• Clinical Research •

Clinical feature and predictive factor analysis for spontaneous regression of retinopathy of prematurity in a Chinese population

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Abstract

● **AIM:** To investigate the ratio of spontaneous regression of retinopathy of prematurity (ROP) and to explore the possible relevant predictive factors.

● **METHODS:** A retrospective review of 405 infants who were diagnosed with ROP and mother during pregnancy were collected. Stage, zone, and duration of ROP were recorded. Statistical analysis was performed on 51 possible predictive factors.

● **RESULTS:** Totally 356 infants showed spontaneous regression. The incidence was 100%, 95.3%, and 22.7% in stage 1, 2, and 3, respectively. The 13.4% of the ROP with plus disease eventually resolved spontaneously. All affected eyes of aggressive posterior retinopathy of prematurity (AP-ROP) failed to spontaneously regress. The mean duration of ROP was 7.2wk in patients with spontaneous resolution of ROP. Days of mechanical ventilation (OR=0.981, 95%CI, 0.965-0.997, *P*=0.021), retinal hemorrhage (OR=0.173, 95%CI, 0.064-0.470, *P*=0.001), delivery pattern (OR=2.750, 95%CI, 1.132-6.681, *P*=0.025), maternal anemia in pregnancy (OR=0.142, 95%CI, 0.036-0.563, *P*=0.005), the stages (at initial diagnosis OR=0.183, 95%CI, 0.041-0.816, *P*=0.026; at final diagnosis OR=0.031, 95%CI, 0.006-0.167, *P*<0.001), and with plus disease or not (OR=0.005, 95%CI, 0.001-0.031, *P*<0.001) were independent predictive factors of the spontaneous regression of ROP.

● **CONCLUSION:** Most mild ROP can spontaneously resolve. Active treatment is still recommended for stage 3 ROP, zone I ROP, AP-ROP, and ROP with plus disease. Prolonged mechanical ventilation and concurrent retinal hemorrhage reduce the likelihood of spontaneous ROP resolution. The pattern of delivery and the mother's anemia during pregnancy can also affect the prognosis of ROP.

● **KEYWORDS:** retinopathy of prematurity; predictive factors; spontaneous regression; anemia during pregnancy; mechanical ventilation; pattern of delivery; retinal hemorrhage

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INTRODUCTION

Retinopathy of prematurity (ROP) is the leading cause of infant blindness. The number of infants at risk of ROP is increasing rapidly as the ratio of preterm birth increases worldwide and medical technology is able to better treat preterm complications[1]. Although the course of ROP and treatment to reduce visual loss are well known, it is still crucial to detect ROP and determine the best follow-up and treatment plan for high-risk premature infants[2]. Because of the different medical level and heterogeneity in screening, the occurrence and development rate of ROP in different regions are different[3-5]. In eastern China, after years of development, increasing attention has been paid to ROP and the regulated use of oxygen in Neonatal Intensive Care Unit (NICU), thus ultimately fewer children with ROP need treatment than expected. To better manage ROP, we need to study the disease as an event affected by various factors occurring during pregnancy, and after birth. During the follow-up of ROP screen and treatment for many years in our hospital, it was found that a large part of ROP could spontaneously resolve. However, there were few reports on such patients. Unnecessary examinations may increase the medical costs for ROP screening. Although over-screening ROP has been considered acceptable because missing severe ROP can cause devastating results, developing novel screening protocols with both high sensitivity and specificity across various populations would be ideal. Those patients were summarized in this paper

to evaluate the possibilities and ratio of spontaneous regression of ROP and discuss possible relevant predictive factors. It is expected to contribute to the development of more effective ROP screening and prevention strategies.

SUBJECTS AND METHODS

Ethical Approval This study was a retrospective study on the infants with a history of ROP at Children's Hospital of Fudan University from August 2013 to March 2017. The study was conducted at the Neonatology, NICU, and Department of Ophthalmology. And this study was carried out in high-income areas of East China. All research adhered to the tenets of the Declaration of Helsinki. All research has been approved by the Institutional Review Board of our institution. Informed consent was obtained.

Inclusion criteria: 1) gestational age (GA) <37wk or birth weight (BW) <2500 g; 2) the parents or legal guardians agreed with screening for ROP; 3) refracting media had no turbidity and fundus image was clear; 4) the diagnosis was ROP; 5) the medical information was reliable and complete.

The first screening round was 4-6wk after birth. All infants with ROP were followed up at least 45wk of postmenstrual age (PMA) or until the completely retinal vascularization or formation of ROP degenerated scar or when the treatment was conducted. Infants who died or lost follow-up before the end of the follow-up period were excluded. If no reexamination from the ROP was observed at 45-week PMA, the infant was considered to be lost to follow-up. In this study, completely spontaneous regression of ROP was defined as the regression of active neovascularization and normal retinal vascular development beyond zone III or the formation of ROP degeneration scar without any treatment. Diagnosis was made according to the international classification of ROP[6]. The eye with more severe ROP was recruited for staging of ROP. The diagnosis was divided into two parts: the initial diagnosis and the final diagnosis (the most severe disease during the course of the disease).

According to this standard, frequency of follow-up was customized: stage 1 or 2 ROP in zone II without plus disease, or stage 1 or 2 ROP in zone III without plus disease: examination was performed once every 2wk; threshold ROP: laser or intravitreal ranibizumab (IVR) was conducted within 72h or examination was carried out every 2-3d according to the situation; pre-threshold ROP: type 1: the retinal examination was executed once weekly or laser or IVR was performed according to the situation; type 2: the retinal examination was completed once weekly, and stage 4 or 5 ROP: surgical intervention was required. No ROP but incomplete retinal vascular development: once every 2wk; aggressive posterior retinopathy of prematurity (AP-ROP): IVR.

The infant data were collected, such as the gender, race, GA, BW, PMA of onset, and Apgar score, *etc*. Maternal data were collected, such as pattern of delivery (eutocia/cesarean section), fertilization way (nature conceived/artificial insemination/test-tube baby), scarred uterus, *etc*.

Statistical Analysis All data were entered into a spreadsheet and analyzed using SPSS for Windows statistical software Version 22.0 (SPSS Inc., Chicago, IL, USA). The subjects were divided into treatment group and spontaneous regression group. Clinical characteristics of the two groups were described by mean values and standard deviations (SD). Univariate comparison of predictive factors between the two groups was evaluated using the *t*-test for continuous variables and Chi-square test for categorical variables. A value of bilateral $P<0.05$ was considered statistically significant. Through univariate analysis and stepwise logistic regression analysis to determine the correlation between the related factors and the spontaneous regression of ROP. Effect estimates were expressed in the form of odds ratio (OR), and profile likelihood was based on 95% confidence interval (CI).

RESULTS

From August 2013 to March 2017, a total of 2745 premature infants were screened at Children's Hospital of Fudan University, among which 501 (18.3%) met the inclusion criteria. In addition, 96 (19.2%) among the 501 infants were lost to follow-up or died. Thus, 405 infants were finally included. There were 232 males (57.3%) and 173 females (42.7%; M/F: 1.34:1). Among these infants, 356 patients exhibited spontaneous regression of ROP with the ratio of 87.9%. The mean GA and BW (29.2wk and 1243.7 g) of ROP in spontaneous regression group were larger than that of the treated ROP group (28.5wk, 1151.1 g). GA had significant difference (P=0.021), while BW had no significant difference (P=0.051). The difference of PMA of onset in the ROP regression group and the treatment group was not statistically significant (P=0.504; Table 1).

In the final diagnosis, the spontaneous regression rates of stage 1, 2 and 3 ROP were 100%, 95.3% and 22.7%. Only 5 cases (13.2%) with plus disease spontaneously subsided. In addition, none of the 7 cases with AP-ROP had spontaneous regression. However, the regression rate was slightly different from the initial diagnosis. In the initial diagnosis, the spontaneous regression rates of stage 1, 2, and 3 ROP were 97.9%, 82.2% and 21.4%, respectively. There were 1 case (5.9%) with plus disease spontaneously subsided. Still, none of the 6 cases with AP-ROP had spontaneous regression (Table 2).

Similarly, there were 123 cases with any ROP in zone III, which were all completely regressed (100%). In zone II, regression in 230 (85.8%) cases of 268 was detected. There were 3 cases with natural involution in the 7 cases with ROP in zone I (42.9%). The initial diagnosis and the final diagnosis

Table 1 Demographic data of ROP patients

Parameters	Spontaneous regression ROP, *n*=356	Treated ROP, *n*=49	t/χ^2	*P*
Male (%)	203 (57.0)	29 (57.32)	0.082	0.774
Female (%)	153 (43.0)	20 (42.68)		
Gestational age (wk)	29.2±2.1	28.5±2.6	2.312	0.021
Birth weight (g)	1243.7±314.6	1151.1±280.2	1.955	0.051
Postmenstrual age (wk)	35.9±3.7	35.5±3.1	0.668	0.504

ROP: Retinopathy of prematurity.

Table 2 Spontaneous regression and disease course of ROP in different stage and area

Stage or area	Spontaneous regression rate (%)		Disease course (final diagnosis course, wk)
	Initial diagnosis	Final diagnosis	
Stage 1	228 (97.9)	185 (100)	4.2±3.5
Stage 2	125 (82.2)	161 (95.3)	10.1±6.0
Stage 3	3 (21.4)	10 (22.7)	14.6±6.7
Zone I	N/A	3 (42.9)	11.9±5.5
Zone II	N/A	230 (85.8)	8.9±6.2
Zone III	N/A	123 (100)	3.9±3.4
AP-ROP	0	0	N/A
Plus disease	1 (5.9)	5 (13.2)	12.5±7.1

ROP: Retinopathy of prematurity; AP-ROP: Aggressive posterior retinopathy of prematurity.

were not discussed separately, because they were basically the same in area. Table 2 shows the spontaneous regression and disease course of ROP in different stages and areas.

Table 3 shows univariate analysis of predictive factors for the spontaneous regression of ROP. The possible relative predictive factors (neonatal and maternal factors) were assigned values, followed by univariate analysis. The significant variables for spontaneous regression of ROP were GA (*P*=0.021), 1-minute Apgar score (*P*=0.006), mechanical ventilation or not (*P*=0.023), days of mechanical ventilation (*P*=0.046), retinal hemorrhage (*P*<0.001), pneumonia (*P*=0.029), the pattern of delivery (*P*=0.002), maternal anemia in pregnancy (*P*=0.025), using dexamethasone in pregnancy (*P*=0.002), the stage at final diagnosis (*P*<0.001), zone at final diagnosis (*P*<0.001), stage at initial diagnosis (*P*<0.001), with plus or not at final diagnosis (*P*<0.001) and with plus or not at initial diagnosis (*P*<0.001). The other variables (neonatal data: BW, PMA of onset, days of oxygen supplement, sex, single or multiple birth, neonatal respiratory distress syndrome (NRDS), bronchopulmonary dysplasia (BPD), pulmonary hemorrhage, neonatal encephalopathy, digestive system disease, cholestasis, pathological jaundice, congenital heart disease (CHD), sepsis, coagulation disorders, anemia, cytomegalovirus infection, hypoglycemia, hyperglycemia, hypoalbuminemia, acid metabolic imbalance, shock; maternal data: fertilization way, scarred uterus, gestational hypertension, hypothyroidism, gestational diabetes mellitus (GDM), placental abruption, threatened abortion, colds, fever before delivery, placenta previa, antibiotic, insulin, tocolytic agents, hypotensor, euthyrox) were not considered significant for the spontaneous regression of ROP (*P*>0.05).

Table 3 Univariate analysis of predictive factors of the spontaneous regression of ROP

Predictive factors	t/χ^2	*P*
Neonatal		
Gestational age	2.312	0.021
Apgar score (1min)	2.768	0.006
Mechanical ventilation	5.153	0.023
Days of mechanical ventilation	-2.04	0.046
Retinal hemorrhage	17.07	<0.001
Neonatal pneumonia	4.79	0.029
Stage at final diagnosis	235.40	<0.001
Zone at final diagnosis	34.34	<0.001
Stage at initial diagnosis	92.69	<0.001
Plus disease at final diagnosis	250.18	<0.001
Plus disease at initial diagnosis	110.52	<0.001
Maternal		
Pattern of delivery	9.33	0.002
Anemia in pregnancy	5.06	0.025
Dexamethasone	9.47	0.002

ROP: Retinopathy of prematurity.

For the above factors, logistic regression analysis was further performed. The severity of ROP is a variable of the disease itself, which obviously has a direct impact on the natural regression of ROP. Such variables should not be discussed in conjunction with other variables that influence disease relatively indirectly. Therefore, the analysis was divided into two parts, one for other factors (GA, BW, other diseases, maternal factors, *etc.*) and the other for severity of ROP (stage,

zone, *etc*.). Among those predictive factors, days of mechanical ventilation, retinal hemorrhage, pattern of delivery, maternal anemia in pregnancy, stages and with plus disease or not were independent on the spontaneous regression of ROP (Table 4).

Table 4 Logistic regression analysis of the spontaneous regression of ROP

Predictive factors	β	P	OR (95%CI)
Stage at final diagnosis	-3.471	<0.001	0.031 (0.006-0.167)
Stage at initial diagnosis	-1.701	0.026	0.183 (0.041-0.816)
Plus disease at final diagnosis	-5.279	<0.001	0.005 (0.001-0.031)
Days of mechanical ventilation	-0.019	0.021	0.981 (0.965-0.997)
Retinal hemorrhage	-1.756	0.001	0.173 (0.064-0.470)
Pattern of delivery	1.012	0.025	2.750 (1.132-6.681)
Anemia in pregnancy	-1.950	0.005	0.142 (0.036-0.563)

ROP: Retinopathy of prematurity; OR: Odds ratio; CI: Confidence interval.

DISCUSSION

Most ROP regresses spontaneously through the process of involution or evolution from a vasoproliferative phase to a fibrotic phase. The first sign for the stabilization of ROP is that retinopathy failure progresses to the next stage[7]. With the peripheral advance of retinal vascularization, the process of regression mainly occurs at the junction of vascular and avascular retinal. The anteroposterior location of retinopathy may change gradually from zone I to zone III. The color of the ridge may change from salmon pink to white[6].

ROP is a multifactorial disease, and many risk factors are still not clarified. In addition, there are well-known differences between ROP incidence rate and risk factors in different hospitals, which are related to case determination, case mix, sampling variability and differences in obstetrics and neonatal clinical practice. The predictors were considered as many as possible in this paper, including the child's own factors and prenatal and perinatal variables that may be relevant to the severity of the disease. In our study, the ratio of ROP was 18.3% which is similar to that in previous studies (12.8%-36.4%; Table 5)[8-14]. The lower ratio of this study may be related to the wide screening range and the high survival rate of very low birth weight infants in developed countries.

In order to precisely record the natural history of ROP, initial diagnosis and final diagnosis were recorded separately. In our study, the ratio for spontaneous regression of ROP was 87.9%, which is comparable to other studies. In some studies[8-14], the regression rate was converted by treatment rate (1-treatment rate). Prost[14] observed 168 cases of stage 1-3 ROP and 91 cases of stage 4-5 ROP, revealing that 85% of stage 1 ROP retinal and vitreous lesions spontaneously subsided, 56% of stage 2 ROP and 25% of stage 3 ROP. The spontaneous resolution rates of zone I, II, and III lesions were 6%, 45% and 95%, respectively. Ju *et al*[12] reported 56 infants with spontaneous regression of ROP, the spontaneous regression rates of stage 1, 2, and 3 were 86.7%, 57.1%, and 5.9%, respectively, and the spontaneous regression rates of zone I, II, and III were 0, 46.2%, and 100%, respectively. Repka *et al*'s[7] study demonstrated that acute-phase ROP subsided at an average of 38.6wk. In 99% of cases, it started to fade by 44wk. In our study, the resolution of stage 2 and zone II ROP were higher than other reports, which may be related to ROP was generally treated actively at that time. Stage 4 or 5 ROP did not appear in our study, because such patients were transferred to specialized hospitals for treatment and were considered lost to follow-up cases. The duration of ROP is equivalent.

In the natural course of ROP, the dilated tortuosity and congestion of the vessel in the posterior pole was used as an indicator to distinguish whether the lesions are active or not, and to indicate whether it is still in the active stage[6]. Similarly, decreased tortuosity and congestion indicates early regression. The disease process in ROP is self-limited, with a clinically recognizable onset time and an end-stage when the disease process becomes inactive. The mean duration of ROP in the spontaneous regression group was 7.2±5.9wk, longer than that of Ju *et al*[12] (5.65±3.14wk). Eliason *et al*[15] reported that there was no significant difference in the average duration of untreated ROP in white non-Hispanics (8.6±5.4wk) and Hispanics (8.9±7.0wk).

Because the occurrence, development and regression of ROP is a process, the duration of untreated ROP is not very accurate. In some patients, a possible reason for the longer (but not shorter) ROP duration may result from measurement errors due to missed appointments. The course of many stage 3 zone I ROP may be shorter than that of only one week, and sometimes some mild ROP may be missed.

Some researchers have proposed that treatment-requiring ROP, stage 3 ROP, and zone I and II disease are related to mechanical ventilation time[5,16-17]. A study from Japan reported invasive ventilation ≥28d is a risk factor of treatment-requiring ROP[18]. Chang's[19] study showed that only the duration of mechanical ventilation was an independent rick factor for ROP development, while none of the other oxygen delivery methods were associated with ROP progression. This concept supports our study. Although the concentration of oxygen is strictly in accordance with Chinese Guidelines[20], the results of the present study indicated that days of mechanical ventilation is an inversely predictive factor for the spontaneous regression of ROP. Infants with long duration of mechanical ventilation are more likely to progress serious ROP requiring treatment. It suggests that for preterm infants, in addition to standard oxygen supplement and strict control of indications for mechanical ventilation, the control of duration and avoidance of repeated oxygen supplement are also very important.

Table 5 Incidence of ROP and incidence of spontaneous regression of ROP from different countries

Author	Country and region	Birth weight, g	Gestational age, wk	Study period, y	Sample size	Incidence of ROP, %	Spontaneous regression, %
Larsson *et al*[8]	Sweden	<1500	N/A	1998-2000	253	36.4	87.7
Shah *et al*[9]	Singapore	<1500	N/A	1988-2001	564	29.2	83.0
Prost[14]	Poland	N/A	N/A	1995-2002	168	N/A	85.0
Ahuja *et al*[10]	India	<1900	<36	2011-2013	325	32.6	86.8
Chen *et al*[11]	Taiwan, China	<1500	<32	2005-2007	698	29.7	60.9
Ju *et al*[12]	China	<2000	<37	2008-2011	957	N/A	86.7
Liu *et al*[13]	China	<2500	<37	2009-2012	1864	12.8	N/A
Current study	China	<2500	<37	2013-2017	2745	18.3	87.9

ROP: Retinopathy of prematurity.

Neonatal retinal hemorrhage caused by birth trauma is common, benign, and self-limited, and was the single most frequently seen ocular anomaly among newborn babies[21]. Other retinal hemorrhage in infancy may indicate accidental or non-accidental injury, intracranial aneurysm, as well as a variety of eye diseases or systemic diseases. Most of the retinal hemorrhage of ROP occurs on the surface of the neovascular ridge, which is characterized by the arteriovenous shunt formed by retinal primitive vascular anastomosis, and the vulnerability of the vessels also leads to the hemorrhage. Studies[22] have shown that most retinal hemorrhages spontaneously resolved without any specific sequelae. In our population, all retinal hemorrhage eventually resolved. Furthermore, presence of retinal hemorrhage is also an inversely predictive factor for the spontaneous regression of ROP. Wang *et al*'s[23] study also proved retinal hemorrhages was confirmed as dependent factors for delayed regression. In the case of retinal hemorrhages from a birth trauma, the mechanism of hemorrhage inducing, or aggravating ROP is still not clear. We hypothesized that infants with retinal hemorrhage showed some abnormalities in retinal vessels (such as arteriovenous shunts or increased vascular fragility), which aggravated the condition of ROP and prevented the natural regression of ROP. On condition that ROP lesion causes bleeding, that is, retinal hemorrhage is a serious indicator of ROP. Cases of retinal hemorrhage need to be followed up closely to prevent the deterioration of the disease.

Caesarean section (C-section) is positively predictive factor for the spontaneous regression of ROP. In the study of Badeeb *et al*[24], single factor analysis showed that C-section has a protective effect on ROP. Although this association cannot be verified in multivariate analyses that control for many confounding factors. Similar to our study, Manzoni *et al*'s study[25], showed that C-section was confirmed by logistic regression as an independent predictor of threshold ROP. Manzoni *et al*[25] believed that the "protective" effect of C-section may be related to some reasons and conditions that must be considered together. In fact, none of them alone can have a significant impact on the prognosis of newborns. Meanwhile, Figueras-Aloy *et al*'s study[26] in 2010 also confirmed that infants without C-section were more severe with ROP.

Obviously, the relationship between vaginal delivery and threshold ROP may be a link, although not necessarily a causal relationship[27]. During the natural delivery process, the mechanism of vaginal delivery and the stress dynamics may be harmful to the fetal cerebral blood vessels, leading to ischemia and subsequent reperfusion and/or oxidative stress, accompanied by related imbalance of hyperoxia-hypoxia[28]. Both of the mechanisms can promote the release and formation of neoangiogenesis mediators induced by hypoxia. Long term fetal hypoxia and/or ischemia may play a role in the pathogenesis of ROP[1,29]. In addition, premature vaginal delivery can often cause vaginal infection of newborn, which also increases the occurrence of ROP and retinal neovascularization[30-31].

Maternal anemia during pregnancy is an inversely predictive factor for the spontaneous regression of ROP. There are few studies on maternal anemia and ROP, and more studies have discussed the relationship between neonatal anemia. Dai *et al*'s study[32] showed that mothers with iron deficiency anemia during pregnancy were more likely to have ROP in preterm infants. It was assumed that compared with the preterm infants born to mothers with normal iron level, the ROP of preterm infants born to mothers with iron deficiency is more likely to progress to a serious level. In addition, it has been reported that blood transfusion volume and iron load by transfusions are associated with the risk of ROP in preterm infants[33-35]. Excessive exogenous iron can increase the amount of free iron, which may catalyze Fenton reaction that will produce free hydroxyl radicals from superoxide and hydrogen peroxide, thus damaging the retina, causing oxidative damage in premature infants, and causing or aggravating retinopathy in premature infants. Low levels of erythropoietin may play an important role in suppressing retinal vascularization in the early weeks of life and lead to the later development of severe ROP[36].

The stages and with plus disease or not are positively predictive factors for the spontaneous regression of ROP. It suggested

that the stage 3 ROP in any zone should be treated actively. And obviously, ROP with plus disease, as a marker of disease activity, is also an indicator of need for treatment. The ROP with plus disease needs to be treated first. On the contrary, patients with stage 1 and 2 ROP, as well as those without plus disease, can appropriately extend the follow-up time to avoid over examination.

However, there are limitations in this study. One major limitation of the present study was its retrospective design and was based on data from a single neonatal center, so future studies should include multiple hospitals in order to reach findings that allow for more accurate inference. Another limitation of the study is that it is difficult to pinpoint exactly the time of ROP regression. In addition, the method to calculate the duration of ROP, as the time difference between observing ROP for the first time and discovering ROP regression, may artificially increase the measurement of the duration. For example, infants with mild ROP tend to prolong the follow-up interval, thus artificially increasing the course of ROP. Considering the cost of follow-up and the possible psychological impact of an examination on infants, it is necessary to extend the follow-up time properly, thus this deficiency may need to be improved by other aspects. In the analysis of risk factors, the factors of pregnant women were analyzed based on medical records. However, the medical records may contain errors, thus prospective and large-scale trials with detailed analysis of maternal and neonatal issues are required before any firm conclusions can be made. But in this paper, our findings are still worth considering and expected to be verified in hospitals in other regions.

In conclusion, ROP is a kind of self-limited disease, and most of the stage 1 and 2 ROP will eventually spontaneously regress. Active treatment is still recommended for stage 3 ROP, lesions in zone I, AP-ROP, and with plus disease to prevent progression. Prolonged mechanical ventilation and concurrent retinal hemorrhage reduce the likelihood of spontaneous ROP resolution. The pattern of delivery and the mother's anemia during pregnancy also could affect the prognosis of ROP. Further multicenter and documented studies may help quantify those differences and determine their clinical significance.

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