Risk Factors for Retinopathy of Prematurity in Extremely Preterm Chinese Infants

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Abstract: To investigate the incidence and risk factors of retinopathy of prematurity (ROP) and Type 1 ROP in extremely preterm Chinese infants.

A retrospective review of medical records was performed of all extremely preterm neonates (gestational age, GA ≤ 28 weeks) screened for ROP from 2007 to 2012 at an ophthalmology centre in Hong Kong. Thirty-three maternal and neonatal covariates were analyzed using univariate and multivariate regression analyses for both ROP and Type 1 ROP.

The mean gestational age (GA) was 26.4 ± 1.3 weeks and the birth weight (BW) was 855.0 ± 199.0 g. The incidence of ROP development was 60.7% and 16.2% for Type 1 ROP. On univariate analysis, 6 risk factors were identified for ROP development including: lighter BW; lower GA; postnatal hypotension; inotrope use; surfactant use; and invasive mechanical ventilation (all $P \leq 0.01$). On multivariate analysis, neonatal congenital heart disease and greater GA were protective factors for ROP development ($P \leq 0.04$). On the other hand, 4 risk factors were associated with Type 1 ROP development in univariate analysis, including: lower GA, lighter BW, multiple pregnancies, and invasive mechanical ventilation (all $P \leq 0.02$); while there was no significant risk factors on multivariate analysis.

A lighter BW and lower GA were the only common independent risk factors for both ROP and Type 1 ROP while neonatal congenital heart disease and greater GA were the protective factors against ROP.

Abbreviations: ANS = antenatal steroid, BW = birth weight, CRYO-ROP = Cryotherapy for retinopathy of prematurity, ETROP = early treatment for retinopathy of prematurity, GA = gestational age, GDM = gestational diabetes mellitus, IVF = in vitro fertilization, IVH = intraventricular hemorrhage, NEC = necrotizing enterocolitis, NICU = neonatal intensive care units, NNJ = neonatal jaundice phototherapy, NSAID = non-steroidal anti-inflammatory agents, PDA = patent ductus arteriosus, PET = pre-eclampsia, RDS = respiratory distress syndrome, ROP = retinopathy of prematurity, TPN = total parental nutrition.

INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative disease of the developing retina, most vulnerable to low birth weight, pre-term neonates.[1] ROP has emerged as one of the leading causes of childhood blindness in developed nations.[2] With advancement and modernization in neonatal intensive care units, the increased survival rates for extremely preterm infants (gestational age, GA ≤ 28 weeks), has increased over the past decades.[3–10] The aim of this study was to determine the incidence and risk factors of ROP development and Type 1 ROP in extremely preterm Chinese infants.

PATIENTS AND METHODS

The study was approved by the Institutional Review Board of the Hospital Authority of Hong Kong. The study was conducted in accordance with the Declaration of Helsinki and no patient personal data were disclosed in the study. The authors declare no financial or proprietary interests.

This was a retrospective study conducted at pediatric ophthalmic unit of Caritas Medical Centre, Hong Kong Special Administrative Region, China, which provides pediatric ophthalmological service to 2 local Neonatal Intensive Care Units (NICU) at Princess Margaret Hospital and Kwong Wah Hospital, for a population of 1.8 million.

Medical records for consecutive subjects screened for ROP between the period of January 2007 and December 2012 were retrieved using the Clinical Data Record System of the Hospital Authority of Hong Kong.

ROP Screening Criterion

All preterm babies admitted to these 2 NICU's with a birth weight (BW) ≤ 1500 g and/or gestational age (GA) ≤ 32 weeks were referred to a pediatric ophthalmologist for evaluation. All eligible preterms were examined according to the screening protocol recommended by the Royal College of Ophthalmologists and United Kingdom-ROP (UK-ROP) guidelines.[11,12] Subjects were first screened at 4 to 8 weeks of postnatal age (≥30 week GA) and were examined weekly to bi-weekly, until retinal vascularization reached zone 3 or feature of established ROP regression.[12] As all pre-terms were in-patients, a close liaison between the attending neonatologist and pediatric ophthalmologist prevented any missed cases. Treatment was diode laser was implemented when the disease progressed to Type 1 ROP as per the early treatment for retinopathy of prematurity (ETROP) study.[13] The staging of ROP was recorded according to the revised International Classification of ROP, including the extent, zone, and presence or absence of "plus" disease.[14] Type 1 ROP was defined as high risk pre-threshold ROP, with either one of the following features: (i) Zone I, any stage ROP with plus disease (≥2 quadrant involvement as per the ETROP study); (ii) Zone I, Stage 3 ROP with or without plus disease; or; (iii) Zone II, stage 2 or 3 ROP with plus disease.[13]

All examinations were performed by 3 experienced pediatric ophthalmologists (SKY, TYT, CYC). Each infant was screened by an indirect ophthalmoscope using a 30-dioptre (D) lens after full pharmacological pupil dilatation with tropicamide 0.5% and phenylephrine 1% eye drops. A lid speculum with scleral indentation after topical anesthesia (amethocaine) was routinely used. All screening was performed under oxygen saturation monitoring and the screening was temporarily withheld in case of desaturations.

The inclusion criteria included all extremely preterm subjects with GA ≤ 28 weeks that received ROP screening. In infants where the diagnosis of ROP could neither be confirmed nor ruled out either due to premature death or insufficient clinical information were excluded. The primary outcome measures included: the severity of ROP (the extent, zone, and presence or absence of "plus" disease) as well as the 33 risk factors (both maternal and neonatal) for the development of ROP as follows:

Antenatal maternal risk factors: (Table 1)

- Maternal diseases: pre-eclampsia (PET), gestational diabetes mellitus (GDM), order of pregnancy (singleton or multiple gestations).

TABLE 1. Univariate and Multivariate Analysis of Maternal and Natal Covariates for ROP Development in Extremely Preterm Infants

Covariates	Univariate Logistic Analysis					Multivariate Logistic Analysis				
	P-Value	Coefficient Estimates	Odds Ratio	95% Confidence Interval		*P*-Value	Coefficient Estimates	Odds Ratio	95% Confidence Interval	
Gender	0.73	−0.14	0.87	0.40	1.90	Excluded from multivariate logistic analysis				
Gestational age	<0.001[#,*]	−1.08	0.34	0.21	0.51	<0.001[#,*]	−0.95	0.39	0.22	0.64
Birth weight	<0.001[#,*]	0.00	1.00	0.99	1.00	0.63	0.00	1.00	1.00	1.00
Multiple pregnancies	0.78	0.15	1.16	0.40	3.77	Excluded from multivariate logistic analysis				
Pre-eclampsia	0.26	−0.66	0.51	0.16	1.65	Excluded from multivariate logistic analysis				
Gestational diabetes mellitus	0.34	−0.88	0.42	0.05	2.60	Excluded from multivariate logistic analysis				
In vitro fertilization	0.54	0.51	1.67	0.34	12.00	Excluded from multivariate logistic analysis				
Postnatal hypotension	<0.001[#,*]	1.30	3.66	1.66	8.45	0.28	0.57	1.77	0.63	5.05
Inotrope use	0.03[#,*]	0.90	2.47	1.10	5.80	Excluded from multivariate logistic analysis				
Antenatal steroid use	0.39	−0.40	0.67	0.25	1.67	Excluded from multivariate logistic analysis				
Apgar score 1 min	0.04[#,*]	−0.21	0.81	0.65	0.99	Excluded from multivariate logistic analysis				
Apgar score 5 min	0.29	−0.11	0.89	0.71	1.10	Excluded from multivariate logistic analysis				
Apgar score 10 min	0.55	−0.09	0.92	0.67	1.22	Excluded from multivariate logistic analysis				
Respiratory distress syndrome	0.76	0.44	1.56	0.06	40.00	Excluded from multivariate logistic analysis				
Bronchopulmonary dysplasia	0.11	0.62	1.86	0.88	4.02	Excluded from multivariate logistic analysis				
Surfactant use	<0.001[#,*]	1.49	4.42	1.69	12.64	0.12	0.93	2.54	0.81	8.50
Invasive mechanical ventilation	0.02[#,*]	1.23	3.40	1.19	10.62	Excluded from multivariate logistic analysis				
Oxygen supplement	<0.001[*]	NA	NA	1.00	1.00	Excluded from multivariate logistic analysis				
Mean oxygen concentration (%)	<0.001[*]	0.00	1.00	1.00	1.00	Excluded from multivariate logistic analysis				
Congenital heart disease	<0.001[*]	0.00	1.00	1.00	1.00	0.04[#,*]	−1.20	0.30	0.09	0.92
Patent ductus arteriosus	<0.001[*]	0.00	1.00	1.00	1.00	Excluded from multivariate logistic analysis				
NSAID use	<0.001[*]	0.00	1.00	1.00	1.00	0.42	0.48	1.61	0.51	5.34
Anemia	<0.001[*]	0.00	1.00	1.00	1.00	Excluded from multivariate logistic analysis				
Thrombocytopenia	<0.001[*]	0.00	1.00	1.00	1.00	Excluded from multivariate logistic analysis				
Blood transfusion	<0.001[*]	0.00	1.00	1.00	1.00	Excluded from multivariate logistic analysis				
Intraventricular hemorrhage	<0.001[*]	0.00	1.00	1.00	1.00	Excluded from multivariate logistic analysis				
Nectrotizing colitis	<0.001[*]	0.00	1.00	1.00	1.00	Excluded from multivariate logistic analysis				
Neonatal jaundice	<0.001[*]	0.00	1.00	1.00	1.00	Excluded from multivariate logistic analysis				
Phototherapy	<0.001[*]	0.00	1.00	1.00	1.00	Excluded from multivariate logistic analysis				
Total parental nutrition	<0.001[*]	0.00	1.00	1.00	1.00	Excluded from multivariate logistic analysis				
Hypoglycemia	<0.001[*]	0.00	1.00	1.00	1.00	Excluded from multivariate logistic analysis				
Sepsis	<0.001[*]	0.00	1.00	1.00	1.00	0.19	0.64	1.90	0.73	5.06
Meningitis	<0.001[*]	0.00	1.00	1.00	1.00	Excluded from multivariate logistic analysis				

[*] Statistically significant.
[#] Clinically significant.

- In vitro fertilization (IVF).
- Use of antenatal steroid (ANS).

     Neonatal risk factors: (Table 1)

- Demographic information (GA, BW, gender).
- Apgar scores at 1, 5, and 10 minutes.
- Postnatal interventions: surfactant administration; mechanical ventilation; use of supplementary oxygen; maintenance supplementary oxygen concentration (mean oxygen concentration); use of non-steroidal anti-inflammatory agents (NSAID) for patent ductus arteriosus (PDA) closure; blood transfusion; and total parental nutrition (TPN).
- Neonatal diseases: respiratory distress syndrome (RDS); bronchopulmonary dysplasia; hypotension; congenital heart disease; PDA; anemia (defined as hemoglobin <110 g/L, hematocrit <25%); thrombocytopenia; neonatal jaundice (NNJ), phototherapy, intraventricular hemorrhage (IVH); necrotizing enterocolitis (NEC); hypoglycemia; sepsis (culture positive or use antibiotics for more than 7 days); and meningitis.

Statistics

     To eliminate the duplication of data from multiple pregnancies, only 1 subject in cases of multiple pregnancies, were randomized (by card shuffling) for inclusion in the statistical analysis. The correlation of the 33 covariates with the development of ROP and Type 1 ROP were analyzed separately using univariate and multiple logistic regression analyses. Univariate correlation between the covariates and ROP development was analyzed using logistic regression and linear regression for categorical and continuous variables, respectively. For multiple logistic regressions, covariates with zero estimate of coefficients were excluded. Variable selection by elastic net method was used to select out redundant covariates to address the high collinearity of the sample. Correlations were expressed in coefficients and odds ratio (OR) and a *P*-value less than 0.05 was considered as statistically significant. All means were expressed as mean ± standard deviation.

RESULTS

     During the study period, a total of 612 preterm infants were screened. Out of the 612 infants that received screening, 139 (22.7%) met the inclusion criteria of extremely preterm (GA ≤ 28 weeks). The diagnosis of ROP could neither be established nor ruled out in 9 (6.5%) subjects since 5 (3.6%) were deceased and 4 (2.9%) had insufficient clinical information. Twenty-six infants belonged to multiple pregnancies and 1 infant from each multiple pregnancy was randomized for inclusion in the study. The remaining 117 eligible extreme preterm infants were included for analysis (Figure 1).

Demographics

     Of the 117 infants included in the study, all were of Chinese ethnicity. There were 76 male (65.0%) and 41 female (35.0%) subjects. The mean GA at birth was 26.4 ± 1.3 weeks (range: 23.4–28.0 weeks) and the mean BW was 855.0 ± 199.0 g (range: 445–1535 g). The majority (104/117) were singletons (88.9%), 12 were twins (10.3%), and 1 were triplets (0.9%). ROP in any stage developed in 71 infants (60.7%) and Type 1 ROP developed in 19 infants (16.2%).
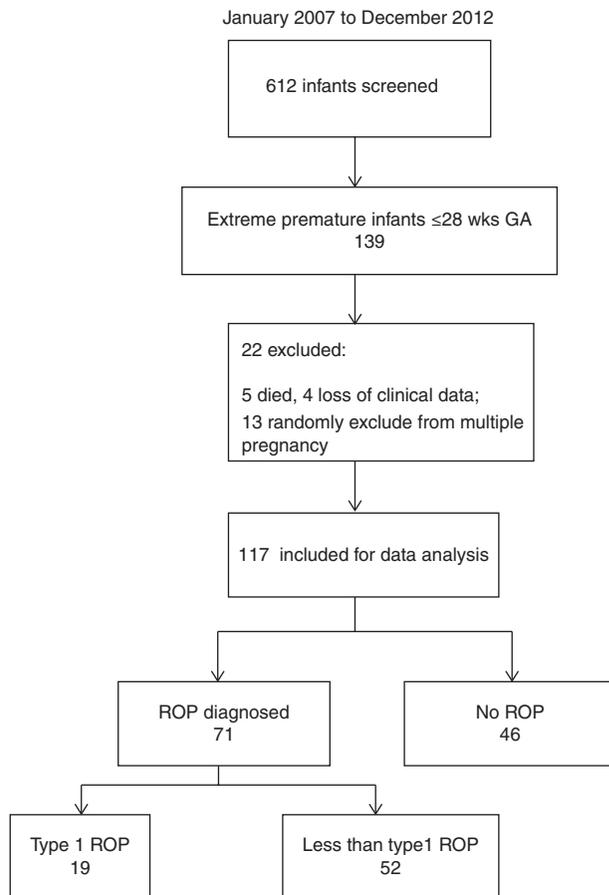
January 2007 to December 2012

FIGURE 1. Schematic diagram of the distribution of extremely preterm infants.

     Out of 117 extremely preterm infants, 68 of them had GA ≤ 27 weeks and the incidence of Type I ROP in infants ≤27 weeks was 27.9%. In our study, no infants with a BW greater than 900 g and a GA more than 27 weeks developed Type 1 ROP requiring treatment.

Risk Factor Analysis for ROP

     Using univariate analysis, the following were significant risk factors for ROP development: lighter BW; lower GA; postnatal hypotension; inotrope use; surfactant use; lower Apgar score at 1 minute; and surfactant use (all *P* ≤ 0.02) (Table 1).

     The following covariates were also significantly associated with ROP on a statistical level (all *P* ≤ 0.01) but as the OR = 1.00, there was no clinical significance of these covariates as predictors of ROP: oxygen supplement; higher mean oxygen concentration; congenital heart disease; presence of PDA; NSAID use; anemia; thrombocytopenia; blood transfusion; IVH; NEC; NNJ; phototherapy; TPN; hypoglycemia; sepsis; and meningitis.

     Using multivariate logistic analysis, the presence of congenital heart disease and a greater GA were protective factors against ROP development (Table 1). All the congenital heart diseases were non-cyanotic (ventricular septal defects or arterial septal defects).

TABLE 2. Univariate and Multivariate Analysis of Maternal and Natal Covariates for Type 1 ROP Development in Extremely Preterm Infants

Covariates	Univariate Logistic Analysis					Multivariate Logistic Analysis				
	P-Value	Coefficient Estimates	Odds Ratio	95% Confidence Interval		*P*-Value	Coefficient Estimates	Odds Ratio	95% Confidence Interval	
Gender	0.37	−0.49	0.62	0.19	1.76	1.00	−30.18	0.00	0.00	Infinity
Gestational age	<0.001[#],[*]	−1.46	0.23	0.11	0.42	1.00	−74.78	0.00	0.00	Infinity
Birth weight	<0.001[#],[*]	−0.01	0.99	0.99	1.00	1.00	−0.27	0.76	0.00	Infinity
Multiple pregnancies	0.02[#],[*]	1.40	4.05	1.28	13.14	1.00	146.70	Infinity	0.00	Infinity
Pre-eclampsia	0.34	−0.92	0.40	0.02	2.22	Excluded from multivariate logistic analysis				
Gestational diabetes mellitus	0.18	−15.98	0.00	NA	Infinity	1.00	85.33	Infinity	0.00	Infinity
In vitro fertilization	0.08	1.48	4.41	0.81	21.87	1.00	47.28	Infinity	0.00	Infinity
Postnatal hypotension	0.20	0.65	1.91	0.71	5.34	1.00	−344.30	0.00	0.00	Infinity
Inotrope use	0.10	0.83	2.29	0.84	6.32	1.00	265.30	Infinity	0.00	Infinity
Antenatal steroid use	0.97	0.02	1.02	0.33	3.87	Excluded from multivariate logistic analysis				
Apgar score 1 min	0.13	−0.19	0.82	0.64	1.06	Excluded from multivariate logistic analysis				
Apgar score 5 min	0.36	−0.12	0.89	0.69	1.16	Excluded from multivariate logistic analysis				
Apgar score 10 min	0.24	−0.20	0.82	0.59	1.16	1.00	−30.64	0.00	0.00	Infinity
Respiratory distress syndrome	0.40	14.95	3,097,665.00	0.00	NA	Excluded from multivariate logistic analysis				
Bronchopulmonary dysplasia	0.10	0.83	2.29	0.85	6.61	Excluded from multivariate logistic analysis				
Surfactant use	0.06	1.59	4.91	0.93	90.84	Excluded from multivariate logistic analysis				
Invasive mechanical ventilation	0.01[#],[*]	17.12	27,127,490.00	0.00	NA	1.00	105.40	Infinity	0.00	Infinity
Oxygen supplement	<0.001[*]	NA	NA	1.00	1.00	Excluded from multivariate logistic analysis				
Mean oxygen concentration (%)	<0.001[*]	0.00	1.00	1.00	1.00	Excluded from multivariate logistic analysis				
Congenital heart disease	<0.001[*]	0.00	1.00	1.00	1.00	1.00	19.28	235,515,500.00	0.00	Infinity
Patent ductus arteriosus	<0.001[*]	0.00	1.00	1.00	1.00	Excluded from multivariate logistic analysis				
NSAID use	<0.001[*]	0.00	1.00	1.00	1.00	1.00	117.00	Infinity	0.00	Infinity
Anemia	<0.001[*]	0.00	1.00	1.00	1.00	1.00	−343.60	0.00	0.00	Infinity
Thrombocytopenia	<0.001[*]	0.00	1.00	1.00	1.00	1.00	−83.88	0.00	0.00	Infinity
Blood transfusion	<0.001[*]	0.00	1.00	1.00	1.00	1.00	345.30	Infinity	0.00	Infinity
Intraventricular hemorrhage	<0.001[*]	0.00	1.00	1.00	1.00	1.00	−144.70	0.00	0.00	Infinity
Nectrotizing colitis	<0.001[*]	0.00	1.00	1.00	1.00	Excluded from multivariate logistic analysis				
Neonatal jaundice	<0.001[*]	0.00	1.00	1.00	1.00	1.00	−109.20	0.00	0.00	Infinity
Phototherapy	<0.001[*]	0.00	1.00	1.00	1.00	NA	NA	NA	NA	NA
Total parental nutrition	<0.001[*]	0.00	1.00	1.00	1.00	Excluded from multivariate logistic analysis				
Hypoglycemia	<0.001[*]	0.00	1.00	1.00	1.00	1.00	119.10	Infinity	0.00	Infinity
Sepsis	<0.001[*]	0.00	1.00	1.00	1.00	1.00	156.50	Infinity	0.00	Infinity
Meningitis	<0.001[*]	0.00	1.00	1.00	1.00	1.00	257.30	Infinity	0.00	Infinity

[*] Statistically significant.
[#] Clinically significant.

Risk Factor Analysis for Type 1 ROP

Using univariate analysis, the following were significant risk factors for Type 1 ROP: a lighter BW; lower GA; multiple pregnancies; and use of invasive mechanical ventilation ($P \leq 0.02$) (Table 2).

The following covariates were also significantly associated with Type 1 ROP on a statistical level (all $P \leq 0.01$) but as the OR = 1.00, there was no clinical significance of these covariates as predictors of ROP: oxygen supplement; higher mean oxygen concentration; congenital heart disease; presence of PDA; NSAID use; anemia; thrombocytopenia; blood transfusion; IVH; NEC; NNJ; phototherapy; TPN; hypoglycemia; sepsis; and meningitis.

When using multivariate analysis, none of the covariates (neither risk nor protective factors) reached a level of statistical significance (Table 2).

DISCUSSION

In several population-based studies involving Caucasians, a lower GA was associated with a higher incidence of severe

ROP.[8−10] In a Norwegian population-study by Markestad et al,[8] none of the infants with GA >25 weeks developed ROP requiring treatment as compared to 33% in those born at 23 weeks. In another Sweden study by the EXPRESS Group, there was a log-linear relationship between severe ROP and GA at birth, whereby a larger GA was associated with a lower risk of severe ROP.[9,10] The overall incidence of Type 1 ROP with GA ≤ 28 weeks was 16.2% in our study, which was comparable to the reported incidence in the first BOOST trial that reported incidences of 16% in the standard target oxygen-saturation group and 8% for the high oxygen-saturation group.[15] In the BOOST-II study, the incidence was 10.6% in the lower target-saturation group and 13.5% in the higher-target group.[16] In Japan, the incidence is higher at 19.6%.[17] The incidence of ROP and severe ROP vary throughout the literatures, most probably related to differences in standard of neonatal intensive care and socioeconomic status of different geographical regions, as well as changing of the supplementary oxygen delivery guidelines throughout the years.[15,16,18−22] The survival rate of extremely preterm infants has increased over the years following improvements in neonatal intensive care, resulting in a greater number of preterm infants developing ROP.[23] To the best of our knowledge, this is one of the largest cohorts reporting the incidence and risk factors of ROP in preterm Hong Kong Chinese infants.

The frequency of ROP in any stage, among babies born before the 27th week of gestation were reported to be 83.4% and 89.0% in the cryotherapy for retinopathy of prematurity (CRYO-ROP) study[24] and ETROP study,[13] respectively. In our study, the incidence of ROP in any stage among extremely preterm infants ≤28 weeks was 60.7%, which was comparable to the reported incidence in Canada (64.7%)[7] but less than that in Turkey (78.26%)[25] and Japan (70.6%).[17] The lower incidence in our cohort when compared to the CYRO-ROP and ETROP studies, may be attributed to the improvement of the neonatal intensive care since their publication as well as the inclusion of more mature infants (GA ≤ 28 weeks) in our study; only 58.1% (68/117) of our infants had GA ≤ 27 weeks. On the other hand, the Turkish study had the same inclusion criteria as our study, thus, differences in incidence may primarily be due to differences in neonatal care.

In univariate analysis, a lower BW and a lower GA increased the risk of both ROP and Type 1 ROP. This finding was consistent with the result of an 18-year study in Australia[4] and with other population studies published over the years.[8−10] On multivariate analysis, GA but not BW was a consistent predictor for ROP develop. This finding was inline with the finding of Woo et al[26] who reported that GA was a better predictor of ROP than BW in preterm twin-pairs. On multivariate analysis, GA but not BW was a consistent predictor for ROP develop. This finding was inline with the finding of Woo et al who reported that GA was a better predictor of ROP than BW in preterm twin-pairs. Similarly, Isaza and Arora reported that premature infants with lower GA had a higher incidence of Type 1 ROP and that no infants with a GA >26 weeks or BW >1000 g developed Type 1 ROP.[27] Likewise, in our study, no infants with a GA more than 27 weeks or with a BW greater than 900 g developed Type 1 ROP requiring treatment.

Mizoguchi et al[28] reported a strong association of inotropes use in management of postnatal hypotension with the development of threshold ROP in preterm infants. In our study, inotrope use was an independent risk factor for ROP development (OR = 2.47　P = 0.03) but not for Type 1 ROP (P = 0.10).

Invasive mechanical ventilation was an independent risk factor for both ROP and Type 1 ROP (P ≥ 0.01) in our study.

There exist controversies about the association of multiple gestation and ROP or threshold ROP. Bossi et al[29] revealed that preterm infants of multiple pregnancies carried a higher risk of ROP while Shaffer et al[24] found a higher risk of threshold ROP in multiple-gestation infants when compared to singletons. On the other hand, Shohat et al[30] and Friling et al[31] did not find such association. In univariate analysis, we found that infants of multiple gestations had a higher risk (OR = 4.05, P = 0.02) of developing Type 1 ROP, requiring diode laser treatment, when compared to singleton infants.

On multiple regression analysis, the presence of congenital heart disease (OR = 0.09, P = 0.04) was significant protective factor against ROP development and this observation was also evident in a previous publication investigating extremely low birth weight (≤1000 g) Chinese infants.[32] Unfortunately, we do not have a solid explanation for this observation as most previously published literature have found a positive correlation of congenital heart disease with ROP development.[31,33,34] For cyanotic heart diseases with right (non-oxygenated) to left (oxygenated) shunts, the oxygen concentration may be lowered, potentially explaining the protective mechanism against ROP. However, in ours series, all the congenital heart diseases were non-cyanotic (ventricular septal defects or arterial septal defects), so the above theory cannot account for our observations. We can only postulate that in preterm infants born with congenital heart disease, more vigilant monitoring and control of oxygen may have offered a better optimization of the target oxygen saturation, conferring an indirect protective mechanism for ROP development.

Our study had its limitations. Firstly, the retrospective nature of this study inevitable generates inconsistencies in data although every effort was made to exclude subjects with incomplete clinical data. Secondly, subjects were screened by 3 pediatric ophthalmologists and minor inter-observer variability can exits but as all were trained to follow a strict ROP screening guideline; digital photographic documentation was not available at the time of the study; given the large population requiring screening, it was the most optimal balance in terms of providing clinical service and standardization for research. Moreover, our study was mainly a hospital-based study rather than a population-based study but our service coverage spans over 2 NICU's, involving more than 1.8 million people. Nevertheless, our study provided information on the incidence and risk factors of ROP in an extremely preterm Chinese population using the UK-ROP screening guidelines. This serves as a platform for future multi-centre, prospective trials among Chinese populations. The findings of this study were generated from a population extremely preterm Chinese infants in Hong Kong and may not be generalizeable to other populations of different ethnicities, gestational ages, and health care practices.

In Chinese extremely preterm infants, a lighter BW and lower GA were the only common independent risk factors for both ROP and Type 1 ROP. Multiple pregnancies and invasive mechanical ventilation were associated with the development of the more aggressive Type 1 ROP on univariate analysis. Neonatal congenital heart disease and a greater GA were protective factors against ROP.

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