Current Practices in Treating Retinopathy of Prematurity in the Philippines

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ABSTRACT

Objective: To identify the current practices of ophthalmology subspecialists involved in the treatment of retinopathy of prematurity (ROP) in the Philippines.

Methods: A survey was conducted among members of the Vitreo-Retina Society of the Philippines (VRSP) and the Philippine Society of Pediatric Ophthalmology and Strabismus (PSPOS) who treat ROP. The electronic questionnaire covered treatment preferences and factors influencing these preferences regarding the use of anti-vascular endothelial growth factor (anti-VEGF), laser indirect ophthalmoscopy (LIO), cryotherapy, and surgical interventions. Questions about referral system and ROP recurrences encountered by the respondents were included.

Results: A total of 73 out of 86 (85.00% response rate) possible respondents were included in the study, majority (80.82%) of whom were retina subspecialists. The initial treatment preference for type 1 ROP was laser indirect ophthalmoscopy (43.84%), while anti-VEGF injection (67.12%) was preferred for aggressive posterior ROP (APROP). Among the available anti-VEGF agents, bevacizumab was the most favored (68.11%). Most ROP consultations (59.79%) occurred through referrals, primarily from pediatricians or neonatologists (91.78%). Subspecialists reported encountering more recurrences with anti-VEGF injections compared to LIO. LIO was the most preferred treatment after failed initial anti-VEGF therapy, with most recurrences occurring in patients older than 50 weeks post-conceptual age.

Conclusion: This study underscored the diverse treatment practices for ROP in the Philippines, influenced by factors such as variable access to equipment or drugs, clinician experience with specific treatments, and ocular factors such as faster regression of neovascularization. LIO was preferred as the initial therapy for Type 1 ROP and for managing recurrences, while anti-VEGF injections were favored for APROP and as an alternative treatment for Type 1 ROP. Given the absence of an established standard for treating recurrent ROP cases, long-term monitoring is necessary to facilitate timely interventions and prevent blindness.

Keywords: retinopathy of prematurity, aggressive posterior retinopathy of prematurity, anti-VEGF injection, laser indirect ophthalmoscopy, bevacizumab

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Retinopathy of prematurity (ROP) is a significant cause of visual impairment and preventable blindness in children from low- and middle-income countries, including the Philippines. A 2010 global estimate reported that 32,300 preterm infants experienced visual loss from ROP in both eyes, with the highest incidence in East and Southeast Asia, as well as the Pacific region.[1,2] ROP remains a global concern and is on its third wave of an epidemic with an estimated global blindness prevalence of approximately 50,000.[3,4] Based on the latest ROP Philippine Preventive Care Plan Strategy, as outlined in a joint statement of the Philippine Society of Newborn Medicine (PSNbM) and the Philippine Academy of Ophthalmology - ROP Working Group (PAO-ROPWG), ROP is the leading cause of childhood blindness in the Philippines.[5]

ROP is a retinal vaso-proliferative disorder involving the undeveloped retinal vessels in premature babies. The pathophysiology involves retinal ischemia, leading to formation of retinal neovascularization and vascular shunts. The primary treatment for ROP is peripheral retinal ablation using cryotherapy or laser indirect ophthalmoscopy (LIO). Landmark studies, including CRYO-ROP and ETROP, showed that immediate peripheral retinal ablation could halt disease progression and improve visual prognosis[5,6,7]. However, cryotherapy was associated with poor visual and structural outcomes in zone 1 ROP, leading to the increased adoption of LIO.[6-8] Advantages of LIO over cryotherapy include reduced inflammation, greater treatment completion in zone 1 ROP, less risk of retinal dragging, and less induced myopia.[8]

With the advent of anti-vascular endothelial growth factor (anti-VEGF) therapy, the BEAT-ROP study revealed that intravitreal bevacizumab injections were more effective than LIO in treating Stage 3 Zone 1 ROP. [9,10] But the downside of anti-VEGF injections is longer post-treatment monitoring, often beyond 55 weeks post-conceptual age (PCA). The advantages of bevacizumab injections include the preservation of peripheral visual field, faster regression of neovascularization, and lower risk of myopia[9]. Surgery is another treatment modality often reserved for advanced stages, such as stage 4 and stage 5 ROP.[11]

The treatment of ROP varies significantly among subspecialists, with pediatric ophthalmologists and vitreo-retina specialists employing different strategies based on their training, expertise, and preferences.[12,13] According to an international survey done by Fouzdar Jain *et al.,* pediatric ophthalmologists preferred LIO over bevacizumab injection, citing concerns over the unknown safety profile of anti-VEGF in the neonatal population, its off-label use in the eye, potential long-term effects, and personal preferences.[13] Bevacizumab injection was preferred for ROP in zone 1 while LIO was preferred for zone 2 ROP cases.[13] Treatment approaches are further influenced by factors such as geographic location, training background, and length of clinical practice.[14]

The ROPWG in the Philippines is composed of subspecialists from the Vitreo-Retina Society of the Philippines (VRSP), Philippine Society of Pediatric Ophthalmology and Strabismus (PSPOS), and community ophthalmologists. They aim to raise awareness about ROP within the community, initiate various ROP-related studies and activities, and collaborate with other medical specialists to develop multispecialty guidelines and recommendations for ROP treatment.

ROP awareness and screening patterns of pediatricians and ophthalmologists have been the focus of many published studies.[12] Despite the availability of numerous clinical trials and literature on ROP treatment modalities and timing, there is currently no data describing the preferred practices in the treatment of ROP of ophthalmology subspecialists in the Philippines. This study aimed to identify the current treatment preferences and practices of pediatric ophthalmologists and retina subspecialists in treating ROP in the country. The study findings may help identify the barriers, factors influencing the practice variation, the effectiveness and deficiencies in the ROP referral system, and the causes of recurrences associated with the different treatment approaches.

METHODS

This was a descriptive, cross-sectional study. Members of the VRSP and the PSPOS who treat ROP cases were surveyed.

The survey form was created using the Survey Monkey program (Momentive Global Inc with API Developer Portal, version 3). It underwent pilot

testing with 5 retina subspecialists and 5 pediatric ophthalmologists. It had 4 sections with questions on the (1) treatment preferences regarding the use of anti-VEGF, LIO, cryotherapy, and surgical treatment; (2) factors influencing treatment preferences; (3) referral systems among specialists; and (4) recurrences encountered after treatment. The respondents first provided their demographic data, followed by questions about their preferred treatment for specific clinical diagnosis. The survey contained both close-ended questions, such as multiple choices and checklist items, and open-ended questions, such as short answers and demographic questions. Once a survey was submitted, the information was automatically stored in a Google Sheet. The survey was designed to exclude specialists who do not treat ROP cases and to only accept only one entry per registered email. The link to the survey was distributed to the members of the VRSP and PSPOS from May 2022 to July 2022 via email and the Viber messaging platform (Customer Developer, Version 18.3.0.1).

This study was approved by the East Avenue Medical Center (EAMC) Institutional Ethics Review Board under the registration number EAMC IERB 2021-108. It was conducted in strict adherence to the basic principles of the Declaration of Helsinki and the guidelines set forth by the International Council for Harmonisation – Good Clinical Practice (ICH-GCP).

Statistical Analysis

Descriptive statistics were performed using STATA 15 (StataCorp LLC Manufacturer). No imputation or replacement was done for missing or incomplete data. The statistical analysis system was used to generate the p-values for the tables. The one-sample proportion test was used to assess whether the population proportion significantly differed from a hypothesized value. A p-value of less than 0.05 was considered statistically significant, indicating that the observed differences between groups were unlikely due to random variation and more likely indicate real differences between the groups.

RESULTS

At the time of the study, there was no official national census of subspecialists treating ROP in the Philippines. Consequently, the number of expected respondents was based on the registered ROP screeners in the ROPWG database as of 2020, which included a total of 86 subspecialists from VRSP and PSPOS. A total of 73 out of 86 subspecialists responded, representing a response rate of 85%. Of these, 59 (80.82%) were vitreo-retina specialists, and 40 (55.56%) practiced in the National Capital Region. Additionally, 36 (49.32%) respondents worked in both private and government sectors, while another 36 (49.32%) were exclusively in private practice. Furthermore, 43 (58.9%) [*P*=0.030] were hospital-based. **Table 1** lists the demographic characteristics of the respondents.

Table 1. Demographic characteristics (N=73)

Characteristics	N (%)	P-Value
Subspecialty		
Pediatric Ophthalmology	14 (19.18)	0.0001
Vitreo-Retina	59(80.82)	
Location of practice by region		--
CAR	2 (2.78)	
NCR	40 (55.56)	
Region 01	4 (5.56)	
Region 03	5 (6.94)	
Region 4A	5 (6.94)	
Region 4B	1 (1.39)	
Region 06	3 (4.17)	
Region 07	3 (4.17)	
Region 08	1 (1.39)	
Region 10	3 (4.17)	
Region 11	3 (4.17)	
Type of practice		
Private	36 (49.32)	0.50
Government	1 (1.37)	
Both	36 (49.32)	
Place of practice		
Hospital-based	43 (58.9)	0.03
Ambulatory or stand-alone clinic	1 (1.37)	
Both	29 (39.73)	
Number of ROP patients seen per week		
0-2	52 (71.23)	0.0002
3-5	16 (21.92)	
6-8	2 (2.74)	
9-10	0 (0)	
>10	3 (4.11)	
Rate of treatment requiring ROP		
0 - 25%	65 (89.04)	0.0001
26 - 50%	7 (9.59)	
51 - 75%	1 (1.37)	

ROP – retinopathy of prematurity; CAR – Cordillera Administrative Region; NCR – National Capital Region

Table 2 shows the initial treatment preference of the respondents. For type 1 ROP, 32 (43.84%) respondents preferred LIO as the initial treatment (43.84%, p=0.1158), while an almost equal number (n=31 or 42.47%) preferred anti-VEGF injection. On the other hand, majority (67.12%) preferred anti-VEGF injection as the initial treatment for APROP.

Table 2. Initial treatment preference (N=73)

Initial treatment preference	N (%)	P-value
For Type 1 ROP		
Anti-VEGF injection	31 (42.47)	0.08
LIO	32 (43.84)	0.11
Anti-VEGF injection + LIO	10 (13.70)	0.0001
Cryotherapy	0	-
For APROP		
Anti-VEGF injection	49 (67.12)	0.002
LIO	4 (5.48)	0.0001
Cryotherapy	0	-
Anti-VEGF injection + LIO	20 (27.40)	0.0008

ROP – retinopathy of prematurity, VEGF – vascular endothelial growth factor; LIO - laser indirect ophthalmoscopy

Table 3 summarizes the treatment preferences for anti-VEGF injections among respondents. Bevacizumab was the most preferred anti-VEGF drug (68.11%, P=0.0014). Among the 69 subspecialists who preferred anti-VEGF injection, 97.10% (P=0.0001) used a dosage of 0.625mg/0.025mL. Interestingly, one respondent preferred a dose of 0.020 ml, while another respondent reported using a lesser dosage without specifying the exact amount. Majority of the respondents (69.56%, P=0.0008) performed anti-VEGF injections in the operating room while others preferred the neonatal intensive care unit (NICU) (18.84%, P=0.0001) or the clinic setting (11.59%, P=0.0001). Among the respondents who used anti-VEGF injection, 36.23% (P=0.0101) administered an additional dose of injection, with the most frequent reason being recurrence. Other cited reasons included incomplete LIO therapy or presence of skipped areas, lack of sufficient response from the initial injection, persistence of abnormal vessels (e.g ridge, extraretinal fibrovascular proliferation), continuity of ROP, reactivation, persistent vitreous hemorrhage, unavailability of an LIO machine, and the need to wait for retinal maturity or full retinal vascularization.

Table 4 lists down the procedural requirements for LIO. Among the 24 respondents who perform LIO, majority used topical anesthesia (91.60%, *P*=0.0002) while a few used general anesthesia (8.40%). When performing LIO, majority required the presence of a pediatrician or neonatologist (70.83%,) and the use of a pulse oximeter (70.83%). Half required oxygen supplementation (50.00%), while a smaller number required the presence of an anesthesiologist (8.30%), or an intravenous line and supplemental oxygen (4.17%).

Table 3. Treatment preference with anti-VEGF agents (N=69)

Treatment preference	N (%)	P-value
Preferred anti-VEGF agent		
Bevacizumab	47 (68.11)	0.001
Ranibizumab	19 (27.53)	0.0001
Aflibercept	3 (4.36)	0.0001
Use of 0.625mg/0.025mL dosage in Anti-VEGF injection (Bevacizumab)		
Yes	67 (97.10)	0.0001
No	2 (2.90)	
Setting of Anti-VEGF injection procedure		
Operating room	48 (69.56)	0.0008
NICU	13 (18.84)	0.0001
Clinic Setting	8 (11.59)	0.0001
Providing more than one dose of anti-VEGF injection		
Yes	25 (36.23)	0.01
No	44 (63.76)	
Possible Reasons for Giving an Additional Anti-VEGF Injection*		-
Persistence of plus disease after 1 month	3 (12.00)	
Incomplete LIO or presence of skipped areas	1 (4.00)	
Recurrence	10 (40.00)	
Lack of sufficient response from first injection	2 (8.00)	
Persistence of new vessels	3 (12.00)	
Rapid progression	1 (4.00)	
Regrowth of neovascularization/Reactivation	4 (16.00)	
Persistent vitreous hemorrhage	1 (4.00)	
No access to LIO	1(4.00)	
Buy time for retinal maturity/full retinal vascularization	1(4.00)	

* Multiple answers were allowed.
VEGF – vascular endothelial growth factor; LIO - laser indirect ophthalmoscopy

Table 4. Treatment preference with laser indirect ophthalmoscopy (N=24)

Treatment preference	N (%)	P-value
Type of anesthesia used when performing LIO Therapy		0.0002
Topical anesthesia	22 (91.60)	
General Anesthesia	2 (8.40)	
Equipment or personnel needed before LIO Therapy*		-
Oxygen supplementation	12 (50.00)	
Pulse oximeter	17 (70.83)	
Presence of pediatrician/neonatology	17 (70.83)	
Others: presence of an anesthesiologist	2 (8.30)	
IV line and supplemental sedation	1(4.170)	

* Multiple answers were allowed.
LIO – laser indirect ophthalmoscopy

The most common clinical findings that the respondents looked for to determine the completeness of treatment included regression of abnormal vessels (73.90%), vascularization of the entire retina (72.60%), decreased tortuosity of new vessels (52.05%), quiet ridge (39.72%), and attached retina (34.25%) (**Table 5**).

Table 5. Clinical findings to determine completeness of treatment (N=73)

Clinical findings*	N (%)
Regression of abnormal vessels	54 (73.90)
Decreased tortuosity of new vessels	38 (52.05)
More quiet ridge	29 (39.72)
Vascularization of the entire retina	53 (72.60)
Attached retina	25 (34.25)
Others	3 (4.10)

* Multiple answers were allowed.

Table 6 summarizes the parameters that influence the respondents to initiate treatment for type 2 ROP. The most frequent answers were development of plus disease (82.19%) and development of stage 3 ROP with an increase of more than 5 clock hours (94.52%).

Table 6. Parameters that influenced initiation of treatment for Type 2 ROP (N=73)

Parameters*	N (%)
Slow retinal vascularization persisting beyond PCA 50 weeks	26 (35.61)
Development of stage 3 ROP with the increase of more than 5 clock hours	60 (82.19)
Development of plus disease	69 (94.52)

* Multiple answers were allowed.
ROP – retinopathy of prematurity; PCA – post-conceptual age

Table 7 summarizes the factors influencing the respondents' treatment preference for ROP. Among those who preferred anti-VEGF injections, the most common reasons included availability of the drug (46.37%), faster regression of the neovascularization compared to LIO (46.37%), and absence of scarring and allowance for full retinal vascularization (43.37%).

On the other hand, among respondents who preferred the LIO, key influencing factors included the availability of the LIO machine (75.00%), and concerns over the risk of infection with anti-VEGF injections (50.00%) (**Table 7**).

For those preferring both anti-VEGF injections and LIO, the primary reasons included the availability of anti-VEGF drug and LIO machine (85.00%), the permanence of peripheral retinal ablation of ischemic areas (75.00%), and faster regression of neovascularization (70.00%) (**Table 7**).

Table 8 presents the data on the referral system. Most respondents (54.79%) received ROP patients through referrals (P=0.24). Other respondents (43.84%) reported receiving ROP consultation via a combination of referrals and walk-in visits (P=0.11). Respondents reported that most of their referrals came from pediatricians or neonatologists (91.78%), followed by general ophthalmologists (47.94%). The most cited reasons for poor follow-up of ROP patients were caregivers' lack of understanding of the disease (58.90%), lack of funds (56.16%), problems with transportation (53.42%), and time constraints for parents/caregivers (41.11%). About a third of the respondents (32.88%, P=0.0011) referred their patients to other specialists, primarily for surgery (41.10%) followed by LIO procedure (20.55%), anti-VEGF injection (16.43%), and cryotherapy (10.96%). For ROP patients requiring surgery, most of the respondents referred at stage 4a (71.23%) followed by stage 4b (54.79%), and stage 5 (45.21%).

Table 7. Factors affecting treatment preference

Factors	N (%)
For anti-VEGF injection (N=69)**	**N (%)**
Availability of anti-VEGF	32 (46.37)
Faster regression of the neovascularization	32 (46.37)
Absence of scarring/allowing full retinal vascularization	30 (43.47)
Lower risk of high or pathologic myopia	18 (26.09)
No access to LIO	17 (24.63)
Lack of experience performing LIO	4 (5.79)
Others: higher success rate in APROP	1 (1.44)
Medical condition of the patient	1 (1.44)
For LIO (N=4)**	
Availability of LIO	3 (75.00)
Risk for infection to anti-VEGF injection	2 (50.00)
Lack of access to anti-VEGF injection	1 (2.00)
Permanent peripheral retinal ablation of ischemic areas	1(25.00)
Lack of experience in performing anti-VEGF injection	1 (25.00)
Others: Need for an intravenous line	1 (25.00)
For both anti-VEGF and LIO therapy (N= 20)**	
Availability of anti-VEGF and LIO	17 (85.00)
Faster regression of the neovascularization	14 (70.00)
Permanent peripheral retinal ablation	15 (75.00)
Lack of experience in performing cryotherapy	5 (25.00)

* Multiple answers were allowed.
VEGF – vascular endothelial growth factor; LIO – laser indirect ophthalmoscopy; APROP – aggressive posterior retinopathy of prematurity

Table 9 presents data on ROP recurrences encountered by the respondents. Majority (75.34%, P=0.0004) reported recurrence after anti-VEGF injection while 41.10% of the respondents (P=0.0620) encountered recurrence after LIO procedure. Among the 20 respondents who perform both anti-VEGF injection and LIO, 8 (40.00%, P=0.1856) reported recurrence. The most common reasons cited for recurrence after injecting intravitreal anti-VEGF were the presence of ischemic or avascular area (34.55%) and unstable clinical

course such as hypoxia, sepsis and anemia (18.18%). Meanwhile, presence of skipped areas (73.33%) was the most common reason cited for recurrence after LIO. In contrast to monotherapy with anti-VEGF or LIO, respondents indicated that an unstable clinical course (25.00%) was the most common risk factor for recurrence when both anti-VEGF and LIO were used in combination. After initial treatment failure with a treatment modality, respondents mostly preferred LIO therapy (53.00%) as the subsequent treatment for recurrences, followed by anti-VEGF injection (37.50%). Lastly, most respondents encountered recurrence in less than 50 weeks PCA irrespective of the treatment modality used. However, a few respondents also reported recurrence in patients more than 60 weeks PCA following any treatment approach (anti-VEGF injection: 5.45%; LIO therapy: 6.67%; combined anti-VEGF injection and LIO therapy: 12.50%).

Table 8. Referral system

Referral system (N=73)	N (%)	P-value
Mode of consultation		
Walk-in	1 (1.37)	0.0001
Referrals	40 (54.79)	0.24
Both	32 (43.84)	0.11
Source of referrals*		-
Pediatrician/neonatologist	67 (91.78)	
Ophthalmologist	35 (47.94)	
Pediatric Ophthalmologist	14 (9.17)	
Vitreo-Retina Specialist	10 (13.70)	
Non-government organizations/Schools for the Blind	1 (1.36)	
Optometrist	0 (0)	
Reasons for poor follow-up*		-
Lack of understanding of the diseases	43 (58.90)	
Lack of funds	41 (56.16)	
Problems with transportation	39 (53.42)	
Lack of time of parents/caregiver	30 (41.11)	
Others: False belief of caregivers	6 (8.21)	
Referral to another specialist		
Yes	24 (32.88)	0.001
No	49 (67.12)	
Reasons for referral to other specialists*		-
Anti-VEGF therapy	12 (16.43)	
Laser indirect ophthalmoscopy	15 (20.55)	
Cryotherapy	8 (10.96)	
Surgery	30 (41.10)	
None of the above	11 (15.09)	
Reasons for referral for surgical management*		-
Stage 4a	52 (71.23)	
Stage 4b	40 (54.79)	
Stage 5	33 (45.21)	
Others: for patient's 2nd opinion	1(1.36)	

* Multiple answers were allowed.

DISCUSSION

This study assessed the current practice preferences among ophthalmology subspecialists in the Philippines for treating ROP. Traditionally, cryotherapy and LIO therapy have been standard treatments for ROP. Consistent with global standards where LIO is widely accepted as the primary treatment modality, our survey found that more respondents preferred LIO monotherapy (43.85%) as the initial treatment for Type 1 ROP.[15,16] However, the survey also indicated that anti-VEGF injection is considered an acceptable alternative for Type 1 ROP by 42.47% of respondents.

With the advent of anti-VEGF injection and the results of the BEAT-ROP study, this treatment modality has emerged as a preferred initial option for APROP. [9,10] Our survey showed that 67.12% of the respondents preferred anti-VEGF injection monotherapy for APROP. This preference aligns with the study by Fouzdar Jain *et al.*, where anti-VEGF injection was predominantly chosen for zone 1 or aggressive posterior zone 2 ROP patients, while LIO monotherapy was favored for zone 2 ROP patients.[15] Cryotherapy was less preferred by the respondents due to poor structural and functional outcomes.

Among the different anti-VEGF agents, the respondents favored bevacizumab (68.11%) in the dose of 0.625mg/0.025mL (97.10%) the most which is in agreement with the survey of Fouzdar Jain *et al.*[15] The dose is typically half the standard adult dosage, as recommended by the BEAT-ROP study.[9,10] Concerns about potential systemic toxicity have led to the exploration of lower doses of bevacizumab.[15] For instance, Harder *et al.* proposed a lower dosage of 0.375mg/0.03ml for type 1 zone I or II ROP while Wallace *et al.* suggested that a dosage as low as 0.004mg might be effective, though their follow-up was limited to about 4 weeks and they recommended further studies on the long-term effects.[17,18] Ranibizumab at a dose of 0.2mg or 0.1mg/0.025mL based on RAINBOW study and aflibercept at a dose 1.0mg/0.025mL have been shown to be effective treatments for type 1 ROP and APROP.[19,20] An ongoing clinical trial, FIREFLEYE, is investigating the effects of aflibercept compared to LIO in ROP.

Table 9. Recurrences encountered by ROP subspecialists after treatment

Parameters	N (%)	P-value
Recurrence after anti-VEGF treatment (N=73)		
Yes	55 (75.34)	0.0004
No	18 (24.66)	
Risk factors for recurrence after anti-VEGF treatment (N=55)*		-
Presence of avascular areas/ischemic areas	19 (34.55)	
Poor health/poor systemic condition/unstable clinical course	10(18.18)	
Slow vascularization	2 (3.63)	
Poor follow up/lost to follow up	2 (3.63)	
Posterior disease	1(1.18)	
Incomplete treatment/presence of skipped areas	1 (1.18)	
Progression of plus disease	1(1.18)	
Persistent use of supplemental oxygen	1 (1.18)	
Pre-treatment zone 1 ROP	1 (1.18)	
LIO not done	1 (1.18)	
Preferred mode of treatment if recurrence is encountered after anti-VEGF injection (N=55)		
Add laser	33 (60.00)	0.0690
Anti-VEGF injection	11 (20.00)	0.0001
Observe until indication for treatment appears	6 (33.33)	0.0058
Others (did not state)	3 (5.45)	0.0001
None of the above	4(7.27)	0.0001
Oldest PCA observed with recurrence of an active disease after anti-VEGF injection (N=55)		-
< 50 weeks	32 (58.18)	
51-55 weeks	9 (16.36)	
56-60 weeks	4 (7.27)	
>60 weeks	3 (5.45)	
None of the above/Did not encounter recurrence	8 (14.54)	
Other (did not state)	1 (1.18)	
Recurrence encountered after LIO therapy (N=73)		
Yes	30 (41.10)	0.0620
No	43 (58.90)	
Risk factors for recurrence after LIO therapy (N=30)*		-
Incomplete laser/skip areas	22 (73.33)	
Unstable clinical course (anemia, sepsis, hypoxia)	6 (20.00)	
Late treatment	1 (3.33)	
Aggressive ROP	1 (3.33)	
Preferred mode of treatment if recurrence is encountered after LIO (N=30)		-
Repeat intravitreal anti-VEGF injection	5 (16.67)	
LIO	16 (53.33)	
Anti-VEGF injection + LIO	5 (16.67)	
Other (please specify)	2 (6.67)	
None of the above/Did not encounter recurrence	2 (6.67)	
Oldest PCA observed with recurrence of an active disease after LIO therapy (N=30)		-
None of the above	6 (20.00)	
< 50 weeks	19 (63.33)	
51-55 weeks	3 (10.00)	
56-60 weeks	0	
>60 weeks	2 (6.67)	
Recurrence encountered after anti-VEGF and LIO therapy (N=20)		
Yes	8 (40.00)	0.1856
No	12 (60.00)	
Risk factors for recurrence after performing combined anti-VEGF injection and LIO therapy (N=8)*		-
Unstable clinical course (persistent episodes of desaturation, presence of pulmonary hypertension, persistent PDA, severe anemia)	2 (25.00)	
Incomplete laser/presence of skipped areas	3 (37.50)	
Aggressive disease	1(12.50)	
Non-progression of normal retinal vascularization	1(12.50)	
Development of tractional membranes	1(12.50)	
Preferred Mode of treatment if recurrence is encountered after combined anti-VEGF and LIO therapy (N=8)		
Repeat intravitreal anti-VEGF injection	3 (37.50)	0.2311
LIO	5(62.50)	
Oldest PCA observed with recurrence of an active disease after combined anti-VEGF injection and LIO therapy (N=8)		-
None of the above	1(12.50)	
< 50 weeks	4 (50.00)	
51-55 weeks	2 (25.00)	
>60 weeks	1(12.50)	

* Multiple answers were allowed.

ROP – retinopathy of prematurity, VEGF – vascular endothelial growth factor; LIO - laser indirect ophthalmoscopy; PCA – post-conceptual age; PDA –patent ductus arteriosus

Literature suggests that ranibizumab, with its shorter half-life and higher binding affinity to VEGF-A compared to bevacizumab, may theoretically have less systemic side effects.[14,20-24] However, ranibizumab is also associated with a higher recurrence rate due to the faster vitreous clearing and shorter half-life.[21,22] In our study, 27.53% of the respondents preferred ranibizumab while 4.36% preferred aflibercept. Our survey showed that approximately one-third of the respondents would give more than one dose of intravitreal anti-VEGF injection, if necessary. The cited reasons for reinjection were ROP recurrence, persistence of the ROP or abnormal vessels, rapid progression, persistence of vitreous hemorrhage, incomplete response after 1 week post injection, and unavailability of a LIO machine. Similar to the study of Fouzdar Jain *et al.*, 44.6% of the respondents would reinject a second dose, while 24.8% would give a third dose.[15] None of the respondents would administer more than 3 doses[15]. In the study of Fouzdar Jain *et al.*, the respondents would wait 7-14 days before re-injection.[15]

ROP subspecialists in the survey favored LIO therapy due to factors such as availability of LIO machine, lack of access to anti-VEGF injection, permanent peripheral retinal ablation using LIO, and lack of experience in performing an anti-VEGF injection. In contrast to the survey, studies by Tawse *et al.* and Fouzdar Jain *et al.* stated that the systemic safety profile of bevacizumab and potential side effects, such as pulmonary and hepatic dysfunctions, were of utmost concerns for subspecialists in favoring LIO therapy over injection.[14,15,18] Other factors in considering LIO therapy found in the studies include personal preference, anti-VEGF medication not being FDA approved for use in the eye, lack of experience or training in ROP injection, need for infant sedation, and difficulty in procuring bevacizumab.[14,15] This disparity in the results may be associated with the lack of resources and accessibility to the drug in most rural areas in the Philippines compared to the urban areas. In addition, the previous published surveys were conducted in high-resource countries.

This survey identified factors influencing treatment preferences. Key reasons for choosing anti-VEGF injections included faster neovascularization regression, lower myopia risk, and limited LIO access. Some barriers from Tawse's study, such as procedure length and pediatric anesthesia issues, were not reported by our respondents.[14]

Based on the survey results, the top factors influencing combined LIO and anti-VEGF injection were the availability of both treatments, permanent peripheral retinal ablation of ischemic areas, and faster regression of neovascularization. Most respondents (69.56%) preferred the operating room for anti-VEGF injections, in contrast to Vartanian *et al.*'s findings, which favored the NICU because it provides accessibility of treatment administration at bedside.[16,25,26] This difference in practice may be attributed to the fact that, in the Philippines, anti-VEGF injections for adults are typically performed in the operating room, a practice that is extended to treatments for infants with ROP.

When performing the LIO therapy, respondents required a pulse oximeter, the presence of a pediatrician/neonatologist, and oxygen supplementation. These reflect how the respondents value patient safety during the procedure.

Most ROP patients were initially seen and referred by pediatricians or neonatologists (91.78%). This emphasizes the importance of ROP awareness and screening among these medical specialists to prevent delayed treatment of advanced disease. Many respondents (41.10%) would refer to a retina subspecialist for surgical intervention and would advise surgery for patients with stage 4 and 5 ROP.

Poor follow-up of ROP patients was mainly due to financial issues, similar to the results of Vartanian *et al.* study.[16] Other reasons cited in the survey were parents' lack of ROP awareness, time constraints, transportation issues, family misconceptions or traditional beliefs. These highlight the critical role of pediatricians, neonatologists, general ophthalmologists, and ROP subspecialists in educating the parents and caregivers on the importance of lifelong monitoring and long-term follow-up of ROP patients. This underscores the need to reinforce the 2013 PAO recommended guidelines on continuity of care and long-term follow-up, as well as to enhance public awareness campaigns on this critical issue.[5]

Key findings to determine ROP treatment completion from the survey were regression of

abnormal vessels, decreased tortuosity of new vessels, full vascularization of the retina, quiet ridge or no signs of activity, and attached retina. In line with the 2013 guidelines, full retinal vascularization up to the ora serrata was also a recommended key feature to evaluate treatment completion among patients treated with bevacizumab injection.[5]

More recurrences were reported by respondents using anti-VEGF injection monotherapy compared to LIO monotherapy or combined anti-VEGF injection and LIO. The factors reported in this survey for recurrence in LIO therapy included the presence of skipped areas and unstable clinical course such as anemia, sepsis and hypoxia. This was similar with the findings of Ling *et al.* in which sepsis, mechanical ventilation, supplemental oxygen, respiratory distress syndrome, persistent patent ductus arteriosus, and lower gestational age were the common factors for recurrence after LIO.[21]

On the other hand, the presence of avascular retina or ischemic areas, progression of plus disease, unstable clinical course or systemic condition of the patient, slow retinal vascularization, persistent supplemental oxygen use, and presence of high levels of VEGF were the risk factors of recurrence obtained in the survey after anti-VEGF injections. These observed factors were similar to the findings seen in the study of Ling *et al.*, in which lower gestational age, lower birth weight, longer duration of hospitalization, extensive retinal neovascularization, supplemental oxygen requirement after treatment, and pre-retinal hemorrhage before treatment contributed to the risk of recurrence.[21]

For combined treatment, presence of skipped areas and unstable clinical courses such as the presence of pulmonary hypertension, severe anemia and episodes of desaturation were the common reasons for recurrence reported in this survey, which were similar to the identified reasons in LIO monotherapy and anti-VEGF injection monotherapy.[27,28]

The survey showed that recurrences were commonly experienced in less than 50 weeks of PCA regardless of the preferred treatment modality. But some respondents experienced recurrence even after more than 60 weeks of PCA. In the study done by Hu *et al.*, late ROP recurrence occurred at 69 weeks after intravitreal bevacizumab injection.[13] With this, Moshfeghi and Beroccal recommended long-term surveillance and extending monitoring up to 80 weeks PCA and beyond.[10] The risk factors for recurrence were low birth weight, zone 1 ROP, and multiple birth.[21] Recurrence after intravitreal bevacizumab injection can occur posteriorly or near the previous site of extraretinal fibrovascular proliferation or anteriorly, creating a more anterior ridge due to anterior progression of the vessels.[13]

The survey showed that the LIO procedure was the most preferred treatment modality for recurrence regardless of the initial treatment. Similar to our survey, Hu *et al.* stated that LIO could be a standard treatment option for recurrences since they noted further persistence or recurrence after giving a second dose of anti-VEGF injection, and these patients still underwent LIO therapy.[13] In contrast, patients who received the LIO therapy after recurrence did not require further treatment, and no progression to retinal detachment was likewise observed.[13]

Limitations of this study include significant potential for recall bias. The data was self-reported, introducing the possibility of recall bias and a dependency on the accuracy of the respondents' input, which may influence the outcomes. This study was also limited to ROP subspecialists, excluding general ophthalmologists who may serve as primary care givers, especially in rural areas where access to subspecialists is limited. Despite the limitations of this study, the large number of respondents allowed for a comprehensive insight into the diverse practices for treating ROP in the country.

In conclusion, this study highlights the variability in the treatment of ROP in the Philippines, which is driven by multiple factors including the availability and accessibility of equipment and medications, more pronounced response to anti-VEGF therapy, and the experience of the practitioners in utilizing specific agents or equipment. The impact of availability and accessibility on the treatment preference highlights the critical need for these resources to be made widely available and accessible across all regions in the Philippines. Variability was observed in several aspects of treatment, including preferences for managing APROP, the choice of anti-VEGF agents and dosage, the setting for an anti-VEGF injection, the type of anesthesia in LIO, the mode of

consultation, recurrence rates following anti-VEGF therapy, and the preferred treatment modality for managing recurrence. LIO remains the treatment of choice for both initial therapy in Type 1 ROP and for recurrent cases, while anti-VEGF injections are the most preferred option in APROP and serve as an alternative therapy in Type 1 ROP. Given the absence of a universally established treatment standard for recurrent ROP, long-term monitoring is essential for early detection of recurrence and timely intervention.

ROP management requires a multidisciplinary team, including medical professionals and caregivers. Therefore, ongoing awareness and education campaigns are crucial to ensure timely referral, prevent treatment delays, and ultimately improve visual outcomes for affected children.

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