OPEN ACCESS
Freely Available Online

JOURNAL OF OPHTHALMIC SCIENCE
ISSN NO: 2470-0436

Research Article

DOI : 10.14302/issn.2470-0436.jos-18-2222

Identification of Eyes At Risk for Severe Retinopathy of Prematurity (ROP) by Third Year Ophthalmology Residents in a Tertiary Hospital

Eleonore B. Iguban [1,*], Milagros H. Arroyo [1]

[1]Department of Ophthalmology and Visual Sciences, University of the Philippines Manila, Philippines.

Abstract

Objective: The aim of the present study is to determine the efficiency of third year ophthalmology residents from a tertiary hospital in performing preliminary retinal examination to identify eyes at risk retinopathy of prematurity on the basis of retinal fundus findings up to International Classification of Retinopathy of Prematurity (ICROP) Zone II.

Methods: This is a single-center, cross-sectional, prospective comparative research conducted from June to October 2015 at a tertiary training hospital in the Philippines. All infants referred for retinopathy of prematurity screening within the study period where included. The presence of retinal vessel dilatation and tortuosity were identified by third year ophthalmology residents using indirect funduscopy. The residents' fundus findings were then compared to that of a retina consultant who is proficient in the diagnosis and management of retinopathy of prematurity (ROP). The Kappa index was used to rate inter-observer agreement. The correlation between ROP risk factors and the presence of abnormal retinal vessels were assessed using odd ratio computations. Fisher's exact test was used to determine the correlation between retinopathy of prematurity and the presence of retinal dilatation and tortuosity. The McNemar's test was also applied to determine significant differences in the retinal findings of the consultant and ophthalmology residents.

Results: A total of 82 eyes of 41 premature infants were evaluated to determine if retinal findings observed by ophthalmology residents were comparable to that of a retina consultant. Odds ratios show that age of gestation, birth weight, and history of blood transfusion are significantly associated with the presence of retinopathy of prematurity. Retinal vessel tortuosity and dilatation are also more common among infants diagnosed with retinopathy of prematurity. There was no significant difference between the retinal vascular findings of the retina consultant and the third year ophthalmology resident in terms of identifying retinal vessel dilatation and tortuosity ($P < 0.05$).

Conclusion: After sufficient and in-depth ophthalmology training, third year ophthalmologists, who will be general ophthalmologists in the future, can reliably identify eyes at risk for severe retinopathy of prematurity on the basis of retinal vascular dilatation and/or tortuosity.

Corresponding Author: Eleonore B. Iguban, Department of Ophthalmology and Visual Sciences, University of the Philippines Manila, Philippine General Hospital, Sentro Oftalmologico Jose Rizal, Taft Avenue, Manila, Philippines 1000, Telefax: +63-2-3365203

Citation: Eleonore B. Iguban, Milagros H. Arroyo (2018) Identification of Eyes At Risk for Severe Retinopathy of Prematurity (ROP) by Third Year Ophthalmology Residents in a Tertiary Hospital. Journal of Ophthalmic Science - 2(1):1-15. https://doi.org/10.14302/issn-2470-0436.jos-18-2222

Keywords: retinopathy of prematurity, ROP screening, plus disease, premature babies, ophthalmology residents

Received: July 12, 2018 **Accepted:** Aug 4, 2018 **Published:** Aug 06, 2018

Editor: Brian Tieu, University of Mississippi Medical Center, American Samoa.

Introduction

Retinopathy of prematurity (ROP) is a proliferative retinal vascular disorder primarily affecting premature or low birth weight infants.[1]With advancements in neonatal care and increasing survival of preterm infants, there is a parallel increase in the incidence of ROP worldwide. Retinopathy of prematurity accounts for 6-18% of irreversible childhood blindness in both developed and developing countries.[2] Based on the statistics provided by the World Health Organization (WHO), more than half of the estimated 1.5 million blind children in the world are in Asia.[3] In the Philippines, almost half a million Filipinos suffer from blindness and fifty percent of them are known to be from a preventable or treatable cause such as ROP.[3] In fact, it has been reported that 8.4% of children attending a school for the blind in the Philippines have severe visual impairment secondary to ROP.[4]

Retinopathy of prematurity, in its advanced stages, equates to a high economic burden for both the community and the individual since it affects normal motor, social, language, and intellectual development of the child. Numerous studies have shown that blindness as a result of neglected retinopathy of prematurity is preventable when treatment is done at the appropriate time.[5]Some management options for those with ROP include laser photocoagulation, injection of anti-VEGF, and cryotherapy.[5] The proven benefit of these treatment modalities has made it imperative for all susceptible infants to undergo routine screening by an ophthalmologist trained in the evaluation and management of ROP. [5]

Current practice guidelines for ROP screening released in 2006 by the American Academy of Pediatrics, the American Association for Pediatric Ophthalmology and Strabismus (AAPOS), and the American Academy of Ophthalmology (AAO) recommended that retinal screening examination should be done on all infants with the following: (1) birth weight of less than 1500g; (2) gestational age of 32 weeks or less, and (3) birth weight less than 2000g or a gestational age more than 32 weeks but with an unstable clinical course. Screening for ROP should be done between 4-6 weeks of post-natal age or between 31 and 33 weeks of post-conceptional age.[6] A more in depth understanding in the pathogenesis and management of ROP has led to revisions in ROP screening guidelines worldwide with countries creating their own screening strategies tailored to ROP research findings in their population. In the Philippines, the current recommended guidelines for screening and referral of retinopathy of prematurity drafted by the Philippine Retinopathy of Prematurity Working Group (ROPWG) states that all premature infants <35 weeks gestational age (GA), birth weight (BW) <2000grams, and those having an unstable clinical course must be screened for ROP. [7]Older and heavier Filipino premature babies are now being screen since Corpus et.al. (2013) reported that using the international ROP guidelines missed some Filipino neonates with severe ROP.[8] The first examination for ROP screening must be done at 2 weeks post natal age or at 32 weeks post-conceptional age whichever comes earlier.[7]This procedure would entail adequate pan-retinal examination up to the ora serrata, performed under suitable pupillary dilation and with the use of a binocular indirect ophthalmoscope, a 20D or 28D-condensing lens, and infant lid speculum, and a scleral depressor or indentor.[7]

The International classification of ROP (ICROP) of 2005 has served as the basis of numerous multicenter studies on ROP during the last two decades. It has enabled a standardized approach in retinal examination and reporting of findings during ROP screening. The ICROP describes retinal findings with emphasis on the extent of the developing vasculature, the location relative to the optic nerve, which is divided into three zones, and the progressive staging of ROP. The International classification of ROP (ICROP) staging for the severity of ROP has five stages, with stage 1 being the least severe, and stage 5 as the most severe characterized by total retinal detachment. [9]A strong predictor of poor outcome in those diagnosed with retinopathy of prematurity (ROP) is the presence of abnormally increased diameter and tortuosity of retinal blood vessels in the posterior pole in two or more quadrants, or " plus disease."[10]

Examination of the peripheral retina during ROP screening might not always be possible in hospitals and maternal delivery centers. This may be due to either the lack of awareness of pediatricians and midwives regarding ROP screening guidelines[11]or the absence of

available trained ROP specialists in the provinces and far flung communities in the Philippines. Thus, the ability of general ophthalmologists to recognize fundus changes at the posterior pole, suggesting the presence of impending ROP, and who could then refer to ROP subspecialists would promote prompt detection and treatment of the disease.

The gradual and long learning curve associated with mastering the skill of ROP screening coupled with the widespread lack of trained ROP specialists in most health institutions and maternal delivery centers in the Philippine communities have caused neonates to go unexamined. Irreversible and severe blindness has occurred in these babies who were not screened and managed timely due to inadequate ROP screening programs. The frequency of undetected ROP in these areas justifies the need to investigate the feasibility of an alternative method of screening done by general ophthalmologists who are more present in the provinces and smaller communities. These general ophthalmologists should be able to identify neonates with risk factors for ROP development, recognize ophthalmological signs of possible ROP such as poorly dilating pupils and hazy ocular media, and detect retinal vascular abnormalities warranting immediate referral to a Retina-ROP subspecialist. The results of this research would pave the way for the inclusion of ROP screening techniques in the Philippine Ophthalmology residency training program. This would ensure that all ophthalmology residency graduates would be able to adequately do preliminary ROP screening and recognize cases that would warrant urgent referral to an Retina-ROP subspecialist for timely management. This, in turn, would lessen, if not eliminate, the occurrence of at-risk babies developing severe visual impairment due to lack of access to an ROP examination in the provinces and local communities.

The aim of the present study is to determine the efficacy of third year ophthalmology residents from a tertiary hospital in performing preliminary retinal examination to identify eyes at risk retinopathy of prematurity on the basis of retinal fundus findings up to International Classification of Retinopathy of Prematurity (ICROP) Zone II.

Methodology

This is a single-center, cross-sectional, prospective, comparative research conducted from June to October 2015 at the Philippine General Hospital (PGH).

This study has been granted approval for implementation by the UP Manila Research Ethics Board (UPMREB) Panel 3 last 25th of May 2015. All study procedures were done in accordance with the principles for scientific research stated in the Helsinki declaration. All study information were also anonymized and handled in a confidential manner. All study participants, moreover, were required to sign a consent form prior to inclusion in this research.

The Examining Study Group (Third Year Ophthalmology Residents)

The examining study group consisted of eight (8) third year ophthalmology residents from the hospital's Department of Ophthalmology and Visual Sciences (DOVS). They were asked to sign an informed consent prior to being included in this study. The third year resident examined all neonates referred to the UP-PGH DOVS Medical Retina service for Retinopathy of Prematurity screening during the study period. They were accompanied by the Medical Retina fellow and/or the Retina consultant during the said procedure. The third year ophthalmology residents were not given any incentive or compensation for inclusion in this study nor would this entail additional expenses on the part of the resident.

As part of their ophthalmology training, the third year ophthalmology residents in this tertiary center have obtained extensive experience in performing indirect ophthalmoscopy to view various retinal conditions in all age groups during their yearly rotation with the Retina service and at the Out Patient Department- General clinic. The third year residents have also attended conferences and lectures regarding the basics and management of retinopathy of prematurity. Prior to being promoted to the next level of training, they also have annual examinations to assess their understanding of ophthalmologic conditions, including Retinopathy of prematurity, and their proficiency in performing indirect ophthalmoscopy among others.

The retinal findings of the third year ophthalmology residents were compared to the results of the retinal examination of the retina consultant, who will serve as the "gold standard." The retina consultant is considered to be the "gold standard" since she is considered to be the expert in the diagnosis and management of retinopathy of prematurity as evidenced by her vast experience in treating such conditions. The retina consultant has acquired extensive training in retinal conditions from local and foreign institutions, and has been part of the Ophthalmological faculty in this tertiary center for more than twenty (20) years. The retina consultant is also part of the ROP- Working Group in the Philippines, which is a group of ROP experts dedicated to formulate and improve ROP screening, diagnosis, and management in our country.

Determination of Inter-observer Agreement

In order to determine inter-observer agreement between the third year residents, a pretest and posttest retinal picture set evaluation were administered. They were asked to identify if there is positive (abnormal) or negative (normal) retinal vessel dilatation and tortuosity using a given set of pre-determined retinal vessel pictures. The retinal vessel picture set will be composed of 6 pictures pre-selected by the principal investigator and will be composed of 2 pictures of normal retinal vessels as well as 4 pictures of abnormal retinal vessel dilatation and/or abnormal retinal vessel tortuosity. The principal investigator gave a group feedback regarding the correct answers for the picture set after the pretest. Kappa analysis was used to determine the degree of inter-observer agreement.

Preliminary Retinal Examination for Retinopathy of Prematurity and Data Collection

This part of the study will be conducted at three locations within the Philippine General Hospital, namely: Medical Retina clinic, Neonatal Intensive Care Unit, and the Pediatric Wards. All neonates referred for ROP screening within the study period were included in this study. The parents or legal guardians of the neonates referred for ROP screening were asked to sign the informed consent prior to the procedure

Exclusion criteria included media opacities obscuring the posterior pole view, poorly dilating pupils, unstable clinical condition, no consent for the procedure and prior knowledge of referral findings by the examining study group.

Once the neonate has been referred for ROP screening and clearance for the procedure has been given by the referring neonatologist, the first year Medical Retina resident, who is not part of the ROP screening team, administered the informed consent prior to the ROP examination. The neonates and their parents or guardians were not given any incentive or compensation for inclusion in this study nor will this entail additional expenses on the part of the patient.

The third year ophthalmology residents rotated together with the ROP screening team composed of the three Medical Retina fellows and a consultant. The ROP examination of eligible neonates was performed after clearance for ROP screening was given by the attending neonatologist and upon acquisition of the signed consent form. It will entail the visualization of the retina up to International Classification of ROP (ICROP) Zone II, which is approximately 4-5 disc diameters from the optic disc nasally, 3-4 disc diameters from the temporal vascular arcades inferiorly and superiorly, and 3-4 disc diameters temporal to an imaginary line which connects the supero-temporal and infero-temporal vascular arcades.

Examination for retinopathy of prematurity was done using an indirect ophthalmoscope, 20D condensing lens, and a scleral depressor after adequate pupillary mydriasis. Dilation of the pupil will be obtained by sequential instillation of tropicamide 0.5% and Phenylephrine 2.5% (Sanmyd-P) at 15 minutes interval starting one hour before examination. The babies for ROP screening were placed on NPO one hour prior to examination to prevent aspiration. During the ROP examination, topical anesthesia was applied prior to insertion of the infant lid speculum and use of the scleral depressor. Topical lubricant drops were also used to prevent ocular surface dryness that could affect media clarity. Topical antibiotic drops were instilled after every ROP examination.

The ophthalmology resident performed the retinal examination first followed by the Medical retina consultant. The ophthalmology resident's retinal examination initially started by checking the condition of the optic nerve, followed by the fovea. After which, the

appearance of the retinal vessels until about 3-4 disc diameters away from the vascular arcade (approximate ICROP Zone II) was assessed in four quadrants (superior, inferior, nasal and temporal) with the use of a scleral depressor for globe stabilization. The ophthalmology resident was allowed to view each quadrant until he or she is able to adequately assess the retinal vessel characteristics or until 2 minutes per quadrant, which ever is earlier. Retinal vessels were inspected based on (1) vessel tortuosity, and (2) vessel dilation of arteries and veins. Each criterion would be recorded as (-) negative indicating absence of the said characteristic, and (+) positive indicating presence of the said characteristic. Abnormalities in retinal vessels such as increased in tortuosity or dilated veins and arteries are indicators for pre-plus (vessel dilation and tortuosity in less than 2 quadrants and plus disease (vessel dilation and tortuosity in 2 quadrants) which warrant immediate referral. Retinal findings, particularly the presence or absence of retinal vessel dilatation and tortuosity, were recorded on the Case Report form (ROP Examination form) by both the consultant and the third year ophthalmology resident.

These ROP examinations were conducted in a blind test manner, wherein the resident examines each infant independently from the others and had no access to the findings of the Retina consultant. Repeated retinal examinations by the ROP screening team were done to determine if ROP develops in future examinations. The screening for ROP is completed once retinal vascular maturity is achieved, which is characterized as having at least one of the following retinal findings [15]:

Zone III retinal vascularization attained without previous zone I or II ROP (if there is examiner doubt about the zone or if the Post conceptional age is <35 weeks, confirmatory exams may be warranted);

Full retinal vascularization in close proximity to the ora serrata for 360' (at least 1 disc area from the oraserrata);

Post conceptional age of 50 weeks and no pre-threshold disease (stage 3 ROP in zone II, any ROP in zone I) or worse ROP is present;

Regression of ROP

The neonates being examined for retinopathy of prematurity were withdrawn from inclusion in this study in the following circumstances:

Those who become unstable (e.g. apneic and cyanotic) during the course of the retinal examination

Those who are deemed unfit by the neonatologist to undergo retinal examination even if with prior clearance and parental consent (e.g. with recent episode of apnea, seizures, desaturations)

Those who have parents that decided to discontinue their participation in the study

Those that cannot tolerate the retinal examination as observed by the examining third year resident, medical retinal consultant, neonatologist or by the parent/guardian.

In cases of adverse events, the retinal examination was discontinued and immediate medical response to the said adverse event was instituted by the ophthalmologist and /or the neonatologist. Any neonate who has suffered from the adverse event was excluded from the study. The adverse event was also reported to the UP Manila Research Ethics Board (UPMREB). Moreover, those neonates who have been withdrawn from the study due to adverse events were still eligible for ROP screening if deemed stable by the attending neonatologist.

Statistical Analysis

The patients' demographic characteristics were tabulated and analyzed. The Kappa index was used to rate inter-observer agreement. The correlation between risk factors and the presence of abnormal retinal vessels were assessed using odd ratio computations with confidence intervals calculated at 95% and statistical significance at $p < 0.05$. On the other hand, In order to determine the correlation between retinopathy of prematurity and the presence of retinal dilatation and tortuosity, Fisher's exact test was computed. The McNemar's test was also applied to determine significant differences in the retinal findings of the consultant and ophthalmology residents.

Results

Inter-observer Agreement of Examining Study Group

A total of eight (8) third year ophthalmology residents from the PGH- Department of Ophthalmology and Visual Sciences underwent both the pretest and

posttest evaluation for the determination of inter-observer agreement. Calculations using Kappa analysis were based on the residents' assessment of retinal vessel dilatation and tortuosity in a set of pre-determined set of retinal pictures.

Table 1 and 2 show the outcomes of Kappa analysis to determine inter-observer agreement among the examining study group. For the pretest, a very good inter-observer agreement (κ=1.00) was computed for the retinal vessel tortuosity while for the retinal vessel dilatation, there was moderate inter-observer agreement (κ =0.552). On the other hand, posttest results revealed a kappa coefficient of 1.00, which indicates a very good inter-observer agreement for both retinal vessel tortuosity and dilatation.

Demographics and Risk Factors of Preterm Infants Examined for Retinopathy of Prematurity

The study examining group of ophthalmology residents were able to evaluate eighty-two (82) eyes of forty-one (41) premature babies for retinopathy of prematurity screening within the study period. The baseline characteristics of these neonates are tabulated below (Table 3). The study patients were equally represented in terms of gender, wherein 46% were males and 54% were females. The mean maternal age was 27, and ranges from 16-42 years. Most of the referred babies were born at 30 weeks age of gestation, with birthweights ranging from 890-2200 grams. Mean post-conceptional age upon referral for ROP screening was 36 weeks, and four (4) out of the 82 eyes that were examined had rubeosis on presentation.

Table 4 shows a summary of the existing identifiable risk factors associated with the development of retinopathy of prematurity in the preterm infants screened for ROP. Almost half (41%) of the referred preterm infants had exposure to oxygen with mechanical ventilation and nasal cannula/oxygen hood as the most common oxygenation method. Thirteen mothers (32%) had spontaneous premature rupture of membranes leading to early delivery. Meanwhile, almost 29% of the premature infants examined had a history of blood transfusion during the perinatal period.

The correlation between risk factors and the presence of abnormal retinal vessels as diagnosed by the study's retina consultant were assessed using odd ratio computations with confidence intervals calculated at 95%. The summary of these computations is shown in Table 5.

Computations of odds ratio revealed that there is an increase risk in developing retinal vessel dilatation and/or tortuosity in the presence of the following risk factors, namely: (1) exposure to any method of oxygenation, (2) maternal infection, (3) pre eclampsia/ eclampsia, (4) preterm premature rupture of membranes, (5) history of perinatal blood transfusion, (6) neonatal jaundice, (7) lower birth weight, and (8) earlier age of gestation. Most of the risk factors, however, did not show a statistically significant association for the development of abnormal retinal vessels, except for exposure to mechanical ventilation, birth weight and age of gestation.

Table 6 shows the correlation of various risk factors with the presence of a clinically diagnosed retinopathy of prematurity. Based on the computations of odds ratio at a 95% confidence interval, it has been shown that only age of gestation, birth weight, and transfusion are significantly associated with the presence of retinopathy of prematurity. Specifically, the risk of ROP is higher for those infants who have a history of perinatal transfusion, lower birth weight and earlier age of gestation.

Fisher's exact test was computed to determine the correlation between retinopathy of prematurity and the presence of retinal dilatation and tortuosity. A significant association was seen between retinal vessel dilatation and tortuosity with the presence of retinopathy of prematurity (see Table 7). In general, retinal vessel tortuosity and dilatation are more common among infants diagnosed with retinopathy of prematurity than those without the disorder.

The comparison between the retinal vascular findings of the consultants versus the study examining group are summarized in Tables 8 and 9. Results of the McNemar's test showed that at $p<0.05$, there was no significant difference between the retinal vascular findings of the consultant which serves as the " gold standard" and the third year ophthalmology resident in terms of identifying retinal vessel dilatation and tortuosity.

Table 1. Summary of Retinal Vessels Evaluation by Third Year Ophthalmology Residents

Image	No. of residents	Tortuosity		Dilatation	
		Pre-test	Post-test	Pre-test	Post-test
1	8	8	8	8	8
2	8	0	0	8	0
3	8	8	8	5	8
4	8	8	8	1	0
5	8	8	8	5	8
6	8	0	0	0	0

Table 2. Estimated Kappa (κ) coefficient for Inter-observer Agreement

	Pre test	Post test
Tortuosity	1.000	1.000
Dilatation	0.552	1.000

Table 3. Demographics and Baseline Characteristics of Patients Examined for Retinopathy of Prematurity (n= 41)

Baseline Characteristics		
Gender, n(%)	Male	19 (46%)
	Female	22 (54%)
Maternal age (years)	Mean ±SD	27.32 ±6.6
	Median (Range)	27.5 (16 – 42)
Birth weight (grams)	Mean ±SD	1316.46 ±314.0
	Median (Range)	1300 (890 – 2200)
Gestational age (weeks)	Mean ±SD	31 ±1.9
	Median (Range)	31 (26 – 34)
Postconceptional age (weeks)	Mean ±SD	36 ±4.1
	Median (Range)	35 (30 – 51)
Rubeosis (right eye), n(%)	Present	2 (4.9)
	Absent	39 (95.1)
Rubeosis (left eye), n(%)	Present	2 (4.9)
	Absent	39 (95.1)

Table 4.Presence of Risk Factors in Preterm Infants Examined for Retinopathy of Prematurity Infants (n=41)

Risk factor classification	Risk factor	n(%)
Type of Oxygenation	Mechanical ventilation	7 (17.1)
	CPAP	3 (7.3)
	Nasal cannula/oxygen hood	7 (17.1)
Maternal/gestational risk factors	Infection	5 (12.2)
	Placenta previa	0
	Poor nutrition	1 (2.4)
	Pre-eclampsia/ eclampsia	5 (12.2)
	PPROM	13 (31.7)
	Multiple gestation	3 (7.3)
Perinatal risk factors	Transfusion	12 (29.3)
	Jaundice	3 (7.3)
	Sepsis	3 (7.3)
	Syndrome	0
	Seizure	0
	Respiratory distress	1 (2.44)

Table 7. The Correlation Between Retinopathy of Prematurity and Retinal Vessel Dilatation and Tortuosity

		Retinopathy of Prematurity *		
		Positive	Negative	p-value**
Dilatation	Positive	6	0	0.004
	Negative	12	23	
Tortuosity	Positive	9	0	<0.05
	Negative	9	23	

*Diagnosis is based on consultant's assessment. The condition was present on both left and right eye

** Fisher's exact test

Table 5. The Correlation of Various Risk Factors with Presence of Dilatation* and Tortuosity*

Risk factor classification	Risk factor	Odds ratio (95% Conf. interval)	
		Dilatation	Tortuosity
Type of Oxygenation	Mechanical Ventilation	-	6.22 (1.10, 35.36)
	CPAP	3.30 (0.25, 43.47)	1.61 (0.13, 19.91)
	Nasal cannula/ oxygen hood	3.0 (0.43, 20.95)	2.89 (0.52, 16.03)
Maternal/gestational risk factors	Infection	1.55 (0.14, 16.85)	2.33 (0.33, 16.47)
	Placenta previa	-	-
	Poor nutrition	-	-
	Pre-eclampsia/ eclamp-sia	1.55 (0.14, 16.85)	0.75 (0.07, 7.61)
	PPROM	2.5 (0.43, 14.54)	1.63 (0.37, 7.19)
	Multiple gestation	-	-
Perinatal risk factors	Transfusion	1.25 (0.20, 7.94)	3.43 (0.77, 1.34)
	Jaundice	3.3 (0.25, 43.47)	-
	Sepsis	3.3 (0.25, 43.47)	7.5 (0.60, 93.58)
	Syndrome	-	-
	Seizure	-	-
	Respiratory distress	-	-
Other factors	Maternal age	0.90 (0.76, 1.07)	0.93 (0.82, 1.06)
	Birth weight	0.99 (0.99, 1.00)	1.00 (0.998, 1.00)
	Age of gestation	0.45 (0.24, 0.84)	0.66 (0.44, 1.00)

*Diagnosis is based on consultant's assessment. Condition may be present in at least one of the two eyes.

Table 6. The Correlation of Various Risk Factors with Presence of Retinopathy of Prematurity

Risk factor Classification	Risk factor	Odds ratio (95% Conf. interval)
Type of Oxygenation	Mechanical Ventilation	2.42 (0.41, 11.20)
	CPAP	3.07 (0.226, 36.88)
	Nasal cannula/ oxygen hood	2.15 (0.41, 11.20)
Maternal/gestational risk factors	Infection	2.36 (0.35, 15.93)
	Placenta previa	-
	Poor nutrition	-
	Pre-eclampsia/ eclampsia	0.93 (0.14, 6.29)
	PPROM	2.1 (0.55, 7.99)
	Multiple gestation	-
Perinatal risk factors	Transfusion	7.87 (1.69, 36.72)
	Jaundice	3.07 (0.26, 36.88)
	Sepsis	-
	Syndrome	-
	Seizure	-
	Respiratory distress	-
Other factors	Maternal age	0.95 (0.85, 1.06)
	Birth weight	0.99(0.995, 1.000)
	Age of gestation	0.48 (0.29, 0.78)

*Diagnosis is based on consultant's assessment. Condition may be present in at least one of the two eyes.

Table 8. Comparison of Retina Consultant vs Ophthalmology Resident Retinal Vessel Dilatation Findings (n=41)

Eye	Consultant	Resident		Total, n(%)	p-value
		Positive	Negative		
Right	Positive	6	0	6 (14.6)	0.317
	Negative	1	34	35 (85.4)	
	Total, n(%)	7 (17.1)	34 (82.9)	41 (100.0)	
Left	Positive	6	0	6 (14.6)	0.317
	Negative	1	34	35 (85.4)	
	Total , n(%)	7 (17.1)	34 (82.9)	41 (100.0)	

Note:

[1] Percentage is based on total sample size, N=41.

[2] p-value is associated with McNemar's test.

Table 9. Comparison of Retina Consultant vs Ophthalmology Resident Retinal Vessel Tortuosity Findings (n=41)

Eye	Consultant	Resident		Total	p-value
		Positive	Negative		
Right	Positive	6	3	9 (22.0)	0.083
	Negative	0	32	32 (78.0)	
	Total	6 (14.6)	35 (85.4)	41 (100.0)	
Left	Positive	7	2	9 (22.0)	0.564
	Negative	1	31	32 (78.0)	
	Total	8 (19.5)	33 (80.5)	41 (100.0)	

Note:

[1] Percentage is based on total sample size, N=41.

[2] p-value is associated with McNemar's test.

Discussion

Retinopathy of prematurity (ROP), previously known as retro-lental fibroplasia, was initially described by Terry in 1942.[12] This was during the worldwide epidemic wherein an estimated 12,000 neonates in first world countries suffered visual loss from ROP.[13] In the following decades, increasing number of ROP cases were reported in the developed world with the improvements in preterm survival rates and advancements in maternal, delivery, and neonatal care.[14]

The pathogenesis of retinopathy of prematurity is biphasic.[13]The first phase in ROP is initiated with delayed retinal vascular growth after premature birth. The abnormal vascularization of the developing newborn retina creates hypoxia. Phase II commences when the lack of oxygen triggers a release of factors, such as vascular endothelial growth factor (VEGF), which stimulate the growth of new and abnormal retinal vasculature characteristic of ROP.[15]

Retinopathy of prematurity has a multifactorial etiology.[16]The risk factors that have shown a significant association for the developing this condition include low gestational age,[17] low birth weight,[17] poor weight gain,[12]sepsis,[12]oxygen therapy or supplementation,[18] and blood transfusions.[14,19]Moreover, those having a history of anemia, interventricular hemorrhage, jaundice, respiratory distress syndrome, seizure, and congenital syndromes may also warrant referral for ROP screening. [7] Perinatal risk factors, on the other hand, that may also alert the pediatrician or neonatologist for the possible need for ROP screening include: maternal infection during the 3rd trimester, placenta previa, poor nutrition, pre-eclampsia/ eclampsia, premature rupture of membranes (PROM) ≥ 18 hours before delivery, and multiple gestation. [7] For this study, we have seen an increased risk of developing abnormal retinal vasculature in infants with exposure to any method of oxygenation, maternal infection, pre-eclampsia/eclampsia, preterm premature rupture of membranes, perinatal blood transfusion, neonatal jaundice, sepsis, low brithweight, and earlier age of gestation. These associations however, were not statistically significant except for exposure to oxygenation from mechanical ventilation, birthweight and age of gestation, which are good predictors for the presence of abnormal retinal vessels.

Prompt recognition of plus disease is crucial for timely treatment and management of retinopathy of prematurity.[21]In a study by Saunders in 1995, it was concluded that there was a highly significant correlation between the posterior pole vascular abnormalities and the severity of ROP in the retinal periphery.[22] The detection of plus disease, specifically vessel dilatation, vessel congestion and arteriolar tortuosity, depends on the ophthalmologist's subjective evaluation. [23]Pre-plus disease, on the other hand, was defined by the ICROP to be vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arteriolar tortuosity and more venular dilatation than normal.[24]Wallace in 2000 showed that early vascular dilation and tortuosity judged insufficient for plus disease have prognostic significance in the early course of ROP. Those with mild vascular dilation and tortuosity had a significantly higher incidence of progression to laser treatment, stage 3 ROP, and plus disease.[24]Similar findings could be derived from the results of this study wherein a statistically significant positive correlation was seen between retinal vessel dilatation and tortuosity and the presence of retinopathy of prematurity. Those infants that have abnormal retinal vasculature are more likely to have retinopathy of prematurity in subsequent follow-ups. Furthermore, a higher incidence of retinopathy of prematurity are seen in premature babies who were born with a lower birthweight and earlier age of gestation, as well as in those who have had blood transfusion.

The detection of vascular and retinal changes in retinopathy of prematurity is hampered by technical difficulties. Therefore, the screening and management of retinopathy of prematurity is usually done by either a retina specialist or a pediatric ophthalmologist.[25] At present, there are limited reports on the possibility of screening done by non-ROP specialists. Most of the available studies done on this topic were ventured by researchers from developing countries with limited ROP specialists and screening resources similar to the Philippines. Azad in 2006 concluded that given adequate training, Indian general ophthalmologists and non-ophthalmologists (pediatricians and nurse practitioners) are independently reliable in detecting posterior pole changes in ROP babies using direct ophthalmoscope and can be provided with a screening

protocol.[5] Another study by Saunders in 2000 reported that examination of the posterior pole blood vessels can be reliably performed by a non-ophthalmologist, using a direct ophthalmoscope, in situations where ophthalmological consultation is unavailable or difficult to obtain.[22] Meanwhile, in study by Romero etal. in 2011, she stated that after training in the use of an indirect ophthalmoscope, pediatricians and neonatologists could reliably detect posterior pole retinal vessel changes for ROP diagnosis in Mexico. [26]Our results suggest that with adequate training, ophthalmology residents who, eventually will be general ophthalmologists, can identify retino-vascular abnormalities associated with severe retinopathy of prematurity.

In a developing country like the Philippines where ROP specialists are few in number, a retinopathy of prematurity screening protocol with general ophthalmologists in the provinces serving as the first line of examiners could hypothetically be more cost-effective, comprehensive, and efficient. This scenario will ensure that every infant needing retinal examination for ROP could be examined immediately for posterior pole vascular abnormalities by adequately trained general ophthalmologists. An appropriate referral system to an ROP specialist could then be instituted to allow proper and timely transfer to a secondary or tertiary health institution, for all high-risk ROP cases that would need immediate and appropriate medical and/or surgical intervention. Moreover, it should be emphasized that the findings of a normal retinal vessels at the time of examination does not rule out the potential of developing ROP in the future. Thus, repeated retinal examinations are suggested to document normal retinal vessels repeatedly or any vascular changes necessitating referral until the criteria for termination for ROP screening are met. One, however, must also consider that for this referral system to be successful, emphasis on the need for ROP training in the national ophthalmology residency program should also be established. Ophthalmology residents, who will soon be the general ophthalmologists in the provinces, should be comprehensively taught the concepts and skills needed to identify ophthalmologic findings suggestive of ROP, using the appropriate equipment.

The limitations of this study are the small sample size and the sole utilization of retinal vascular dilatation and/or tortuosity as a manifestation of ROP. Since this study focused on a severe presentation of ROP, which is the presence of retinal vessel dilatation and tortuosity (plus disease) only, the results might not be applicable when evaluating less severe cases of retinopathy or prematurity.

Based on the results of this study, we conclude that given sufficient and in-depth training, third year ophthalmologists, who will be general ophthalmologists in the future, can reliably identify eyes at risk for severe retinopathy of prematurity on the basis of retinal vascular dilatation and/or tortuosity. While this scenario may be far from the ideal setting for ROP screening, the role of general ophthalmologists in the provinces who are able to examined referred preterm babies provides an indispensible resource in health institutions where an on-site ROP specialist is not available.

References

1. Wheatley CM, JL Dickinson etal. Retinopathy of prematurity: recent advances in our understanding . Br J Ophthalmol 2002;86:696–701.
2. Athikarisamy, SE, Patole S. etal. Screening for retinopathy of prematurity (ROP) using wide-angle digital retinal photography by non ophthalmologists: a systematic review. Br J Ophthalmol. 2014 Jul 7.
3. Ladores, C. etal. Status of screening for Retinopathy of Prematurity in a Tertiary Hospital. Philipp J Ophthalmol 2013;38:86-93. Vol 36 no. 1, Jan-June 2011.
4. Gilbert C, Fielder A, GordilloL ,et al. Characteristics of infants with severe retinopathy of prematurity in countries with low, moderate, and high levels of development: implications for screening programs. Pediatrics 2005;115;518-25.
5. Azad, Raj etal.Retinopathy of Prematurity Screening by Non-Retinologists.Indian J Pediatr 2006; 73 (6) : 515-518.
6. American Academy of Pediatrics, Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics.* 2006;117:572–576.

7. Philippine Academy of Ophthalmology- Retinopathy of Prematurity Working Group (ROPWG). Proposed Philippine Guidelines for Screening and Referral of Retinopathy of Prematurity. Philipp J Ophthalmol 2013;38:64-71.
8. Corpus, Kristine etal. Proposed New Retinopathy of Prematurity Screening Criteria: Evidence for Including Older and Heavier Filipino Premature Babies. Philipp J Ophthalmol 2013;38:72-79.
9. The International Committee for the Classification of the Late Stages of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. II. The classification of retinal detachment. Arch Ophthalmol 1987;105:906–12.
10. Freedman SF. etal. Observer sensitivity to Retinal Vessel Diameter and Tortuosity in retinopathy of prematurity: a model system. J PediatrOphthalmol Strabismus.1996 Jul-Aug;33(4):248-54.
11. AngbueTe, ND. etal. Awareness and Practice Patterns of Pediatricians Regarding Retinopathy of Prematurity: A Multicenter Study. Philipp J Ophthalmol 2013;38:86-93.
12. De Sagun-Bella, KQ.,Merca, TGB etal. A Study Protocol on the Situational Analysis on the Current Practice of Screening and Treatment of Retinopathy of Prematurity (ROP). Philipp J Ophthalmol 2013;38:94.
13. Tah, V., Sharif W. etal. Retinopathy of Prematurity. Ophthalmology-Current Clinical and Research Updates. Intech Open Science 2014.
14. Kopylov, U. etal. Retinopathy of prematurity-Risk Factors. Harefuah. 2002 Dec;141(12):1066-9, 1089.
15. Smith LE. Pathogenesis of retinopathy of prematurity. SeminNeonatol. 2003 Dec;8(6):469-73.
16. Olea Vallejo JL. etal. Risk factors in retinopathy of prematurity. An EspPediatr. 1997 Aug;47(2):172-6.
17. Lundgren, P. Weight at first detection of retinoathy of prematurity predicts disease severity. Br J Ophthalmol. 2014 Nov;98(11):1565-9
18. Akkoyun I, Oto S, Yilmaz G, Gurakan B, Tarcan A, Anuk D, Akgun S, AkovaYA.Risk factors in the development of mild and severe retinopathy of prematurity. J AAPOS.2006 Oct; 10(5):449-53
19. Lu Chen,Ming Su, Sheng-gang Ren, Hui-lanHua, Jian -cang Wang, and Wei Zheng. Analysis of Current Status and Strategies of Retinopathy of Prematurity Screening during 6 Years in Local Regions of China: Implication and Caution. Journal of Ophthalmology Volume 2014,pp1-6
20. Freedman SF. etal. Observer sensitivity to Retinal Vessel Diameter and Tortuosity in retinopathy of prematurity: a model system. J PediatrOphthalmol Strabismus.1996 Jul-Aug;33(4):248-54.
21. Oloumi F. etal Assessment of vessel tortuosity in retinal images of Preterm infants. ConfProc IEEE Eng Med Biol Soc. 2014 Aug;2014:5410-3
22. Saunders RA etal. The predictive value of posterior pole vessels in retinopathy of prematurity. J PediatrOphthalmol Strabismus. 1995 Mar-Apr;32 (2):82-5.
23. Gelman, R. Diagnosis of Plus Disease in Retinopathy of Prematurity Using Retinal Image multiScale Analysis. Invest Ophthalmol Vis Sci. 2005 Dec; 46 (12): 4734–4738.
24. Wallace DK1, Kylstra JA, Chesnutt DA. Prognostic significance of vascular dilation and tortuosity insufficient for plus disease in retinopathy of prematurity. J AAPOS. 2000 Aug;4(4):224-9.
25. Mordrzejewska M. Retinopathy of prematurity: clinical findings and current opinions on diagnosis and treatment. Ann Acad Med Stetin. 2006; 52 (1): 73-8.
26. Romero, Luz etal. The Utility of Non-ophthalmologist Examination of Eyes at Risk for Serious Retinopathy of Prematurity. Ophthalmic Epidemiology, 2011; 18 (6), 264–268.
27. Cerdana, HG etal. Results of Initial Screening for Retinopathy of Prematurity at a Tertiary Hospital. Philipp J Ophthalmol 2010;35:56-60
28. Blencowe, H. etal. Born Too Soon: The global epidemiology of 15 million preterm births. Reproductive Health 2013, 10(Suppl 1):S2
29. Sekeroglu, MA. Alternative methods for the screening of retinopathy of prematurity: binocular indirect ophthalmoscopy vs wide-field digitalretinal imaging. Eye (2013) 27, pp. 1053–1057.

30. Schaffer DB. etal. Prognostic factors in the natural course of retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. Ophthalmology. 1993 Feb;100 (2):230-7.
31. Dhillon B1, Wright E, Fleck BW. Screening for retinopathy of prematurity: are a lid speculum and scleral indentation necessary? J PediatrOphthalmol Strabismus. 1993 Nov-Dec;30(6):377-81
32. Hartnett ME, Penn JS. Mechanisms and management of retinopathy of prematurity. New England Journal of Medicine. 2012; 367:2515-2526