

Retinopathy of prematurity (ROP) remains an important morbidity factor in extremely preterm infants. Since its risk is the result of premature birth, total elimination of ROP remains a challenge even though various strategies have been attempted to minimize the risk of the disease. In fact, a standard screening program is mandatory to explore the magnitude of the disease and, more importantly, to identify early abnormal vessels to allow for early management that can save an infant's long-term vision. Relatively recent reports about incidence of ROP at any stage of the disease ranges between 9% to 27%.[14-17] However, it is a challenge to compare results because such a big range of incidence can be explained by a few possibilities. The first, and most important reason, is the availability to provide care for very premature infants and associated risk factors. Middle-income countries especially have a high burden of ROP due to improvements in survival rate of extremely premature infants, however, they still have limited resources to monitor and titration of oxygen devices.[1] This phenomenon has been noted after studies have revealed the incidence of ROP in middle-income countries was as high as 69% in extremely-low birthweight infants.[18] Second, criteria for ROP screening suggested from different expertise groups are not uniform, mainly included GA and BW.[6,19] Generally, ROP screening is suggested for infants with GA ≤30 or 32 weeks or a BW of ≤1,500 g. Although we perform screening for all <33 weeks' gestation or ≤1,500 g BW infants, only 7 out of 130 (5.4%) who were 31 to 32 weeks' GA and had BW >1,500 g. So, proportion of at-risk infants who were screened overall should be comparable to the other reported incidence using minor different criterion. Third, various definitions of severe ROP were selected in each report and used treatment requiring ROP or threshold ROP to represent the severity. Our incidence of ROP at any stage of the disease was 14%, which was relatively low when compared to other upper middle-income countries where the incidence ranges between 19% to 33%.[17,20,21] In fact, our incidence showed ROP rates decreased from 2010 to 2013. However, there was a sharp increase in ROP rate from 9.3% in 2013 to 14.3% in 2014. We suspect this rise was secondary due to changes of targeted oxygen saturation which was reported in a previous study.[22,23] However, our incidence of threshold ROP at 2.1% was relatively stable throughout the study period and comparable to the other reports from developed countries.[14]

Timing of abnormal neovascularization usually found during vasoproliferative phase of ROP.[19,24] We found median PNA of initial abnormal vessels detection were 50 days in threshold ROP and 52 days for prethreshold ROP which were correspondence to 32- and 33-weeks PMA. Since their PNA and PMA were comparable between the groups, timing of initial abnormal detection cannot predict their subsequent results of abnormal vessels which emphasize the importance of subsequent follow-up examinations until full development of retinal vessels.

Observational studies have shown several risk factors associated with either ROP at various stages of disease progression or threshold ROP. The most potent risk of baseline characteristics is premature birth,[10,14,25] which was also demonstrated in our study [adjusted OR 0.71 (0.52, 0.98), p=0.04]. Although 66.1% of ROP cases in our study were extremely premature infants (birth weight <1,000 g), we did not find any significant association between BW and threshold ROP. So, premature birth is a more potent risk factor than intrauterine growth. Dysoxemia and clinical unstable are proposed to be at-risk for ROP.[26-29] We did not find any differences in respiratory outcomes such as intubation, duration of mechanical ventilation, surfactant administration, pneumothorax, or bronchopulmonary dysplasia or in hemodynamic parameters (inotropic agents or treatment of patent ductus arteriosus) in infants with threshold ROP and the control group. Postnatal nutrition plays an important role on normal retinal vessels via optimal level of IGF-1 and antioxidative factors in breast milk.[30] Hence, we did not find different rate of threshold ROP in infants who received maternal breast milk or pasteurized donor milk (PDM [adjusted OR 0.68 (0.07, 6.89), p=0.75]. However, due to the limited number of infants who did not receive breast milk, this phenomenon is deserved to be explored further with adequate sample size.

The meta-analysis showed significant association between chorioamnionitis and severe ROP,[31] but no study has found a similar association for postnatal septicemia. Interestingly, we noticed positive-culture septicemia as a risk factor [adjusted OR 4.48 (1.72, 11.68), p=0.002]. The possibility of this relationship can be attributed to inflammation cascade suppressed early retinal vascularization and cause severe neovascularization later or secondary to systemic instability during sepsis contributed to retinal hypoxia and develop ROP later.[32]

We reported our incidence rate in a large number of at-risk infants from the tertiary care referral center in Thailand where the ROP screening program, including patient selections, examination maneuvers and recording, follow-up practices and therapy is already established. All eye examinations were interpreted by only one pediatric ophthalmologist which ensured internal validity. However, some limitations must be considered. First,

due to our cross-sectional design, we could not ensure timely association or if some variables occurred before or after detection of abnormal retinal vessels. Therefore, our results assumed association between these variables and ROP occurrence. Hence, PNA of abnormal findings occurred around 50 days when most clinical stability was already established or had subsided. This was assumed to occur before any findings of ROP. Second, our patients were mainly inborn infants where physicians, caregivers, devices, and monitoring equipment were available. Our incidence rate may not reflect the true incidence rate in the country, especially in rural areas where resources are limited, especially in coverage of the screening program.

CONCLUSION

In conclusion, during the past 10 years, our incidence of ROP at any stage in infants born <33 weeks or with a BW <1,500 g was 14% and 2.1% for threshold ROP requiring treatment. Lower GA and positive-culture septicemia were found to be associated with occurrence of threshold ROP.

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