Annals of Clinical Epidemiology 2023;5(3):80–87

Annals of Clinical Epidemiology

ORIGINAL ARTICLE

The incidence and risk factors associated with the retinopathy of prematurity in a tertiary hospital using 10-year retrospective data

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ABSTRACT

BACKGROUND

The study aimed to examine the incidence and risk factors associated with retinopathy of prematurity at Phramongkutklao Hospital.

METHODS

A retrospective review was conducted on the medical records of premature infants screened for retinopathy of prematurity between January 2011 and December 2021. The screening examination was performed on infants who met the screening criteria, and retinopathy of prematurity was diagnosed according to the International Classification of Retinopathy of Prematurity. Maternal, obstetric, neonatal, and medical data were retrieved. Logistic regression analysis was used to identify the risk factors associated with retinopathy of prematurity.

RESULTS

A total of 403 premature infants were screened. The mean ± SD birth weight and gestational ages were 1,538 ± 543 grams and 31 ± 3 weeks, respectively. The incidence of any retinopathy of prematurity and stages 2 and 3 were 13.6%, 3.5%, and 10.1%, respectively. Multiple logistic regression analysis demonstrated that gestational age (adjusted odds ratio = 1.98, 95% CI:1.15–3.39), low birth weight (adjusted odds ratio = 0.99, 95% CI: 0.99–1.00), and phototherapy (adjusted odds ratio = 0.41, 95% CI: 0.17–1.00) were significant factors associated with the development of retinopathy of prematurity, after controlling for other confounding factors.

CONCLUSIONS

The incidence of total retinopathy of prematurity cases in this population was 13.6%. Overall, retinopathy of prematurity cases classified as stage 2 equated to 3.5% and stage 3 to 4.1%. Our data suggest that factors associated with retinopathy of prematurity consist of birth weight, gestational age, and phototherapy.

KEY WORDS

Incidence, Preterm, Retinopathy of prematurity, Risk factor, Tertiary hospital

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Received: January 4, 2023
Accepted: March 28, 2023
J-STAGE Advance published date: April 8, 2023

No. 23011

INTRODUCTION

Human organ development continues until term birth. Premature birth can impact organ system maturation, including ocular structures. Cataracts, glaucoma, retinopathy of prematurity (ROP), and strabismus are all examples of structural involvement. Not only does ROP affect the structure, but it also causes functional issues such as refractive error and amblyopia. ROP was the leading cause of preterm vision loss or blindness [1].

Premature birth is a risk factor for ROP development. Several research studies also show that comorbidities may increase the incidence of ROP, such as convulsions, septicemia, anemia, necrotizing enteritis (NEC), chronic lung condition (bronchopulmonary dysplasia; BPD), periventricular leukomalacia, hyperglycemia, hypotension, and patent ductus arteriosus (PDA) [2–10]. Furthermore, preterm infants who receive certain procedures are associated with the occurrence of ROP; for example, oxygen supplements, phototherapy in neonatal jaundice, blood transfusion, blood exchange in neonatal jaundice, and parenteral feeding nutrition.

There have only been a few reports of ROP incidence in Thailand, the majority of which are older than 10 years [11–14]. The previous reports were on different regions of Thailand, including the central, northeast, and southern areas. They revealed that the incidence of ROP ranged from 14–31.7%. According to previous studies, the threshold for ROP treatment was 2.1–9.5%, with risk factors for ROP occurrence being low gestational age and low birth weight. Our report on ROP incidence and its associated risk factors could reflect the current status of ROP in the Thai population at a referral-based hospital located in the central region.

This research aims to study the incidence of ROP and the factors associated with its occurrence at Phramongkutklao Hospital. Information on the incidence and related factors causing ROP will help in the planning of an exemplary service for premature babies at our hospital and referral center to reduce complications and the risk of blindness.

METHOD

This is a retrospective cohort study involving a review of the medical records for preterm infants at Phramongkutklao Hospital from January 1, 2010, to December 31, 2021, all of whom meet any of the following criteria:

1) Born at a gestational age of less than or equal to 30 weeks

2) Having a birth weight of less than or equal to 1,500 grams

3) Having a birth weight of between 1,500 and 2,000 grams, with an unstable clinical course

The infants born under these criteria were examined and followed until they met the endpoints; completely vascularized, regressed ROP, or any stage of ROP, whether treated or not.

The primary outcome of the study is ROP occurrence. ROP is defined as a retinal abnormality caused by prematurity. The International Classification of Retinopathy of Prematurity (ICROP) criteria serve as the basis for the diagnostic and staging criteria [15]. There are six ROP stages. Stage 0 ROP is an incomplete vascularized retina. Stage 1 ROP is diagnosed when the demarcation line is observed. Stage 2 ROP is diagnosed when the ridge is observed. Stage 3 ROP is diagnosed when extraretinal fibrovascular proliferation is observed. Stage 4 and stage 5 ROP are diagnosed in the case of partial and total retinal detachment, respectively. Aggressive ROP is defined as a severe form of ROP, which is a posterior location (zone I or posterior zone II), plus disease, and the ill-defined nature of the retinopathy. The zone ROP is classified into three zones. Zone I is defined as a circle whose radius is twice the distance from the center of the optic disc to the macula. Zone II is defined as a circle whose radius is the distance from the optic disc's center to the retina's nasal margin (ora serrata). Zone III is the remainder of the retina, which is a crescent-shaped zone that largely involves the temporal retina. The areas straddling zones I and II were recorded as zone I–II. The areas straddling zones II and III were recorded as zone II–III.

As potential risk factors for ROP occurrence, multiple variables were recorded. Sepsis, PDA, NEC, hypothermia, hypoglycemia, seizure, hyperbilirubinemia, polycythemia, anemia, BPD, blood transfusion, phototherapy, parenteral nutrition, and surfactant were all recorded. The pediatrician in charge determined the diagnosis since these conditions must be diagnosed before ROP occurs. These conditions were marked as present or absent in the records.

General information about the infant, including gestational age, age of mother, delivery procedures, duration of hospitalization, and Appearance-Pulse-Grimace-Activity-Respiration (APGAR) scores, recorded at 1, 5, and 10 minutes, were retrieved from the data record. The ophthalmological screening and diagnosis were performed by vitreoretinal ophthalmologists at Phramongkutklao Hospital, using the diagnostic criteria of ICROP, with the most severe stage of ROP in either eye recorded.

Ocular examinations were performed by a pediatric ophthalmologist using a handheld slit lamp. The anterior segment was the ocular structure anterior to the lens, including the cornea, anterior chamber, and iris. Cataracts were defined as cloudy lenses, revealed after dilatation for fundus examination.

The results for continuous variables were expressed as a median with an interquartile range and the categorical variables as a percentage. Statistical analyses were performed using IBM SPSS Statistics 26 software (IBM Corp.).

We used the t-test and chi-square test to compare continuous variable averages and categorical variable proportions, respectively. For analysis, gestational age, birth weight, and APGAR score were categorized into groups. Lower gestational age was categorized as <30 weeks and higher ≥30 weeks. Birth weight was categorized into three groups: <1,000 grams (extremely low birth weight), 1,000–1,500 grams (very low birth weight), and >1,500 grams (low birth weight). The APGAR score was categorized into three groups: 1–3 (low score), 4–6 (moderate score), and 7–10 (high score).

To calculate logistic regression, variables found to be statistically significant by chi-square and independent sample t-test comparison between ROP and non-ROP groups were chosen. Gestational age in group, birthweight in group, APGAR in group, sepsis, transient tachypnea of newborn (TTNB), respiratory distress syndrome (RDS), PDA, NEC, anemia, phototherapy, and surfactant given were adjusted for multivariate logistic regression as a potential risk factor for ROP occurrence. Due to multi-collinearity, the 1-minute APGAR group was chosen for the logistic regression.

The confounding factors were the extended range of the study, which influenced the ROP incidence results. Perinatology and perinatal care advancements may impact more ROP cases in recent records. Furthermore, the severity of the recording variables was not declared in detail, which may affect the ROP results.

The Institutional Review Board of the Royal Thai Army Medical Department gave ethical approval to the study protocol. The study protocol was S089h/64_Exp and adhered to the tenets of the Declaration of Helsinki.

RESULTS

During the study period, eye examination data records of 735 infants were collected. Of these, 332 infants were excluded due to incomplete data records, resulting in 403 infants being eligible for the study.

We recruited 403 preterm infants for this study, 57.8% male and 42.2% female. The average gestational age was 31.05 (standard deviation [SD] 3.14) weeks and the birth weight was 1,538.14 (SD 543.16) grams. The duration of hospitalization was 47 days, and cesarean section was the mode of delivery in 69.2% of cases. **Table 1** shows the demographic data.

Our study's overall incidence of ROP was 55/404 (13.6%; 95% confidence interval [CI], 10.5–17.2). They were classified as stage 2 ROP 14/404 (3.5%) and stage 3 ROP 41/404 (10.1%). The treatments received were indirect laser ophthalmoscope 51/404 (12.6%) and intravitreal anti-VEGF 3/404 (0.7%).

The groups of infants with and without ROP are compared in **Table 2**. The gestational age and birth weight were significantly lower in the ROP group than in the non-ROP group, with a mean gestational age (GA) of 26.5+/−2.2 weeks vs. 31.8+/−2.6 weeks ($p < 0.001$) and a mean birth weight (BW) of 893.9+/−250.7 grams vs. 1,639.7+/−505.9 grams, respectively. The ROP risks analyzed by chi-square and the independent sample t-test (**Table 2**) indicate that mode of delivery, gestational age, birth weight, APGAR score, sepsis, TTNB, PDA, NEC, seizure, hyperbilirubinemia, anemia, BPD, phototherapy, duration of hospitalization, and surfactant given were significantly associated with the incidence of ROP ($p < 0.05$) in this population. There was no significant difference between the risk factors between ROP stages 2 and 3 in our population.

Logistic regression indicated that gestational age, birth weight, and phototherapy were associated with ROP incidence at an adjusted odds ratio of 0.67 (CI 0.52–0.86), 0.99 (CI 0.99–1.00), and 0.41 (CI 0.17–1.0), respectively (**Table 3**).

Our population's ROP treatments were classified as observation, laser indirect ophthalmoscope, and intravitreal anti-VEGF. Observation was the most likely candidate in 350/404 (86.6%) of cases. In the type 1 ROP population, 51/404 (12.6%) had a laser indirect ophthalmoscope.

Finally, the intravitreal anti-VEGF was chosen at 3/404 (0.7%). One infant had stage 2 ROP in zone II, and subsequently recovered without treatment.

DISCUSSION

The global incidence of ROP in preterm infants varies across countries, with studies being either nationwide or population-based. The variation in ROP incidence is due to differences in population research methodology,

Table 1 Baseline demographic characteristics

	n	%
Birth-related information		
Age of mother (years)	31 (14–49)	
Male	233	57.8
Normal labor	124	30.8
Singleton pregnancy	340	84.2
Gestational age (weeks)	32 (23–40)	
Birth weight (grams)	1,503.5 (520–3,550)	
1-minute APGAR	7 (0–10)	
5-minute APGAR	9 (1–10)	
10-minute APGAR	8 (2–10)	
Duration of hospitalization (days)	32 (2–270)	
Sepsis	229	56.7
Transient tachypnea of newborn	182	45.0
Respiratory distress syndrome	154	38.1
Patent ductus arteriosus	74	18.3
Intraventricular hemorrhage	39	9.7
Necrotizing enterocolitis	48	11.9
Hypothermia	5	1.2
Hypoglycemia	62	15.3
Seizure	19	4.7
Hyperbilirubinemia	313	77.5
Polycythemia	7	1.7
Anemia	149	36.9
Bronchopulmonary dysplasia	10	2.5
Blood transfusion	0	0
Phototherapy	252	62.4
Parenteral nutrition	1	0.2
Surfactant given	23	5.7
Eye-related information		
Abnormal anterior segment	1	0.2
Cataract	3	0.7
Abnormal fundus	52	12.9
ROP stage		
No ROP	349	86.4
Stage 1 ROP	0	0.0
Stage 2 ROP	14	3.5
Stage 3 ROP	41	10.1
Stage 4 ROP	0	0.0
Stage 5 ROP	0	0.0
ROP zone		
Zone I	0	0.0
Zone I–II	0	0.0
Zone II	55	13.6
Zone II–III	20	5.0
Zone III	329	81.4
Treatment		
Observe	350	86.6
Laser indirect ophthalmoscope	51	12.6
Intravitreal anti-VEGF	3	0.7

Data are presented as median (interquartile range) or n (%) of patients.
Abbreviations: APGAR, Appearance-Pulse-Grimace-Activity-Respiration; ROP, retinopathy of prematurity; VEGF, vascular endothelium growth factors

Table 2 The comparison between Retinopathy of prematurity and non- Retinopathy of prematurity groups

	No ROP*		ROP		p-value
	n	%	n	%	
Birth-related information					
Age of mother (years)	31(14–44)		30(16–49)		0.279
Sex					0.217
male	197	84.5	36	15.5	
female	151	88.8	19	11.2	
Mode of delivery					0.020
Normal labor	100	80.6	24	19.4	
Cesarian section	248	89.2	30	10.8	
Pregnancy					0.061
single	289	85.0	51	15.0	
twin	60	93.8	4	6.3	
Gestational age (weeks)					<0.001
<30	64	55.7	51	44.3	
≥30	285	98.6	4	1.4	
Birth weight (grams)					<0.001
<1000	29	42.0	40	58.0	
1000 – 1500	117	89.3	14	10.7	
>1500	203	99.5	1	0.5	
1-minute APGAR					<0.001
1–3	42	61.8	26	38.2	
4–6	93	86.1	15	13.9	
7–10	210	94.6	12	5.4	
5-minute APGAR					<0.001
1–3	8	47.1	9	52.9	
4–6	35	70.0	15	30.0	
7–10	303	90.7	31	9.3	
10-minute APGAR					0.144
1–3	2	50.0	2	50.0	
4–6	14	60.9	9	39.1	
7–10	67	77.9	19	22.1	
Duration hospitalization (days)	30 (2–234)		102 (3–270)		<0.001
Sepsis	184	81.1	43	18.9	0.001
Transient tachypnea of the newborn	173	95.1	9	4.9	<0.001
Respiratory distress syndrome	116	75.3	38	24.7	<0.001
Patent ductus arteriosus	48	64.9	26	35.1	<0.001
Intraventricular hemorrhage	21	53.8	18	46.2	<0.001
Necrotizing enterocolitis	27	56.3	21	43.8	<0.001
Hypothermia	4	80.0	1	20.0	NA
Hypoglycemia	51	82.3	11	17.7	0.303
Seizure	11	57.9	8	42.1	<0.001
Hyperbilirubin	280	89.5	33	10.5	0.001
Polycythemia	7	100.0	0	0.0	NA
Anemia	115	77.2	34	22.8	<0.001
Bronchopulmonary dysplasia	6	60.0	4	40.0	0.014
Blood transfusion	0	0.0	0	0.0	NA
Phototherapy	228	90.5	24	9.5	0.002
Parenteral nutrition	1	100.0	0	0.0	NA
Surfactant given	14	60.9	9	39.1	<0.001
Eye-related information					
Abnormal anterior segment	1	100.0	0	0.0	NA
Cataract	3	100.0	0	0.0	NA
Abnormal fundus	1	1.9	51	98.1	<0.001
ROP zone					<0.001
Zone I	0	0.0	0	0.0	
Zone I–II	0	0.0	0	0.0	
Zone II	1	1.8	54	98.2	
Zone II–III	20	100.0	0	0.0	
Zone III	328	99.7	1	0.3	
Treatment					<0.001
Observe	349	99.7	1	0.3	
Laser indirect ophthalmoscope	0	0.0	51	100.0	
Intravitreal anti-VEGF	0	0.0	3	100.0	

Data are presented as median (interquartile range) or n (%) of patients.
Abbreviations: ROP, retinopathy of prematurity; APGAR, Appearance-Pulse-Grimace-Activity-Respiration; NA, not applicable; VEGF, vascular endothelium growth factors

Table 3 Logistic regression between retinopathy of prematurity occurrence and associated risk factors

	Crude Odds ratio	95%CI	p-value	Adjusted Odds ratio	95%CI	p-value
Gestational age (weeks)						
<30	1			1		
≥30	56.78	19.81–162.77	<0.001	9.25	2.61–32.69	0.001
Birth weight (grams)						
<1,000	184.83	24.41–1,399.58	<0.001	28.56	2.85–286.44	0.004
1,000 – 1,500	16.03	2.08–123.79	0.008	5.33	0.56–51.23	0.147
>1,500	1			1		
1-minute APGAR						
1–3	10.83	5.07–23.17	<0.001	1.89	0.59–6.03	0.284
4–6	2.82	1.27–6.27	0.011	0.41	0.13–1.29	0.126
7–10	1			1		
Sepsis	3.16	1.61–6.19	0.001	1.77	0.63–4.97	0.282
Transient tachypnea of the newborn	0.20	0.10–0.42	<0.001	0.39	0.12–1.27	0.118
Respiratory distress syndrome	4.49	2.43–8.29	<0.001	0.82	0.27–2.54	0.732
Patent ductus arteriosus	5.62	3.05–10.36	<0.001	1.36	0.51–3.64	0.537
Necrotizing enterocolitis	7.37	3.77–14.41	<0.001	2.33	0.81–6.75	0.117
Anemia	3.29	1.83–5.93	<0.001	0.95	0.36–2.51	0.916
Phototherapy	0.41	0.23–0.73	0.003	0.32	0.13–0.81	0.017
Surfactant	4.68	1.92–11.43	0.001	2.31	0.53–10.05	0.265

Abbreviations: CI, confidence interval; APGAR, Appearance-Pulse-Grimace-Activity-Respiration

timing, and screening criteria. According to a nationwide study in the UK, the incidence of ROP in 2011 was 12.6% among infants with a GA <32 weeks and/or BW <1,501 grams [16]. In the US, between 2000 and 2012, the incidence of ROP was reportedly 16.4% among premature infants [17]. In Taiwan, between 2002 and 2011, a 36.6% incidence of ROP was reported among premature infants using the exact definition [18]. In South Korea, an incidence of 31.7% was reported among premature infants with a BW <1,500 grams between 2006 and 2014 [19]. A population-based study uses a national registry database for recruitment. Reports from South Korea, Sweden, and Turkey show the incidence of ROP at around 30% (27.7%–34.1%) [20–23]. In contrast, the incidence was lower in the Netherlands and Switzerland at 21.9% and 9.3%, respectively [24, 25].

In Thailand, various incidences of ROP have been reported. Siriraj Hospital (2010–2019), Songkhla Nakarin Hospital (2004–2006), and Khon Kaen Hospital (2013–2014) reported incidences of 14%, 16%, and 31.7%, respectively [11–13]. When considering only the threshold ROP infants who required treatment, Siriraj Hospital and Songkhla Nakarin Hospital found incidences of 2.1% and 9.5%, respectively. According to previous reports, the incidence declines over time. These research centers, including ours, were found to be similar in that they served as tertiary referral centers. Incidentally, they were in different parts of Thailand. Siriraj Hospital is located in the country's center, while Songkhla Nakarin Hospital and Khon Kaen Hospital are located in the south and northeast, respectively. The incidence of overall ROP in our study was 55/404 (13.6%), and ROP was higher than stage 3 at 41/404 (10.1%), respectively. The incidence of ROP in this study was similar to that reported in previous studies on the Thai population.

Regarding the associated factors in ROP occurrences, previous studies indicate that gestational age and birth weight are significantly related. In this study, GA and BW were found to have a similar association with ROP incidence. The median and mean gestational age at birth were 27 weeks and 26.5+/−2.2 weeks ($p < 0.001$), respectively. The average birth weight in the ROP group was

significantly lower than in the non-ROP group, with a mean of 893.9+/−250.7 grams compared to 1,639.7+/−505.9 grams. In similarity to our research, data from a recent cohort study in Siriraj Hospital undertaken in 2021, which monitored 1,247 infants for ten years, reported an incidence of 14% [14], mean+/−standard deviations in gestational age for ROP cases of 27.2+/−2.2 weeks. The mean birth weights in the threshold and the pre-threshold groups were 775 and 870 grams, respectively. The similarity in results could be due to the study period and referral center being the same for both studies.

The other associated factors of ROP incidence in this study were analyzed using the chi-square test. According to the analysis, the mode of delivery, APGAR score, sepsis, TTNB, RDS, PDA, IVH, NEC, seizure, hyperbilirubinemia, anemia, BPD, phototherapy, duration of hospitalization, and surfactant given were significantly correlated with ROP occurrence ($p < 0.05$). These risk factors, previously reported to be associated with ROP incidence [2–10], are now supported by our data.

The adjusted odds ratio significantly shows that gestational age, birth weight, and phototherapy increase the risk of ROP occurrence in this study. The association between phototherapy and ROP incidence has previously been reported [26, 27]. This present study shows that phototherapy increases the risk of ROP with an adjusted odds ratio of 0.41 (95% CI, 0.17–1.00).

Some previous reports indicate the correlation between ROP occurrences and phototherapy treatment in preterm infants [28, 29]. There is no established mechanism for how light affects ROP etiology. We propose that it might be related to the quantity of bilirubin, a strong antioxidant in newborns [30]. The low level of bilirubin in preterm infants may affect ROP development. The impact of bilirubin levels on the development of ROP has been the subject of debate in earlier publications. Higher levels of bilirubin in neonates may serve as a preventative measure against ROP, according to a recent case-control study [31]. Additionally, ROP is thought to be less severe when bilirubin levels are higher [31]. Dejonge revealed no significant difference in the average duration of phototherapy on ROP development but found an association between ROP development and bilirubin levels instead [32]. The effect of the phototherapy mechanism on ROP occurrences has yet to be proven, and more research is needed to confirm their correlation.

Notably, recent data from our populations revealed a new treatment trend. Intravitreal anti-VEGF injection has been a new option in the aggressive ROP group since its discovery in the treatment of various eye conditions, including ROP problems.

The strength of this study is that it provides an extensive cohort report on other associated risk factors. The limitation of the study is that it is retrospective. A single study center could not have sufficient heterogeneity in ethnic or racial populations. Multi-center research should therefore be conducted to include a wider population.

CONCLUSION

The burden of ROP disease tends to be high. This study shows that the total incidence of total ROP cases is 13.6%. Lower gestational age, low birth weight, and phototherapy increase the risk of developing ROP. Therefore, preparations should be made for personnel and other resources to be ready for the systematic screening and caring of ROP patients, allowing them access to the necessary and appropriate treatment for reducing vision loss in the future. Advanced treatment in the future will reduce morbidities in affected preterm infants.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest in relation to the work presented in the manuscript.

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