• Investigation •

Survey of current retinopathy of prematurity practices in China

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Abstract

• **AIM:** To understand retinopathy of prematurity (ROP) screening and treatment preferences among Chinese ophthalmologists.

• **METHODS:** A Chinese language survey was administered anonymously using WebQ (Catalyst, Seattle, WA, USA) among Chinese ROP screeners from December 2016 to January 2017.

• **RESULTS:** Among 70 ophthalmologists contacted, 65 responded (93%; 78% female, mean age 40y, 57% pediatric ophthalmologists and 25% retina specialists). Most used screening criteria of birth weight ≤2 kg (62%) with variation in cut-off gestational age (≤37wk, 34%; ≤34wk, 22%; ≤32wk, 31%). RetCam (Natus Medical Incorporated, Pleasanton, CA, USA) wide-field fundus photography assisted most screeners (72%) and was exclusively used by many (29%). Among 55 ophthalmologists treating ROP, anti-vascular endothelial growth factor (VEGF) was preferred over laser for both zone I (76% *vs* 24%) and zone II ROP (58% *vs* 42%). Retina specialists (P=0.004) and ophthalmologists with >3mo of training (P=0.03) were more likely to use anti-VEGF over laser for zone I ROP. Lack of laser training (8/20, 40%), access (6/20, 30%) and anesthesia (4/20, 20%) were common barriers to laser treatment.

• **CONCLUSION:** Chinese ROP screeners favor anti-VEGF injection and RetCam imaging for ROP management. A better understanding of ROP screening and treatment informs future research and education efforts in China.

• **KEYWORDS:** pediatrics; retina; retinopathy of prematurity; survey; telemedicine
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INTRODUCTION

Retinopathy of prematurity (ROP) is characterized by abnormal vascular development in premature infants of low birth weight. Risk of ROP blindness is reduced through appropriate screening and treatment. Both retinal laser photocoagulation and intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy prevent retinal detachment in >90% of treated infants[1-2]. Nonetheless, ROP remains a leading cause of blindness worldwide with an estimated 50 000 children blind from ROP today[3]. While the first and second ROP epidemics of the 1940's and 1970's affected industrialized nations, a third ROP epidemic is now impacting the developing world[4]. Recent expansion of neonatal care in lower-middle-income and low-income countries has led to the increased survival of premature infants, but without adequate infrastructure to care for their ocular health[5-6].

With nearly one sixth of the world's population and a rapidly advancing medical system, China's ROP epidemic is overwhelming its ophthalmology community[5]. In addition, bevacizumab is currently banned throughout the country due to contamination and safety concerns. The alternative to bevacizumab, ranibizumab, is associated with a 50% to 64% rate of ROP recurrence[7-9]. These factors create unique challenges in the screening and treatment of ROP in China, where a large geographic expanse and dense population are already barriers to access to care. With this background, our survey study aims to understand ROP screening and treatment preferences among ophthalmologists throughout China to better direct research and educational efforts.

SUBJECTS AND METHODS

Ethical Approval All procedures were in accordance with the ethical standards of the Institutional Review Board and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The email communication included informed consent, and clicking on the link constituted consent to participate. This research was conducted under institutional review board exempt status from Seattle Children's Hospital in Seattle, WA, United States and institutional review board approval from Hunan People's Hospital, Changsha, Hunan Province, China. This study conformed to the requirements of the United States Health Insurance Portability and Privacy Act.

Study Participants A single investigator (Feng J) identified active ROP specialists throughout China through personal and professional networks. This network consisted of ROP providers with whom the investigator had been in contact with for referrals, as well as those in attendance at local ROP conferences. These prospective participants were contacted directly by telephone and/or a popular texting platform, WeChat (Tencent Holdings Limited, Nanshan District, Shenzhen, China) to confirm eligibility and encourage participation in our online survey. Ophthalmologists were excluded from the study if they were not actively screening and/or treating ROP at the time of the survey. Following initial contact, an email was sent to all eligible prospective participants with a link to the anonymous online survey platform.

Survey Instrument The authors believed that a survey instrument would best reach a wide audience, and that a short survey (under 5min from start to finish) would more likely be completed by prospective participants. Previous ROP screening surveys by Tawse *et al*[10] and Mora *et al*[5] provided a framework for demographic and baseline questions presented in our Chinese survey. The response choices were adjusted to reflect local differences, taking into account the hospital tier system in China and densely populated city sizes. An anonymous online Chinese language survey instrument was created using the online survey platform WebQ (Catalyst, Seattle, WA, USA). The survey included 28 multiple choice questions, reviewed, and approved by all authors (both Chinese and American) to confirm that they covered appropriate subject matter and response choices relevant to Chinese ROP practitioners. The original questions were written in English, then translated to Mandarin Chinese by one of our bilingual authors (Hu R) and then back-translated to English by a second bilingual author (Ding L) to ensure implicit meaning was conveyed across languages. The survey was beta tested by our Chinese authors (Feng J and Hu R) to ensure that it was understandable and functional for Chinese participants accessing the online survey from within China. The survey was open from December 20, 2016 through January 24, 2017. A reminder email was sent to all prospective participants mid-way through the survey period, and again one week prior to closing the survey.

Statistical Analysis Associations between subspecialty area of practice and treatment preferences were assessed using the Pearson's Chi-square and Fisher's exact tests. A two-sided value of $P<0.05$ was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS institute, Inc., Cary, NC, USA).

RESULTS

A total of 70 prospective participants were recruited, of which all were found to be eligible for the study. Sixty-five (92.8%) submitted online responses. Participant characteristics are shown in Table 1. Based on our survey, most ROP screeners were female (72.3%) with training in pediatric ophthalmology (56.9%). Screening most often took place in large tertiary hospitals (78.5%) and in densely populated cities, with over ten million people (36.9%). In spite of many practitioners having few years of experience (43/65 or 66% having 5 or less years of experience) and minimal training (20/65 or 31% had less than 3mo or no training), screeners (39/65, 60.0%) examined >30 infants per week with a significant portion (19/65, 29.2%) seeing >60 infants per week (Table 2).

Other ROP screening practices and preferences of respondents are provided in Table 2. A large percentage of practitioners performed only inpatient (10/65, 15.4%) or outpatient (16/65, 24.6%) screening, therefore it is unclear whether infants in these locations received adequate follow up. Oxygen saturation levels were mostly maintained at recommended levels of 90%-95% (19/65, 29.2%). Treatment and referral patterns are shown in Table 3. Most practitioners preferred tropicamide with or without phenylephrine for pharmacologic dilation (63/65, 97%), likely reflecting the dark eyed population less likely to adequately respond to phenylephrine and cyclopentolate. Most practitioners screened infants with maximum birth weight 2000 grams (40/65 or 61.5%), while gestational age screening criteria were highly variable among Chinese ophthalmologists surveyed. Practitioners frequently preferred 20 diopter condensing lenses (33/65, 50.8%) for indirect ophthalmoscopy, and less commonly 28 or 30 diopter lenses (25/65, 38.5%) while the majority of practitioners utilized a commercially manufactured scleral depressor (38/65, 58.5%), and less commonly a muscle hook (17/65, 26.2%). Screening modalities commonly incorporated RetCam (Natus Medical Incorporated, Pleasanton, CA, USA) photography with 19/65 (29.2%) relying on RetCam alone and 28/65 (43.1%) using RetCam in combination with binocular indirect ophthalmoscopy. A lower proportion of participants, 16/65

Table 1 Participant characteristics (*n*=65) unless otherwise stated

Demographics	*n* (%)
Mean age in years	40.4±8.3
Female sex	47 (72.3)
Main area of practice in ophthalmology	
Retina and vitreous	16 (24.6)
Pediatric ophthalmology	37 (56.9)
General ophthalmology	9 (13.8)
Other	3 (4.6)
Duration of ROP practice in years	
<3	28 (43.1)
3-5	15 (23.1)
5-10	17 (26.2)
>10	5 (7.7)
ROP training	
During residency	7 (10.8)
International experience >3mo	5 (7.7)
Domestic experience >3mo	6 (9.2)
While in practice under supervision of an experienced ophthalmologist >3mo	27 (41.5)
ROP training <3mo	13 (20)
No ROP training	7 (10.8)
Current practice setting	
Tertiary hospital 3A[a]	51 (78.5)
Tertiary hospital 3B[a]	6 (9.2)
Tertiary hospital 3C[a]	2 (3.1)
Secondary hospital[b]	5 (7.7)
Private hospital	1 (1.5)
City population (number of people)	
<500 000	3 (3.6)
500 000 to 1 000 000	4 (6.2)
1 000 000 to 5 000 000	18 (27.7)
5 000 000 to 10 000 000	16 (24.6)
>10 000 000	24 (36.9)

ROP: Retinopathy of prematurity. [a]Tertiary hospital refers to large and comprehensive hospitals (more than 500 beds). These hospitals are further designated grades A, B, or C, by the Chinese Ministry of Health, with "A" being the benchmark in terms of standard of care. Grade B and C tertiary hospitals have fewer personnel and equipment in comparison. [b]Secondary hospital refers to regional general hospitals (101-500 beds).

Table 2 ROP screening practices and preferences (*n*=65)

Maximum birth weight	*n* (%)
≤1500 g	8 (12.3)
≤2000 g	40 (61.5)
≤2500 g	13 (20.0)
Other	4 (6.2)
Maximum gestational age	
≤30wk	4 (6.2)
≤32wk	20 (30.8)
≤34wk	14 (21.5)
≤37wk	22 (33.8)
Other	5 (7.7)
Site for ROP screening	
Neonatal intensive care unit	10 (15.4)
Outpatient	16 (24.6)
Both	36 (55.4)
Average number of babies screened for ROP each week at facility	
0-5	9 (13.8)
5-10	7 (10.8)
10-30	10 (15.4)
30-60	20 (30.8)
>60	19 (29.2)
Preferred dilation drops prior to ROP screening	
Tropicamide + phenylephrine	28 (43.1)
Tropicamide + cyclopentolate	1 (1.5)
Phenylephrine + cyclopentolate	1 (1.5)
Tropicamide only	35 (53.8)
Modality for ROP screening	
Binocular indirect ophthalmoscope only	16 (24.6)
RetCam only	19 (29.2)
Binocular indirect ophthalmoscope + RetCam	28 (43.1)
Other	2 (3.1)
Preferred indirect lens in diopters	
20	33 (50.8)
28	20 (30.8)
30	5 (7.7)
Other	7 (10.8)
Preferred device for scleral indentation during ROP screening	
Plastic coated paperclip	3 (4.6)
Muscle hook	17 (26.2)
Scleral depressor (commercially manufactured)	38 (58.5)
Other	7 (10.8)
Goal oxygen saturation in neonatal intensive care unit	
85%-90%	9 (13.8)
90%-95%	19 (29.2)
95%-99%	3 (4.6)
"I don't know"	34 (52.3)

ROP: Retinopathy of prematurity.

(24.6%), screened using binocular indirect ophthalmoscopy alone. While at least half of the screening facilities had access to laser, cryotherapy, or intravitreal anti-VEGF, less than one third of facilities surveyed had access to surgery for later stage ROP in our study. The vast majority (41/65, 63.1%) of available procedures for retinal detachment were pars plana vitrectomy with scleral buckle. The nearest ROP treatment facility when not onsite was usually within 100 km (20/65, 30.8%) although sometimes beyond (16/65, 26.2%). Most providers appropriately referred for treatment of type 1 ROP in accordance to the Early Treatment for Retinopathy of

Table 3 Treatment and referral patterns (*n*=65)

Items	*n* (%)
Availability of laser, cryotherapy, or intravitreal anti-VEGF	
Yes	34 (52.3)
No	31 (47.7)
Availability of surgery for later stage ROP at facility	
Yes	20 (30.8)
No	45 (69.2)
Nearest ROP treatment facility (laser, cryotherapy, surgery)	
Onsite	28 (43.1)
Within 100 km	20 (30.8)
Within 1000 km	11 (16.9)
>1000 km	6 (9.2)
Stage of ROP referred for consideration of surgical treatment	
Type I (high risk prethreshold)	32 (49.2)
Type II (low risk prethreshold)	1 (1.5)
Threshold	29 (44.6)
Other	3 (4.6)
Stage of ROP referred for surgical treatment	
Stage 4A or above	49 (75.4)
Stage 4B or above	13 (20.0)
Stage 5	1 (1.5)
Not applicable	2 (3.1)
Available operative procedures	
Pars plana vitrectomy only	3 (4.6)
Scleral buckle only	1 (1.5)
Pars plana vitrectomy with scleral buckle	41 (63.1)
Other	3 (4.6)
Not applicable	17 (26.2)
Preferred anesthesia for laser or cryotherapy	
General anesthesia	26 (40.0)
Intravenous sedation and topical anesthesia	3 (4.6)
Topical anesthesia only	10 (15.4)
We do not perform laser or cryotherapy	26 (40.0)
Largest perceived barrier to anti-VEGF for ROP	
Uncertain long term side effects	10 (15.4)
Uncertain outcomes in anti-VEGF treatment	1 (1.5)
Lack of experience/training in ROP injection	2 (3.1)
Costs too high for anti-VEGF	2 (3.1)
Not applicable: this is preferred	50 (76.9)
Largest perceived barrier to laser for ROP	
Difficulty in obtaining anesthesia or operating room time	4 (6.2)
Length of time needed for procedure	2 (3.1)
Lack of experience/training with ROP laser	8 (12.3)
Lack of access to laser	6 (9.2)
Not applicable: this is preferred	45 (69.2)

VEGF: Vascular endothelial growth factor; ROP: Retinopathy of prematurity.

Prematurity study (ETROP)[1], however a significant number (44.6%) referred for delayed treatment of threshold disease in accordance to the older Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study[11]. We were surprised to learn that a significant minority (14/65, 21.5%) of practitioners did not refer Stage 4A for surgical intervention (Table 3).

Among those with access to ROP treatment, most participants preferred intravitreal anti-VEGF therapy (42/55, 76%) to laser photocoagulation (13/55, 24%) for initial treatment of zone I ROP. This preference was also seen in treating zone II ROP (anti-VEGF: 32/55, 58% compared to laser: 23/55, 42%). Most laser or cryotherapy treatments were performed under general anesthesia (26/65, 40%) with fewer performing laser under topical anesthesia with or without intravenous sedation (13/65, 20%). We identified a correlation between the subspecialty area of practice and the treatment preference for zone I ROP (P=0.004), with more retina providers preferring anti-VEGF to laser compared to pediatric ophthalmologists. However, no such correlation was seen in treating zone II ROP (P=0.412). Additionally, we found a correlation between length of prior ROP training and anti-VEGF treatment preference in zone I ROP (P=0.019), where those who received >3mo of ROP training were more likely to prefer anti-VEGF as initial treatment. This correlation was not seen in zone II ROP (P=0.377). The most common reason for avoiding anti-VEGF treatment was uncertain long-term side effects (10/15, 66.7% among those who prefer laser). Among those who preferred not to perform laser, lack of laser training (8/20, 40%), access (6/20, 30%), anesthesia (4/20, 20%), and length of time needed for the procedure (2/20, 10%) were barriers to laser treatment.

DISCUSSION

Our anonymous survey study identified that almost half of Chinese ROP screeners lacked access to any ROP treatment options. Among those treating ROP, ophthalmologists had a strong preference for anti-VEGF therapy over laser photocoagulation for both zone I and zone II ROP in China. These results differ from practice patterns in Turkey[12] and the United States[10], where clinicians are hesitant to rely on intravitreal bevacizumab therapy for ROP treatment particularly in zone II disease, where an advantage of bevacizumab over laser is less clear[2]. The BEAT-ROP study identified favorable outcomes for intravitreal bevacizumab in zone I type 1 ROP[2] along with improved long-term refractive outcomes[13] compared to laser photocoagulation. In China, greater than three months of prior ROP training and practitioner specialization in retina were associated with greater utilization of anti-VEGF in zone I ROP, suggesting that training may impact decision-making. Disadvantages to bevacizumab treatment include risk of late recurrence necessitating long term follow up, long-term retinal vascular changes on fluorescein angiogram[14], and unknown systemic effects due to suppression of serum VEGF levels[15]. As ranibizumab is the primary available anti-VEGF treatment in China, disadvantages of anti-VEGF are even more significant in China. Ranibizumab has been associated with much higher rates of disease recurrence in China, with over half of treated patients requiring repeat treatment[7]. Infants who depart from the hospital following administration of anti-VEGF therapy would need to return for frequent eye examinations, which is often impractical for families living in remote regions. The widespread use of anti-VEGF treatment in China may in part result from lack of laser training (as answered by 40% of Chinese participants who did not use laser). Access to laser (30%) and anesthesia (20%) were also significant barriers to laser treatment. Future training efforts should focus on these areas.

In 2014, the Chinese Medical Association updated ROP screening recommendations (birth weight ≤ 2000 grams and/or gestational age ≤ 32wk), in addition to defining type 1 and type 2 ROP[16]. Among 68 countries recently surveyed with standard screening criteria, criteria varied widely (<30-37wk gestational age, <1000-2500 grams birth weight)[5]. Nonetheless, while most practitioners surveyed in the present study followed local screening criteria with regard to birth weight (61.5%), gestational age screening criteria were highly variable among Chinese ophthalmologists surveyed. Furthermore, 44.6% of ophthalmologists referred patients for consideration of ROP treatment later than currently recommended (threshold rather than pre-threshold type I ROP)[1].

Wide-field fundus photography using RetCam (Natus Medical Incorporated, Pleasanton, CA, USA) has been extensively validated for ROP diagnosis and remote screening[17-18]. The authors were surprised to learn that nearly a third of screeners in our study relied on RetCam alone for ROP screening, and nearly half of screeners used RetCam in addition to indirect ophthalmoscopy. According to this survey, almost all practice settings were located in tertiary hospitals in very densely populated cities (populations ≥ one million), therefore the screeners were likely in geographic proximity to the hospital and therefore capable of performing bedside examinations. Most surveyed Chinese screeners (60.0%) examined >30 infants per week while a large proportion of these (29.2%) saw >60 infants per week. These results concord with a Worldwide Survey of ROP Screening by Mora *et al*[5], which estimates 184 000 live births per screener in China. This was the highest among all 92 countries surveyed; nearly 1.5 times greater than the next understaffed country (Egypt), and over 96 times greater than the most staffed (Sweden), despite income or socioeconomic status. This highlights the financial burden of ROP screening, as well as the significant staffing challenges faced by ophthalmologists in China. While ROP telemedicine may allow clinicians to manage ROP screening more efficiently in high volume settings[19], there are disadvantages to this approach compared to indirect ophthalmoscopy. Inadequate peripheral imaging to diagnose retinal vascular maturity adds unnecessary examination sessions and infant

morbidity. Furthermore, reliance on the RetCam as the sole screening modality may diminish skills in indirect ophthalmoscopy and scleral indentation. This is especially important for implementing effective retinal laser treatment. These results highlight the challenges faced by scarce ROP screening personnel in managing the high premature patient volume in China.

Limitations of this study include sampling error since a single investigator identified all prospective participants through personal and professional networks. For example, other methods of identifying study participants may have resulted in fewer tertiary hospital settings, and therefore differing practice patterns. Nonetheless, our study had an excellent response rate, which we attribute to personal contact with every prospective participant, an approach that would not have been possible without such pre-existing connections. Furthermore, China's ophthalmologic care is mainly accessible at higher level hospitals[20], making the tertiary hospitals in this study representative of a large portion of the Chinese population.

The results of this study can help guide future research and public health efforts to improve access to laser and anesthesia for the premature population. Investigating follow-up adherence after anti-VEGF treatment and enhancing training strategies to optimize and expand the ROP screening workforce are vital to meet the needs of this important public health burden.

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