Retinopathy of Prematurity Trends in Taiwan: A 10-Year Nationwide Population Study

Eugene Yu-Chuan Kang,[1,2] Reyin Lien,[2,3] Nan-Kai Wang,[1,2,4] Chi-Chun Lai,[1,2] Kuan-Jen Chen,[1,2] Yih-Shiou Hwang,[1,2] Ciao-Ming Lin,[5] Wei-Chi Wu,[1,2] and Kuang-Hung Hsu[5–7]

[1]Department of Ophthalmology, Chang Gung Memorial Hospital, Linkou, Taiwan
[2]Chang Gung University, College of Medicine, Taoyuan, Taiwan
[3]Division of Neonatology, Department of Pediatrics, Chang Gung Memorial Hospital, Linkou, Taiwan
[4]Department of Ophthalmology, Edward S. Harkness Eye Institute, Columbia University, New York, New York, United States
[5]Laboratory for Epidemiology, Department of Health Care Management, Chang Gung University, Taoyuan, Taiwan
[6]Healthy Aging Research Center, Chang Gung University, Taoyuan, Taiwan
[7]Department of Urology, Chang Gung Memorial Hospital, Linkou, Taiwan

Correspondence: Wei-Chi Wu, Department of Ophthalmology, Chang Gung Memorial Hospital, No. 5, Fu-Hsin Road, Taoyuan 333, Taiwan; weichi666@gmail.com.
Kuang-Hung Hsu, Laboratory for Epidemiology, Department of Health Care Management, Chang Gung University, No. 259, Wen-Hwa 1st Road, Kwei-Shan, Taoyuan 333, Taiwan; khsu@mail.cgu.edu.tw.

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Purpose. To investigate the 10-year epidemiology and risk factors of retinopathy of prematurity (ROP) in Taiwan using the National Health Insurance Research Database.

Methods. All premature infants (n = 34,192) from 2002 to 2011 were screened, and those with length of stay (LOS) longer than 28 days who survived after the initial discharge were enrolled (n = 11,180). The annual incidence of ROP and the risk factors associated with it were analyzed.

Results. A total of 4096 ROP infants, 36.6% of premature babies with LOS longer than 28 days, were identified. The numbers of newborns, premature infants, and cases with ROP decreased over time, but the proportion of extremely low birth weight infants increased over time ($P <$ 0.01 for test of trend in number). Also, the proportion of ROP infants receiving treatment increased over time ($P <$ 0.01 for test of trend in number). However, the incidence of ROP was steady throughout the study period. Multivariable analysis revealed that low birth weight, male sex (odds ratio [OR] = 1.12, P = 0.007), and multiparity (OR = 1.17, P = 0.002) were positively associated with ROP, whereas necrotizing enterocolitis (OR = 0.72, P = 0.002) had a negative association with ROP.

Conclusions. The average incidence of ROP from 2002 to 2011 in Taiwan showed no significant change over the 10-year period. Proportion of treatment-requiring ROP increased. Low birth weight, multiparity, and male sex were independent risk factors of ROP.

Keywords: retinopathy of prematurity, nationwide, epidemiology, Taiwan

Retinopathy of prematurity (ROP) is one of the major causes of childhood blindness worldwide and associated with many ocular,[1–4] neurologic, and medical problems.[5] In 2010, there were approximately 32,300 preterm babies worldwide who suffered from long-term visual impairment related to ROP.[6] Also, ROP has resulted in high hospitalization charges of up to USD$192,000 for each case.[7]

Recently, nation-based studies of ROP have been performed in several countries, with different outcomes reported.[7–11] In England, the yearly ROP incidence was 1.28% in 1990 and 12.55% in 2011 in babies born weighing less than 1500 g.[8] In the United States, Lad et al.[7,9] reported that the incidence of ROP was 15.58% in premature infants from 1997 to 2005. In Sweden, a high incidence of ROP of up to 72.7% was found in premature babies with gestational age (GA) less than 27 weeks.[10] In the Netherlands, the reported incidence of ROP in infants with GA less than 32 weeks and/or birth weight (BW) less than 1500 g was 21.9%.[11] The most commonly reported risk factors were BW and GA.[7,12–14] Although some articles using national datasets have been reported, few studies have been conducted in Asian populations.[15–17] Previous ROP studies in Asian populations were also limited by small sample sizes or constrained by specific ranges of BW.[15–17]

The National Health Insurance Research Database (NHIRD) in Taiwan contains extracted claims data from all ambulatory and in-hospital patients. The incidence of ROP and its risk factors has not been explored systematically at the national level in Taiwan. Therefore, the current population-based study was designed to investigate the 10-year trends of ROP incidence cross sectionally and the risk factors of ROP in Taiwan.

Materials and Methods

Data Acquisition

The present study was designed as a retrospective cross-sectional study and was conducted for a 10-year period using data from the NHIRD, which is one of the most comprehensive population-based datasets worldwide and covers 99.9% of the population.[18] The high representativeness of the population in Taiwan has been confirmed.[19] The Ethics Institutional Review Board of Chang Gung Memorial Hospital approved this study

(institutional review board No. 102-1925B), and principles of the Declaration of Helsinki were followed. We analyzed the incidence of ROP in the total population of Taiwan for the period of 10 years, from 2002 to 2011. These data enabled us to adopt a long-term observational approach. To ensure the privacy of all of the participants, all data had been de-identified.

Study Design

The NHIRD consisted of all claims data, including diagnostic codes, represented by the International Classification of Disease, 9th revision, Clinical Modification (ICD-9-CM), demographic information, medical prescriptions, and insurance registry data. The study cohort included all premature infants who were admitted to hospitals from 2002 to 2011 with ICD-9 code 765. Diagnosis of ROP was defined as participants with ICD-9 codes 362.20 or 362.21. ICD-9 codes 765.0 and 765.1 were used to classify the BWs of participants. In addition, we compared multiple variables, including area of birth, family income, neonatal disease, and number of pregnancies, to reveal the associations of ROP. Each claim made by an ophthalmologist containing qualifying ICD-9-CM codes relevant to ROP was screened and classified.

Inclusion and Exclusion Criteria

All premature infants in the 10-year database from 2002 to 2011 were enrolled in this study. Participants were identified as premature babies according to the ICD-9-CM codes. Because ROP develops within the first year after birth, we enrolled patients who had a diagnosis of ROP in the first year after birth. Subjects with abnormal registry claim data, such as unknown sex, inconsistent birth date, or incomplete insurance data, were excluded. We also excluded infants who had lengths of stay (LOS) of 28 days or less and infants who died before discharge in the birth hospital. As most ROP screening examinations were performed 4 weeks after birth[20] and most newborn mortalities in premature infants occurred within the first week after birth,[9] excluding infants with LOS of 28 days or less, could limit the effect of mortality and ensure that the participants were examined in the same hospital. In addition, infants with ROP and longer LOS were mostly treated at teaching hospitals with better assessment and possibly more accurate diagnosis of the ROP.[7] Infants with mortality before discharge were mostly in an unstable condition, and that precludes the detailed assessment of ROP status, such as highest stage of ROP or whether ROP had regression or in progression.

Incidence of ROP and Treatments

The patients with ROP were all premature babies admitted to neonatal intensive care units (NICUs). All of the medical service providers are required to report these medical bills to the National Insurance Bureau. Therefore, we recorded annual cumulative numbers of live births, premature infants, and cases of prematurity with ROP. Furthermore, incidences were calculated and stratified by birth weight, number of pregnancies, and sex.

For understanding the proportion of ROP infants with treatments, which represented the severe ROP group, operative procedures including cryotherapy, laser photocoagulation, intravitreal injection, scleral buckle, and vitrectomy were documented. Because clinical decision of treatments varied between different ophthalmologists, the results were shown as proportion of all treatments in each year during our study period.

Demographics and Risk Factors

Demographic information was obtained from the registry files. Regional distribution was classified into five categories (Taipei, Northern, Central, Southern, and Eastern Taiwan) based on the geographic location in Taiwan. In the NHI, insurance premiums vary based on the income of each household. The subjects were classified into different insurance groups depending on the monthly income of the family. The region and the insurance amount of each participant first indicated in the record were used for the analysis.

Neonatal comorbidities, such as intraventricular hemorrhage, necrotizing enteritis (NEC), sepsis, respiratory distress syndrome (RDS), persistent ductus arteriosus (PDA), and bronchopulmonary dysplasia (BPD), were considered to be risk factors for ROP according to previous studies.[21–25] BW was stratified into different groups to determine the incidence of ROP in different BWs. The mean LOS in the birth hospital and the number of pregnancies were also recorded.

Data Analysis

Descriptive statistics of demographic information were analyzed by using Pearson's χ^2 test and the *t*-test. To determine the relationship between incidence and risk factors, multivariable analyses using logistic regression were performed. For calculating multivariate-adjusted odds ratio of developing ROP, areas, BW, and pregnancy, central area, BW greater than or equal to 2000 g, and singleton were used as reference, respectively. In addition, baseline factors, including sex, insurance area, multiparity, and neonatal comorbidities, were adjusted and corrected for analysis. The 95% confidence intervals (CI) of the multivariate-adjusted odds ratios (OR) were calculated, and the two-sided significance level was set at 0.05. All incident cases from 2002 to 2011 were analyzed simultaneously. The SAS statistical software package, version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all estimations.

Results

Patient Enrollment

In this study, there were 34,192 premature live births recorded from 2002 to 2011 in Taiwan. We included 11,393 patients who had complete data and LOS of 28 days or more, and excluded 213 patients with LOS of 28 days or more and died before being discharged from the birth hospital, yielding a total of 11,180 premature infants for the study. Among these patients, 4096 (36.6%) were diagnosed with ROP and 7084 (63.4%) were not diagnosed with ROP. A flowchart and numbers of the enrollment of the patients are presented in Figure 1 and Supplementary Table S1.

Demographics of the Study Patients

Demographic characteristics, neonatal diseases, BW, LOS, and number of pregnancies in the study cohort were analyzed (Table 1). Although there was a difference in ROP incidence in different areas of Taiwan ($P < 0.001$), sex ($P = 0.180$), and the income of the patient's family ($P = 0.400$) did not affect ROP incidence. With regard to neonatal diseases, the incidence of BPD was higher in the ROP group ($P = 0.010$), whereas NEC was higher in the premature patients without ROP ($P = 0.002$). ROP patients had longer LOS in birth hospitals than cases of prematurity without ROP ($P < 0.001$), and the distribution of BW ($P < 0.001$) and number of offspring were different between the two groups ($P = 0.010$). Lower BW and

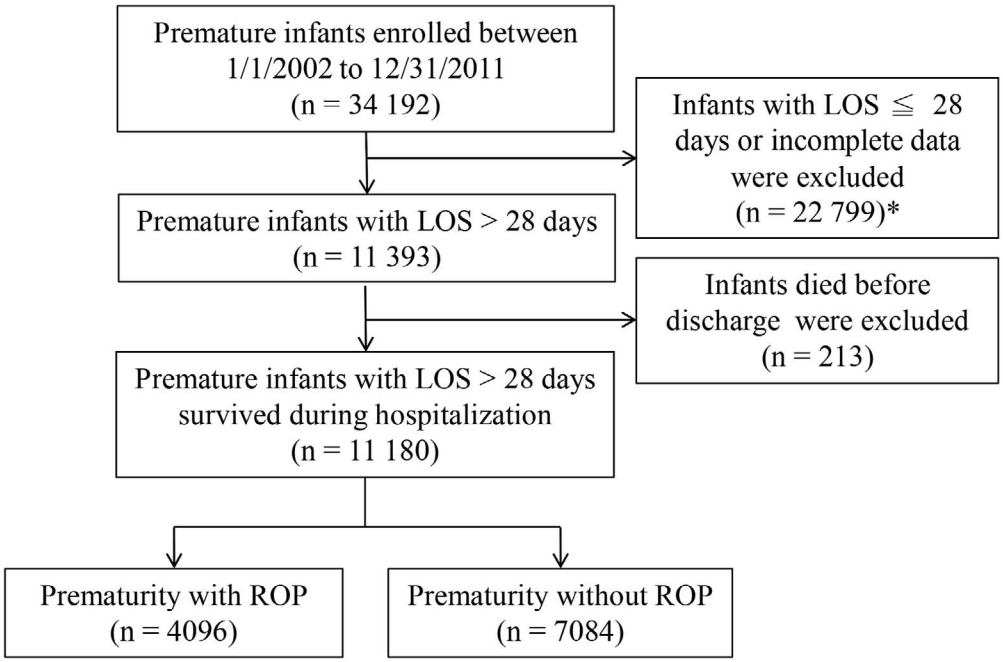

Figure 1. The enrollment of study patients. Premature infants with a LOS longer than 28 days and who survived during hospitalization were enrolled. *Including mortality within 28 days ($n = 759$), LOS $\leq$ 28 days ($n = 18\ 137$), and incomplete data ($n = 3903$).

multiparity were found more frequently in prematurity with ROP.

Incidence of ROP and Treatments in Prematurity with LOS of 28 Days or More

The average incidence of ROP in the current study was 36.6% of premature infants with LOS of 28 days or more. The long-term changes in the incidence of ROP in different groups are shown in Figures 2 and 3. During the 10-year period, ROP incidence was significantly higher in cases of prematurity with lower BW ($P = 0.027$; Fig. 3). In the extremely low birth weight (ELBW) group (i.e., BW < 1000 g)[26] the incidence of ROP in 2011 was higher than in the earlier years (53.8% in 2002, 62.5% in 2007, and 66.7% in 2011, $P < 0.01$ for test of trend in number). The overall incidence of ROP in the study population fluctuated between 31% and 41% during our study period. The actual numbers of cases of prematurity, infants with BW less than 1500 g, infants with BW less than 1000 g, and ROP cases in each category are summarized in Table 2, showing gradual growth in proportions of the very low birth weight (VLBW; i.e., BW < 1500 g)[26] and ELBW groups ($P < 0.01$). Ten-year trend of treatments for ROP is shown in Figure 4. The overall proportion of ROP infants receiving treatment was 6.5%, and it increased significantly from 2.0% of ROP infants in 2002 to 9.3% of ROP infants in 2011 ($P < 0.01$ for test of trend in number).

Multivariable Analysis of Risk Factors

Multivariable logistic regression analyses revealed that male infants had a higher incidence of ROP (OR: 1.12; 95% CI: 1.031–1.207; $P = 0.007$; Table 3). Regarding adjusted risk for different areas compared with central Taiwan, premature infants treated in Taipei (1.51; 1.352–1.682; $P < 0.001$) and southern Taiwan (1.19; 1.065–1.332; $P = 0.002$) were reported to have higher risks of ROP. Compared with infants with BW greater than or equal to 2000 g, premature infants weighing

Table 1. Demographic Information of Study Patients with Prematurity

	Prematurity With ROP ($n = 4096$)	Prematurity Without ROP ($n = 7084$)	*P* Value
Male sex, *N* (%)	2206 (53.9)	3720 (52.5)	0.18
Areas, *N* (%)			
Taipei	1236 (30.2)	1671 (23.6)	<0.001
Northern	746 (18.2)	1434 (20.2)	
Central	961 (23.5)	1920 (27.1)	
Southern	1065 (26.0)	1905 (26.9)	
Eastern	88 (2.1)	154 (2.2)	
Monthly income, *N* (%)*, USD			
≥1447.3	424 (10.4)	677 (9.6)	0.40
720.5–1447.3	1226 (30.0)	2137 (30.2)	
≤720.5	2446 (59.7)	4270 (60.3)	
NEC, *N* (%)	135 (3.3)	321 (4.5)	0.002
Sepsis, *N* (%)	1203 (29.4)	1989 (28.1)	0.15
RDS, *N* (%)	2465 (60.2)	4160 (58.7)	0.13
IVH, *N* (%)	329 (8.0)	499 (7.0)	0.059
PDA, *N* (%)	756 (18.5)	1248 (17.6)	0.28
BPD, *N* (%)	1381 (33.7)	2219 (31.3)	0.010
Birth weight, *N* (%), g			<0.001
≥2000	189 (4.6)	707 (10.0)	
1750–1999	449 (11.0)	1079 (15.2)	
1500–1749	1026 (25.0)	2053 (29.0)	
1250–1499	1118 (27.3)	1841 (26.0)	
1000–1249	782 (19.1)	1025 (14.5)	
750–999	415 (10.1)	316 (4.5)	
≤749	117 (2.9)	63 (0.9)	
LOS, mean (SD), d	52.4 (23.8)	47.0 (19.4)	<0.001
Pregnancy, *N* (%)			
Singleton	3204 (78.2)	5687 (80.3)	0.010
Multiparity	892 (21.8)	1397 (19.7)	

IVH, intraventricular hemorrhage.

* Exchange rate was 1 Taiwan New Dollar to 0.0316 USD based on the mid-market rate on August 21, 2016.

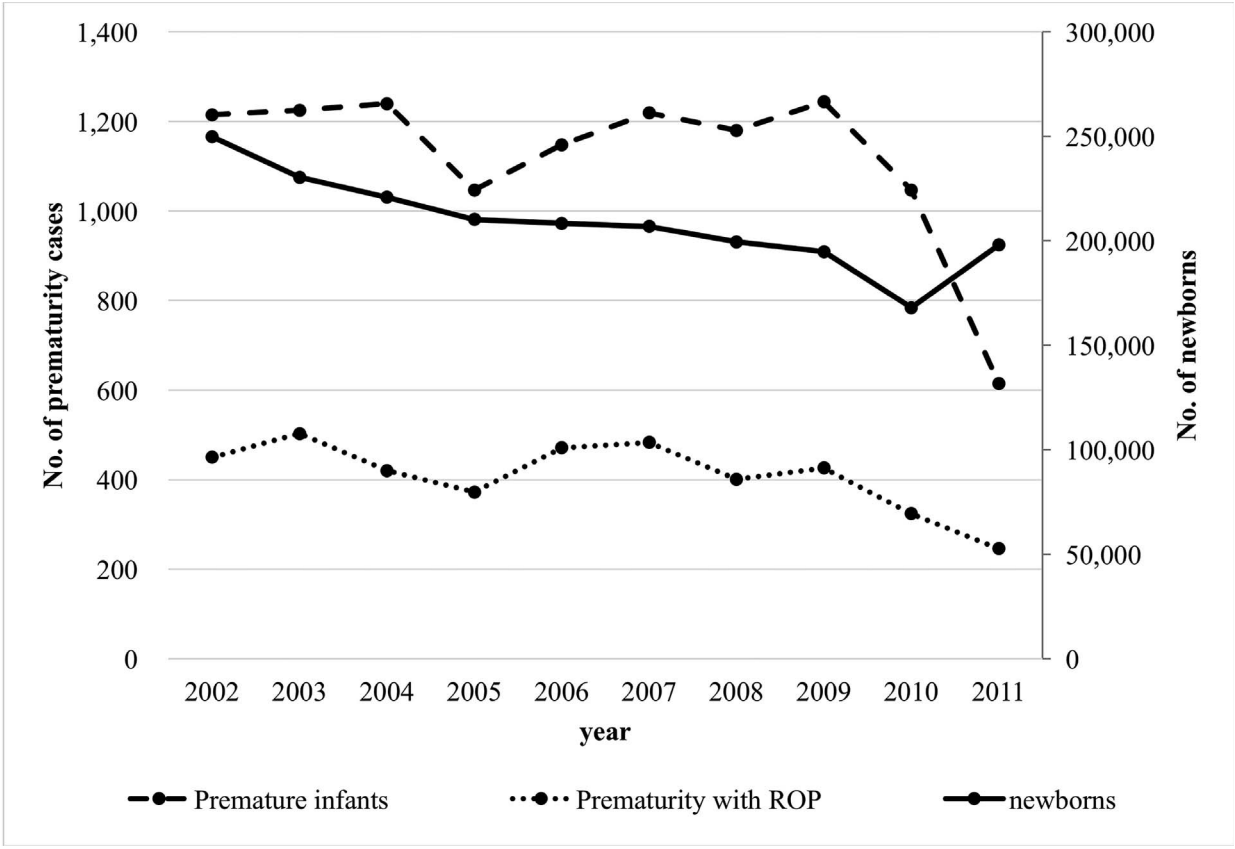

FIGURE 2. Ten-year trend of number of newborns, prematurity, and prematurity with ROP.

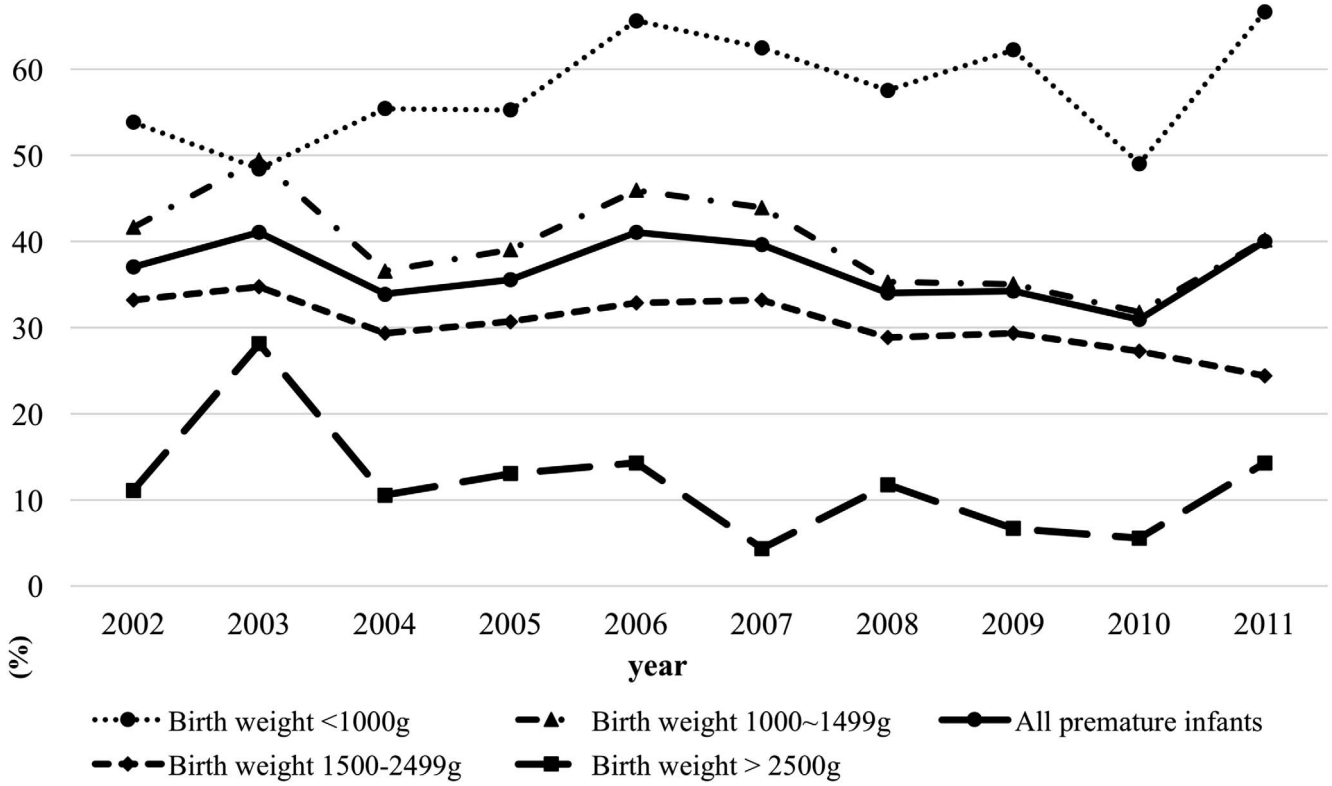

FIGURE 3. Ten-year Trend of ROP incidence by birth weight. $P = 0.027$ interactive effect of birth weight group and time, performed by generalized estimating equations adjusted for sex, insurance area, multiparity, NEC, sepsis, and RDS.

Table 2. Annual Number of Cases of Prematurity with Retinopathy of Prematurity, Very Low Birth Weight Infants, and Extremely Low Birth Weight Infants Among Premature Infants With Length of Stay > 28 Days

Year	Premature Infants, *n*	Prematurity With ROP, *n* (%)	VLBW* Infants, *n* (%)	ELBW† Infants, *n* (%)
2002	1215	450 (37.04)	531 (43.70)	65 (5.35)
2003	1225	503 (41.06)	545 (44.49)	64 (5.22)
2004	1240	420 (33.87)	611 (49.27)	83 (6.69)
2005	1047	372 (35.53)	509 (48.62)	76 (7.26)
2006	1148	471 (41.03)	612 (53.31)	96 (8.36)
2007	1219	483 (39.62)	629 (51.60)	96 (7.88)
2008	1180	401 (33.98)	622 (52.71)	106 (8.98)
2009	1244	426 (34.24)	663 (53.30)	98 (7.88)
2010	1047	324 (30.95)	548 (52.34)	104 (9.93)
2011	615	246 (40.00)	407 (66.18)	123 (20.00)

* VLBW was defined as birth weight < 1500 g.
† ELBW was defined as birth weight < 1000 g.

less than 2000 g showed increased risk of ROP, and the risk grew as BW declined. BW less than 749 g was correlated with the highest risk of ROP (7.17; 5.059–10.172; $P < 0.001$). As for the number of offspring, multiparity was associated with a higher risk of ROP than singleton pregnancies (1.17; 1.062–1.290; $P = 0.002$). None of the neonatal diseases in our study showed a significant association with ROP except for NEC, which had a protective association with ROP (0.72; 0.585–0.889; $P = 0.002$). The results of all premature infants in the study, including infants with LOS of 28 days or less, are presented in the Supplementary Appendix.

Discussion

This study is the first national database analysis examining ROP incidence in Taiwan, and it used the most up-to-date database from 2002 to 2011. Our main findings were that the numbers of premature and ROP patients decreased gradually over the 10 years while the incidence of ROP from 2002 to 2011 in Taiwan remained stationary ($P = 0.486$). This outcome might be related to the decrease in fertility (Fig. 2) and improvements in neonatal care for premature infants in Taiwan. Advances in neonatology and technology in neonatal care have been reported to result in an increased survival rate of premature infants with low BW,[27,28] and therefore, the proportion of cases of prematurity with ELBW increased in the study cohort. In the United States, the incidence of ROP remained the same and the incidence of ELBW increased from 1997 to 2002.[7] In the current study, there was a near 4-fold increase in the percentage of cases of ELBW prematurity in Taiwan during the 10 years (5.3% of prematurity with LOS > 28 days in 2002 and 20% of prematurity with LOS > 28 days in 2011).

The ROP incidence of 36.6% of prematurity with LOS of 28 days or more in our study seemed to be higher than that reported in Western countries (Table 4). A United States–wide study reported a 15.6% ROP incidence in cases of prematurity with LOS of 28 days or more,[9] and a study in England reported a rate of 12.6% among infants with BW less than 1500 g without LOS limitation.[8] According to previous studies, Taiwanese infants were found to have an earlier postmenstrual age for developing various stages of ROP compared with infants in Sweden and in the Early Treatment of Retinopathy of Prematurity study.[10,29] Furthermore, a study has stated that Asian infants had higher rates of developing more severe ROP than white infants.[30] Lang et al.[31] also found that Alaskan natives and Asians had higher incidence rates of threshold ROP. These data suggest an ethnic difference in ROP development. We only enrolled infants with LOS of 28 days or more for the aforementioned reasons. This criterion might have excluded some premature infants with milder illness who underwent ROP screening after discharge from the hospital before 28 days. Although the inclusion criteria might have caused a selection difference in ROP incidence, our incidence of ROP was still higher than that in the United States–wide study[9] and a New York study (20.3% among infants with BW < 1500 g),[13] both of which used LOS of 28 days or more as an inclusion criterion.

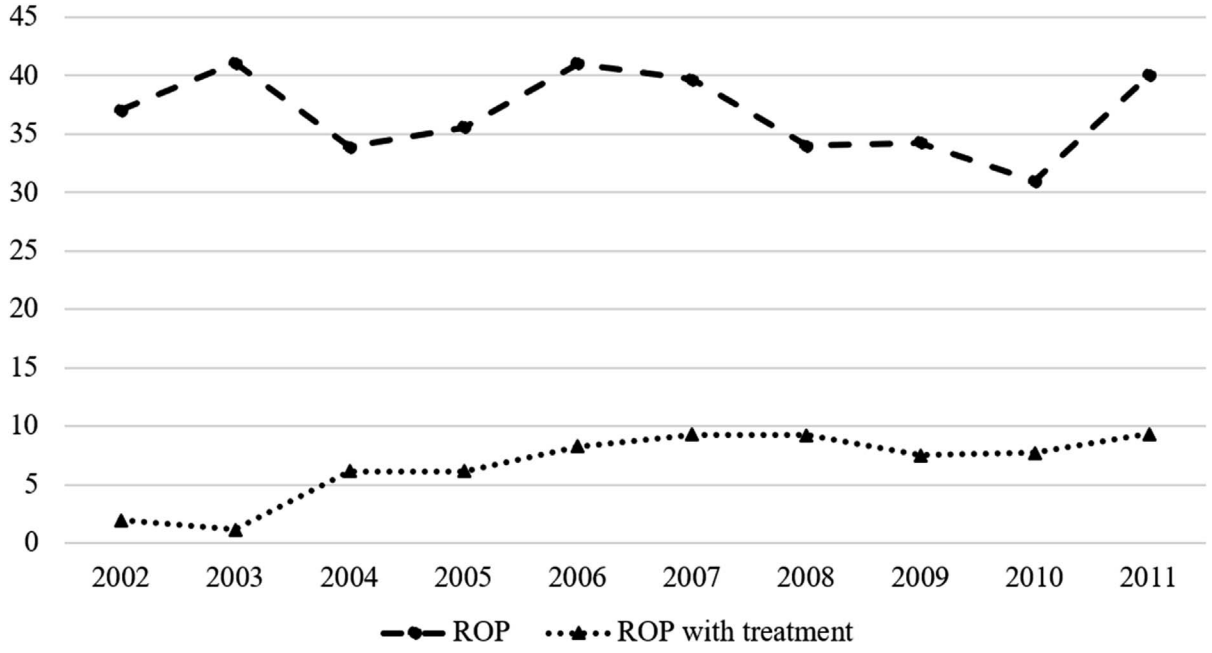

Figure 4. Ten-year trend of incidence of ROP and proportion of ROP with treatment. $P < 0.01$ for test of trend.

Table 3. Multivariate-Adjusted Odds Ratio of Factors Associated with Retinopathy of Prematurity Among Premature Infants with Length of Stay > 28 days

Independent Variable	Number of Infants	Number of ROP Cases (%)	Unadjusted OR	Adjusted OR	95% CI	*P* Value
Sex						
Male	5926	2206 (37.2)	1.06	1.12	1.031–1.207	0.007
Areas						
Taipei*	2907	1236 (42.5)	1.48†	1.51	1.352–1.682	<0.001
Northern Taiwan*	2180	746 (34.2)	1.04	1.05	0.933–1.187	0.41
Southern Taiwan*	2970	1065 (35.9)	1.12†	1.19	1.065–1.332	0.002
Eastern Taiwan*	242	88 (36.4)	1.14	1.16	0.879–1.536	0.29
Birth weight						
1750–1999 g‡	1528	449 (29.4)	1.56†	1.53	1.261–1.865	<0.001
1500–1749 g‡	3079	1026 (33.3)	1.87†	1.85	1.545–2.208	<0.001
1250–1499 g‡	2959	1118 (37.8)	2.27†	2.23	1.863–2.664	<0.001
1000–1249 g‡	1807	782 (43.3)	2.85†	2.88	2.389–3.478	<0.001
750–999 g‡	731	415 (56.8)	4.91†	5.03	4.038–6.274	<0.001
≤749 g‡	180	117 (65.0)	6.95†	7.17	5.059–10.172	<0.001
Pregnancy						
Multiparity§	2289	892 (39.0)	1.13†	1.17	1.062–1.290	0.002
Risk factor						
NEC	456	135 (29.6)	0.72†	0.72	0.585–0.889	0.002
Sepsis	3192	1203 (37.7)	1.07†	1.07	0.978–1.168	0.14
RDS	6625	2465 (37.2)	1.06†	0.93	0.860–1.014	0.10

* Adjusted odds ratios for areas are compared with the reference category of central area.
† *P* value < 0.15.
‡ Adjusted odds ratios for birth weights are compared with the reference category of BW ≥ 2000 g.
§ Adjusted odds ratios for pregnancy are compared with the reference category of singleton.

An increased trend of ROP receiving operative interventions was also observed during the 10-year period (overall 6.5% of ROP patients, 2.0% in 2002 and 9.3% in 2011; overall 4.0% of premature infants with BW < 1500 g [data not shown]). Comparing with several investigations including the one in Northern Ireland (overall 3.96% of infants with BW < 1501 g or GA < 32 weeks)[32] and the other one in Scotland (overall 4.4% of infants with BW < 1500 g or GA < 32 weeks),[33] the incidence of ROP requiring treatment in premature newborns in the current study was similar to their outcomes. The increased trend of ROP requiring treatment may be related to increased proportion of premature infants with lower BW, especially those with ELBW.

Regarding to BW in ROP, which was the most commonly reported factor associated with the disease,[7,13,34–36] there were 13% of ROP infants with BW less than 1000 g in our study cohort. On the other hand, ROP infants with BW less than 1000 g accounted for 50% and 63% of ROP cases in the United States–wide study[9] and the New York study,[13] respectively. This finding indicated that the majority of ROP infants in Taiwan had higher BW than those in the United States. Although ethnic difference could affect ROP development, this sole factor was unable to explain why these patients developed ROP even with high BW. Because the development of ROP is closely linked to care for premature babies, it is likely that care for premature babies remains suboptimal in Taiwan, such as the use of higher oxygen saturation targets during the neonatal period.[29] Hence, we advocate following published guidelines, such as the World Health Organization recommendation in 2015,[37] for perinatal or neonatal care, to decrease risks of ROP development.

In the present study, BW was highly associated with ROP. There were stepwise increases in the risk of ROP with lower BW (OR: 1.53 in group with 1750–1999 g; 7.17 in group with BW ≤ 749 g). However, ROP in infants with BW greater than 2500 g was still found in our study. Although the annual incidence of ROP in infants with BW greater than 2500 g ranged from 4% to 28% in the patient group, the total number of infants with BW greater than 2500 g was relatively small (*n* < 10 each year). Such low number of incidents could contribute to the high variation of ROP incidence in this group of patients. From the previous study in our hospital between 1981 and 2008, 3060 g was the highest BW reported among cases of prematurity with ROP[38] and this emphasizes the importance of screening guidelines that meet the needs of individual countries. The current national screening criteria in

Table 4. Nationwide Studies of Retinopathy of Prematurity Published in the Last 10 Years

	England[8]	United States[9]	Sweden[10]	Netherlands[11]	Present Study
Population	BW < 1500 g	Prematurity With LOS > 28 d	GA < 27 wk	BW < 1500 g or GA < 32 wk	Prematurity With LOS > 28 d
Years	1990–2011	1997–2005	2004–2007	2009	2002–2011
ROP, *n*	NA	58,722	368	302	4096
ROP incidence	1.3% in 1990 12.6% in 2011	15.6%	73%	21.9%	36.6%
Yearly change	Increased	Steady	NA	NA	Steady
Risk factors	NA	BW, Hispanic, RDS, IVH	GA, BW	GA, BW, iNO, NICU stay, ventilation	BW, multiparity, male

NA, not available; iNO, inhaled nitric oxide.

Taiwan based on the policy stated by American Academy of Pediatrics Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, and American Association of certified Orthoptists in 2013.[39] We suggest to screen premature babies with BW over 1500 g for ROP in Taiwan if they have unstable or complicated clinical course judged by the pediatricians or neonatologists because these babies could still develop ROP based on this and prior studies,[38] though the incidence was low.

In addition to BW, male infant and multiparity were independent risk factors for ROP in premature infants with LOS of 28 days or greater. ROP has been reported more frequently in male infants since 1949,[40] and severe ROP has been reported to be associated with male sex.[41,42] Different angiogenic or hormonal factors have been suggested as possible explanations.[43,44] As for multiple pregnancies, it is closely associated with assisted reproductive technology and a well-known risk factor for preterm labor.[45,46] Compared with babies born from single pregnancies, those born from multiple-birth pregnancies were prone to having lower BW[47] and a higher incidence neurologic disorders, such as cerebral palsy.[48] In contrast with a previous study that found no association between multiple births and ROP,[49] our study indicated a small, but significant, elevation of ROP incidence in the multiparity group. As the reproductive technology advanced for patients with infertility or advanced maternal age, multiple pregnancies could become a crucial risk factor for ROP development. In the population of all prematurity, sepsis, and RDS were additionally found as independent risk factors of ROP development. The comorbidities have been identified previously and may be related to prolonged oxygen exposure and systemic inflammatory response.[9,50,51] Our national database study has the strength to detect the association of ROP with above factors, but it could not provide insights into the mechanisms or molecular events of such association. We still need more in vitro or in vivo researches to find out the underlying mechanisms associated with such phenomenon.

NEC was found to be protective against the development of ROP (OR: 0.72; 95% CI: 0.585–0.889; $P = 0.002$) in all premature infants and premature infants with LOS of 28 days or more. NEC was also reported to be protective against developing ROP in some US studies,[7,9,50] but the results were considered paradoxical. According to the BOOST II group's report in 2013, lower target of oxygen saturation for prematurity was associated with an increased rate of NEC and a reduced rate of ROP.[52] Therefore, the presence of NEC is associated with the lower incidence of ROP. The level of oxygen saturation may be the main factor that affects the interpretation of the result.

In the current study, we found a regional difference in ROP incidence on multivariate analysis. Taipei is the capital city of Taiwan, and it has the best medical resources. The Southern area, including Tainan and Kaohsiung, also has considerable medical resources. Among the 25 medical centers in Taiwan, nine medical centers are located in Taipei and six in southern Taiwan, and all of them are equipped with comprehensive facilities for intensive care for neonates.[53] Pregnant women at high risk for preterm labor or premature infants with serious medical problems are usually transferred to medical centers in these areas, which might have increased the number of cases of ROP reported in Taipei and southern Taiwan.

This study had several limitations. First, the diseases in the study were identified by ICD-9-CM codes, and additional disease details, such as severity of ROP, were not provided by NHIRD. The NHIRD has been validated for some diseases, such as diabetes, acute myocardial infarction, and acute ischemic stroke.[54–56] Accuracy of birth registry in Taiwan was also validated.[57] Those studies all indicated a high reliability of the NHIRD, though validation for ROP in the NHIRD has not been done yet. Because ROP is a serious disease associated with prematurity and the medical cost is high, almost all reimbursements for treating ROP are claimed by the NHI. Therefore, ROP data from NHIRD assumed to be reliable. Second, we were unable to obtain information about the GA of the participants. The disease classification used in the NHIRD is based on the 1992 ICD-9-CM codes before 2006 and the 2001 ICD-9-CM codes after 2006. There was no subcategory for GA in the two versions of ICD-9-CM codes. Hence, the epidemiology of GA and ROP in Taiwan may need further large-scale investigation. Third, the participants' personal information and information regarding family histories were not available because NHIRD encrypted all personal links and cases of consanguinity. In addition, time sequence of medical events and ROP occurrence was not available, because the ICD-9 code was identified as discharge diagnosis. This precluded us from analyzing the association between ROP and the comorbidities in detail. Forth, there was a lack of information about therapeutic oxygen levels, which have been reported to be crucial for the potential risk of developing ROP.[11] This factor may also be associated the neonatal comorbidities and the severity of ROP, which we were unable to clearly clarify it. Fifth, information related to the referral cases was not available, which may have affected the outcome that some areas were found to have higher ORs of ROP. Last, we excluded patients with LOS of 28 days or less to ascertain that participants received ROP screening in their birth hospital. This may affect our interpretation of the results. However, the significant factors identified in premature infants with LOS of 28 days or more remained significant in the analysis of entire group (Supplementary Table S4). There were some advantages of the study. First, this was a population-based study with a large number of study participants. Second, the number of missing data from these babies should be very low because the treatment costs and risks were so high in these patients, all of whom were admitted and treated in hospitals equipped with NICUs. Our findings should provide reliable information related to ROP, and therefore may be of value for understanding the epidemiology of ROP in Taiwan.

In conclusion, this study is the first nationwide study reporting 10-year changes in ROP incidence in Taiwan and the East Asia. We found that the numbers of newborns and premature babies decreased from 2002 to 2011, but the overall incidence of ROP of prematurity with LOS of 28 days or more was unchanged (36.6% on average, ranging from 31%–41%). This incidence of ELBW and proportion of ROP infants with treatments increased over the 10-year study period. This outcome might be related to the decrease in fertility and improvements in prenatal care for premature infants in Taiwan. Birth weight, multiple pregnancies, and male sex were found to be major independent risk factors for ROP. Further investigations to improve care for premature infants to reduce the incidence of ROP, especially ROP in larger babies, are needed.

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