• Investigation •

Risk factors for retinopathy of prematurity development and progression in the Philippines

Roland Joseph D. Tan[1], Rachel R. Milante[2,3], Adriel Vincent R. Te[4], Esther Carmen Arvella G. Ereño[4], Redentor Caesar G. Gonzales[4], Jewel Faith Flores-Anotado[5], Christopher Sebastian J. Uy[5], Knedrick Kevin Macalma[6], Jennifer Joy Y. Santos-Rayos[6], Lorenz Jacob D. Mangahas[7], Karen R. Cabrera[7], Lyka R. Agcaoili[1], Clyde Joshua A. Ecija[1], Tamilyn Chelsea C. Laddaran[8], Kristine D. Corpus-Velasquez[8], Jose Melvin Jimenez IV[8], Kyla S. Ilagan[9], Ian J. Daguman[9], Xavier Daryl L. Martinez[10], Almira A. Manzano[10], Ron Joseph R. Moreno[11], Gabrielle S. Evangelista[11], Kanja Drisa Taclobao[12], Marie Christine T. Marcelo-Tan[12], Christian Q. Castillo[13], Manuel Benjamin B. Ibañez IV[13], Maijann D. Precia[14], Patricia S. Tacata[14], Robert Kelvin Carbonell[15], Dominico Carlo S. Dator[15], Jemeson M. Tiburan[16], Rachelle G. Anzures[16], Niño Enrico D. Marohom[17], Lois Agnes E. Lumontod[17], Margarita E. Quitos[17], Beltran Alexis A. Aclan[18], Angeline Therese Y. Uy[18], Claire Baldovino Barja[18], Van Alvin Gambalan[19], Jona May S. Ongkeko[19], Gabriel L. Villanoy[20]

[1]Southern Isabela Medical Center, Santiago City 3311, Isabela, Region II, Philippines
[2]Bicol Regional Hospital and Medical Center, Legazpi City 4500, Albay, Region V, Philippines
[3]Legazpi Eye Center, Legazpi City 4500, Albay, Region V, Philippines
[4]Southern Philippines Medical Center, Davao City 8000, Davao del Sur, Region XI, Philippines
[5]Western Visayas Medical Center, Iloilo City 5000, Iloilo, Region VI, Philippines
[6]Mariano Marcos Memorial Hospital and Medical Center, Batac 2906, Ilocos Norte, Region I, Philippines
[7]Ilocos Training and Regional Medical Center, San Fernando City 2500, La Union, Region I, Philippines
[8]St. Luke's Medical Center, Quezon City 1112, National Capital Region, Philippines
[9]Eastern Visayas Medical Center, Tacloban City 6500, Leyte, Region VIII, Philippines
[10]Region 1 Medical Center, Dagupan City 2400, Pangasinan, Region I, Philippines
[11]Northern Mindanao Medical Center, Cagayan de Oro City 9000, Misamis Oriental, Region X, Philippines
[12]Baguio General Hospital and Medical Center, Baguio City 2600, Benguet, Cordillera Administrative Region, Philippines
[13]Bataan General Hospital and Medical Center, Balanga City 2100, Bataan, Region III, Philippines
[14]Jose R. Reyes Memorial Medical Center, City of Manila 1003, National Capital Region, Philippines
[15]Cagayan Valley Medical Center, Tuguegarao City 3500, Cagayan, Region II, Philippines
[16]Ospital ng Makati, Taguig City 1642, National Capital Region, Philippines
[17]Amai Pakpak Medical Center, Marawi City 9700, Lanao del Sur, Bangsamoro Autonomous Region of Muslim Mindanao, Philippines
[18]National Children's Hospital, Quezon City 1113, National Capital Region, Philippines
[19]Ospital ng Maynila Medical Center, Manila 1004, National Capital Region, Philippines
[20]Cebu Velez General Hospital, Cebu City 6000, Cebu, Region VII, Philippines
Correspondence to: Roland Joseph D. Tan. Rm 212, Pueblo de Maria Bldg, Notre Dame de Chartres Hospital, General Luna Road, Baguio City 2600, Philippines. Olantan385e@yahoo.com
Received: 2025-12-03 Accepted: 2026-02-06

Abstract

● **AIM:** To determine the clinico-epidemiologic profile of premature infants diagnosed with retinopathy of prematurity (ROP), and treated for type 1, severe, and aggressive (TOSA) ROP in the different regions of the Philippines.

● **METHODS:** A multiregional ambispective cohort study of premature infants (<37wk gestational age) referred

for ROP screening across 20 hospitals in 12 Philippine regions between January 2024 and September 2025 was conducted. Demographic, neonatal, and maternal risk factors were analyzed. Outcomes were compared between National Capital Region (NCR) and non-NCR cohorts.

● **RESULTS:** Of 2085 referred infants, 1900 premature infants were included. Mean gestational age was 32.34±2.31wk; mean birthweight was 1593±439 g. ROP developed in 483 infants (25%), of whom 177 (37%) progressed to TOSA ROP. Lower gestational age, lower birthweight, male gender, and packed red blood cell transfusion were significantly associated with ROP development, whereas sepsis and oxygen supplementation were not. Among TOSA ROP cases, 87% received treatment, most commonly anti-vasular endothelial growth factor (VEGF) injection (46%) or laser photocoagulation (24%). At the last follow-up, 34% of treated infants had not reached full regression or retinal maturity. ROP incidence was higher in NCR (32%) than in Region I and Cordillera Administrative Region (8%, *P*=0.001), Region III (13%, *P*=0.005), and Region XI (14%, *P*=0.001), but lower than Region VI (55%, *P*=0.001).

● **CONCLUSION:** Lower gestational age and birthweight, male, and packed red blood cell transfusion are risk factors of ROP development. This study also provides the first multiregional multicenter data on ROP in the Philippines, demonstrating substantial incidence and progression beyond NCR.

● **KEYWORDS:** retinopathy of prematurity; epidemiology; Philippines; risk factors; screening; multicenter study

DOI:10.18240/ijo.2026.08.16

Citation: Tan RJD, Milante RR, Te AVR, Ereño ECAG, Gonzales RCG, Flores-Anotado JF, Uy CSJ, Macalma KK, Santos-Rayos JJY, Mangahas LJD, Cabrera KR, Agcaoili LR, Ecija CJA, Laddaran TCC, Corpus-Velasquez KD, Jimenez IV JM, Ilagan KS, Daguman IJ, Martinez XDL, Manzano AA, Moreno RJR, Evangelista GS, Taclobao KD, Marcelo-Tan MCT, Castillo CQ, Ibañez IV MBB, Precia MD, Tacata PS, Carbonell RK, Dator DCS, Tiburan JM, Anzures RG, Marohom NED, Lumontod LAE, Quitos ME, Aclan BAA, Uy ATY, Barja CB, Gambalan VA, Ongkeko JMS, Villanoy GL. Risk factors for retinopathy of prematurity development and progression in the Philippines. *Int J Ophthalmol* 2026;19(8):1573-1582

INTRODUCTION

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness worldwide, affecting nearly 32 000 infants each year, with 20 000 blinded and a further 12 000 visually impaired[1]. Locally, 48% of childhood blindness was attributed to ROP[2]. The so-called "third epidemic" of ROP disproportionately affects low- and middle-income countries (LMICs), where improved neonatal survival has not been matched by consistent high-quality intensive care or robust screening systems[3]. In contrast with high-income countries, where ROP is now confined largely to extremely preterm infants (<28wk, <1000 g), older and heavier infants remain at risk in LMICs[3]. In the Philippines, most published data on ROP originate from the National Capital Region (NCR). Single-center studies in NCR have reported incidences of 14%–30%[4-6]. Outside the capital, only one provincial study has been published, reporting an incidence as high as 43%[7]. Yet most premature births occur outside NCR, and neonatal care quality varies substantially across regions, shaped by differences in infrastructure, trained personnel, and referral networks[8-9]. The absence of comprehensive national data leaves the national epidemiology and health system implications of ROP poorly understood[4-6].

Very premature birth (28–32wk) and very low birthweight (<1500 g) are among the most established contributing factors for ROP development and progression[7,10-11]. Other contributing factors include being treated for sepsis, needing a blood transfusion, and being given unregulated use of oxygen supplementation, as well as having a stormy clinical course[10-11]. Although there are variations, ROP screening guidelines globally use gestational age (GA) of ≤30–32wk and birthweight of ≤1500 g as major criteria[10-11]. A consensus statement was released in 2020 which is commonly used in the country for ROP screening. It sets the screening criteria at GA of ≤32wk, birthweight of ≤1500 g, and those with GA of 32–36wk with risk factors of sepsis, underwent transfusion of packed red blood cell (pRBC), oxygen use without an oxygen blender, and premature infants with unstable clinical course (STOP)[10].

The present study addresses the absence of national data on ROP through the first multicenter, multiregional cohort of ROP in the Philippines. We analyzed 1900 premature infants screened across 20 hospitals in 12 regions between January 2024 and September 2025. Our objectives were to 1) estimate the incidence and severity of ROP nationally and by region, 2) correlate neonatal and maternal risk factors for ROP development and progression, 3) compare profiles between NCR and non-NCR cohorts.

PARTICIPANTS AND METHODS

Ethical Approval This study was approved by the Department of Health Single Joint Research Ethics Board (2024-04) and the individual institutional Research Ethics Boards. A waiver of consent was also issued by the Department of Health Single Joint Research Ethics Board. Participants did not received stipend. The conduct of this study adhered to the Declaration of Helsinki and the Philippine Data Privacy Law of 2012.

A multiregional ambispective cohort study screened for ROP in premature infants referred at 20 hospitals across 12 regions of the Philippines for 12mo, between January 1, 2024, and September 30, 2025. Participating institutions included 15 Department of Health-retained tertiary hospitals, two local government hospitals, and three private centers. These institutions serve as referral hubs for their catchment areas, managing both inborn and outborn infants. Eligible participants were infants born at <37wk gestation, assessed by Ballard scoring, who were referred for ROP screening in neonatal intensive care units (NICUs) or outpatient clinics. Data were abstracted from medical records using standardized forms and entered into a central database. Variables included infant demographics, neonatal course, maternal factors, and ophthalmic findings. Specific neonatal exposures captured were treatment for sepsis, pRBC transfusion, and oxygen supplementation. In selected hospitals, the number of transfusions and mode of oxygen delivery were also recorded. Maternal variables included age, parity, prenatal care, and pregnancy complications. Ophthalmic findings were documented using the international classification of ROP, third revision (ICROP-3)[12]. ROP development is defined as developing any ROP stages, from 1–5 or aggressive ROP. It was counted per infant. In infants with different stages in their 2 eyes, the worst eye is considered. ROP progression pertains to the progression to type 1, severe, or aggressive (TOSA) ROP, as defined by the Early Treatment of Retinopathy of Prematurity (ETROP) Study and by the ICROP-3[12-13]. Sepsis was defined as participant received treatment for septicemia. There was no microbiological confirmation as it was not consistently available, a limitation common to LMIC cohorts.

Continuous variables were summarized as means (standard deviation, SD) and categorical variables as frequencies and percentages. Differences between NCR and non-NCR cohorts were tested using χ^2 tests for presence or absence of ROP, presence or absence of TOSA ROP, sepsis, oxygen supplementation, and pRBC transfusion. The *t*-tests was used to compare GA and birthweight. Visual inspection of histogram was used to test for their normality and the assumption of their normality was met. Levene's test was used to test for equality of variance. A Welch correction was used for data with unequal variances. Bonferroni correction of $P<0.006$ was used for comparing presence or absence of ROP, presence or absence of TOSA ROP, treated or not treated for sepsis, received oxygen supplementation or not, received pRBC transfusion or not, GA, and birthweight in the nine regions represented. Logistic regression models identified apriori independent predictors of ROP development and progression, reporting coefficients, 95% confidence intervals (CIs), and *P*-values. Regression covariates included GA, birthweight, sex, sepsis, pRBC transfusion, and oxygen supplementation, with expanded analyses including transfusion number and oxygen delivery mode where available. All subjects with missing data were excluded from the analysis. Maximum likelihood estimation was used after performing model purpose. Multicollinearity of independent variables was checked using the variance inflation factor (VIF). Both VIF for ROP development and progression to TOSA were <5. Analyses were performed in Stata version 14 (StataCorp, College Station, Texas, United States of America). Two-tailed $P<0.05$ was considered statistically significant unless otherwise specified.

RESULTS

Twenty institutions from 12 regions participated in the study (Table 1). Fourteen were from Luzon, with five from the NCR, and three each from Visayas and Mindanao (Figure 1). Five regions had no participants. Between January 2024 and September 2025, 2085 premature infants were referred for retinopathy of screening. Of these, 1997 (96%) underwent screening. Of the 88 not screened, 34 were discharged and did not follow up after, 25 expired, 6 had other ophthalmic pathologies, 3 wanted to be screened in another institution, 2 refused, and 18 with no stated reason. Two participating institutions were eventually excluded due to minimal data during the study duration. Ninety-seven infants were excluded for GA ≥37wk, leaving 1900 (91%) in the analytic cohort. More than a fifth (407, 21%) of the infants were from region 1, and 14% each from region 5 (266) and region 11 (261). About 47% (901) were female, one in five (352, 19%) resided outside the city or province of the screening institution, and 90 (5%) were even from a different region, reflecting referral patterns. The mean GA was 32.34±2.31wk, ranging from 20–36wk. The mean birthweight was 1593±439 g, ranging from 500–3500 g.

Neonatal Risk Factors There were 1182 (62%) infants with a GA of ≤32wk and/or birthweight of ≤1500 g. Of the remaining infants aged >32wk with birthweight >1500 g, 541 (29%) had ≥1 risk factor of being treated for sepsis, transfused with pRBC, and received oxygen supplementation. One hundred and sixty-seven (9%) were referred by their attending pediatrician for an unstable clinical course, with none of the 3 risk factors present, while 10 did not have data available. In total, 843 infants were treated for sepsis, 299 received pRBC transfusion, and 1262 received oxygen supplementation. There were 216 premature infants born from twin pregnancy and 7 from triplet pregnancy.

Maternal Factors The mean maternal age was 28.85±6.7y, ranging from 13 to 47. Of the 1759 infants with maternal data, 398 (23%) mothers were aged <18 or >35y. Hypertension was the leading cited cause of premature birth (Table 2). Of those with data, 1455 mother had prenatal check-ups, having a median of 5 visits. Prenatal check-ups were done at the hospital

Table 1 Premature infants were referred, screened, and included in the study at the different participating institutions

Region	Institution	Duration	Infants				
			Referred	Screened	%	Included in the study (<37wk)	%
I	Mariano Marcos Memorial Hospital & MC	1–12/2024	237	237	100	202	85
	Ilocos Training & Regional MC	1–12/2024	160	146	92	141	97
	Region 1 MC	7/2024–6/2025	64	64	100	64	100
Cordillera Administrative Region	Baguio General Hospital & MC	1–12/2024	69	69	100	69	100
II	Cagayan Valley MC	1–12/2024	48	42	88	42	100
	Southern Isabela MC	1–12/2024	178	139	78	132	95
III	Bataan General Hospital & MC	5/2024–4/2025	60	60	100	52	87
National Capital Region	Jose R. Reyes Memorial MC	1–12/2024	50	50	100	50	100
	Ospital ng Maynila MC[a,c]	1–12/2024	-	-	-	-	-
	National Children's Hospital	8/2024–7/2025	23	23	100	22	96
	St. Luke's MC[b]	7/2024–5/2025	126	126	100	122	97
	Ospital ng Makati[c]	1–12/2024	40	40	100	40	100
V	Bicol Regional Hospital & MC Legazpi Eye Center[b]	1–12/2024	289	285	99	266	93
VI	Western Visayas MC	1–12/2024	237	213	90	203	95
VII	Cebu Velez General Hospital[a,b]	1–12/2024	-	-	-	-	-
VIII	Eastern Visayas Regional MC	2/2024–1/2025	118	118	100	115	97
X	Northern Mindanao MC	4/2024–3/2025	86	85	100	82	96
XI	Southern Philippines MC	6/2024–5/2025	263	263	100	261	99
Bangsamoro Autonomous Region of Muslim Mindanao	Amai Pakpak MC	10/2024–9/2025	37	37	100	37	100
Total			2085	1997	96	1900	95

[a]Not included in the analysis, [b]Private institution, [c]Local government unit hospital. MC: Medical center.

Table 2 Causes of premature birth

Causes	Infants
1. Uncontrolled pregnancy-related hypertension (preeclampsia, eclampsia, chronic, gestational)	406
2. Premature labor/contraction	321
3. No identified reason	259
4. Non-reassuring fetal status/fetal distress/fetal bradycardia/variable deceleration	270
5. Premature rupture of membrane	243
6. Placenta previa/accreta/abruptio	42
7. Infection (*e.g.*, urinary tract infection)	37
8. Multiple gestation-related (*e.g.*, twin pregnancy, discordance)	38
9. Malpresentation/Breech	31
10. Others	60
11. No data	193

for 272 mothers, 186 at health centers (local, barangay, or rural health unit), 37 at lying-in clinics, and 26 at private clinic. The 55 mothers did not have prenatal check-up. Of those with data, 1027 gave birth in a hospital, 20 in lying-in clinic or birthing home, and 12 at home or while in transit.

ROP Development and Progression There were 483 (25%) premature infants who developed ROP (Table 3). The mean GA was 31.44±2.30wk, ranging from 24 to 36wk. The mean birthweight was 1428±399 g, ranging from 500 to 3500 g. There were 375 (78%) infants with GA of ≤32wk and/or birthweight of ≤1500 g. There were an additional 100 infants with ROP aged 32–35wk and/or with birth weight of 1500–2000 g, 26 of whom did not have any of the 3 risk factors. Of the 8 remaining infants >35wk and >2000 g, 7 received oxygen supplementation, with 2 treated for sepsis and 1 receiving pRBC. The remaining infant was only treated for sepsis as a risk factor.

There were 177 (37%) premature infants who progressed to TOSA ROP (Table 3). The mean GA was 30.89±2.20wk, ranging from 24 to 36wk. The mean birthweight was 1381±410 g, ranging from 500 to 3500 g. There were 150 (85%) infants with a GA of ≤32wk and/or a birthweight of ≤1500 g. There

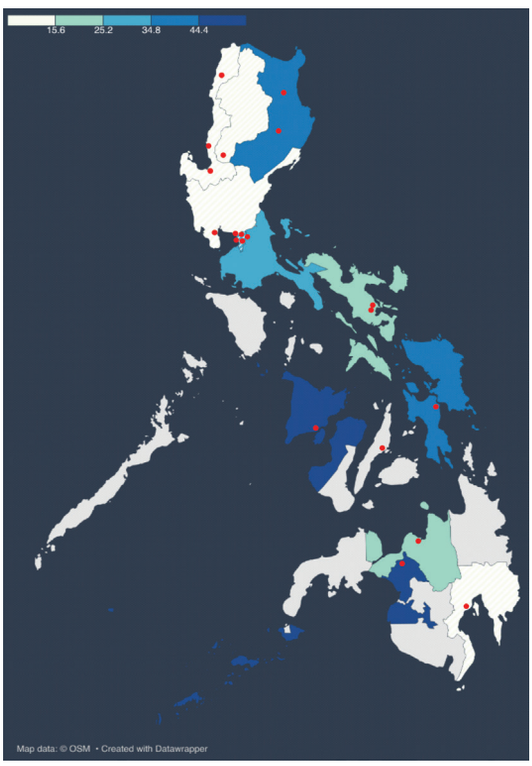

Figure 1 Geographic distribution of participating institutions (red dots) and incidence of retinopathy of prematurity across Philippine regions Incidence varied substantially, from 8% in Northwestern Luzon to 55% in Western Visayas, compared with 32% in the National Capital Region (Regions with no participating institution are in gray).

were 174 (99%) infants with GA of ≤35wk and/or birthweight of ≤2000 g. Seven of those with GA of >32 to 35wk or birthweight of >1500 to 2000 g did not have any of the 3 risk factors. Of the 3 remaining infants >35wk and >2000 g, all received oxygen supplementation, with 2 treated for sepsis and 1 receiving pRBC transfusion.

Correlation of Risk Factors to ROP Development and Progression Using multivariable analysis, GA, birthweight, receiving pRBC transfusion, and being male were significantly associated to ROP development while being treated for sepsis, receiving oxygen supplementation, multiple gestation, and maternal age were not (Table 4, Figure 2). For ROP progression to TOSA, GA and receiving pRBC transfusion were significantly associated. Sex, birthweight, being treated for sepsis, receiving oxygen supplementation, multiple gestation, and maternal age were also not significantly associated with ROP progression to TOSA. A subanalysis was done on 3 hospitals, involving 585 infants, with data on the number of pRBC units transfused and the oxygen supplementation route used. When adjusted for the other variables, GA [odds ratio (OR)=0.98, 95%CI: 0.96–0.99, P<0.003] was the only risk factors significantly associated with ROP development. GA (OR=0.99, 95%CI: 0.98–0.99, P<0.04), receiving pRBC transfusion (OR=1.09, 95%CI: 1.03–1.18, P<0.004), and the

Table 3 Comparison of gestational age, birthweight, 3 other risk factors, ROP development, and ROP progression of infants seen outside the NCR to those seen in NCR

Region	Infants	Gestational age (wk)	Cohen's d_s, P	Birthweight (g)	Cohen's d_s, P	Sepsis	RR, P	pRBC	RR, P	O_2	RR, P	ROP	RR, P	TOSA ROP	RR, P
NCR	234	32.04±2.79	-	1614±494	-	148 (63%)	-	56 (24%)	-	191 (82%)	-	74 (32%)	-	35 (47%)	
Region IV-A[b]	29	31.72±2.68		1515±379		22		5		21		8 (28%)		7 (88%)	
Region I & CAR	476	32.44±2.46	-0.155, 0.03	1748±514	-0.266, 0.006[a]	123 (29%)	2.19, 0.001[a]	21 (5%)	4.36, 0.001[a]	304 (64%)	1.29, 0.001[a]	39 (8%)	0.74, 0.001[a]	16 (47%)	0.99, 0.97
Region II	174	31.78±2.06	0.103, 0.67	1428±349	0.435, 0.001[a]	-[c]	-	-[c]	-	-[c]	-	68 (39%)	1.12, 0.13	23 (34%)	1.40, 0.10
Region III	52	32.49±2.09	-0.169, 0.04	1541±330	0.172, 0.20	38 (74%)	0.85, 0.11	32 (59%)	0.40, 0.001[a]	41 (80%)	1.03, 0.64	7 (13%)	0.79, 0.005[a]	6 (85%)	0.63, 0.14
Region V	266	32.46±2.33	-0.166, 0.03	1599±398	0.033, 0.83	80 (30%)	2.11, 0.001[a]	16 (6%)	3.99, 0.001[a]	167 (63%)	1.31, 0.001[a]	59 (22%)	0.88, 0.02	25 (42%)	1.12, 0.57
Region VI	203	32.39±2.20	-0.235, 0.06	1450±368	0.439, 0.02	77 (39%)	1.65, 0.001[a]	19 (10%)	2.49, 0.001[a]	66 (34%)	2.46, 0.001[a]	111 (55%)	1.50, 0.001[a]	41 (37%)	1.29, 0.14
Region VIII	115	32.18±2.07	-0.054, 0.64	1453±306	0.391, 0.001[a]	45 (39%)	1.61, 0.001[a]	29 (25%)	0.94, 0.78	94 (82%)	1.01, 0.87	51 (44%)	1.22, 0.02	6 (14%)	3.94, 0.001[a]
Region X & BARMM	119	32.59±2.23	-0.211, 0.02	1540±385	0.166, 0.44	-[c]	-	-[c]	-	-[c]	-	37 (31%)	0.99, 0.92	13 (36%)	1.35, 0.22
Region XI	261	32.53±1.90	-0.208, 0.03	1559±380	0.124, 0.17	198 (76%)	1.12, 0.03	69 (26%)	0.93, 0.66	214 (82%)	0.99, 0.83	37 (14%)	0.79, 0.001[a]	12 (32%)	1.45, 0.12

[a]Statistical significance based on Bonferroni correction of P<0.006; [b]Subgroup of patients from Region IV-A seen in the 4 NCR hospitals; [c]Southern Isabela MC (Region II) and Amai Pakpak MC (BARMM) have incomplete data on the three risk factors and were not included in the analysis. ROP: Retinopathy of prematurity; pRBC: Received packed red blood cell; TOSA: Type 1, severe, or aggressive; MC: Medical center; CAR: Cordillera Administrative Region; BARMM: Bangsamoro Autonomous Region of Muslim Mindanao; NCR: National Capital Region; RR: Relative risk.

Table 4 Multivariable predictors of ROP

Predictor	ROP (Odds ratio)	Lower 95%CI	Upper 95%CI	*P*	TOSA ROP (Odds ratio)	Lower 95%CI	Upper 95%CI	*P*
Gestational age (per week)	0.97	0.96	0.98	<0.001[a]	0.98	0.97	0.98	<0.001[a]
Birthweight (per 100 g)	0.99	0.99	0.99	<0.001[a]	0.99	0.99	1.00	0.53
Male sex	1.05	1.00	1.09	0.03[a]	1.02	0.99	1.04	0.09
Sepsis	1.01	0.96	1.05	0.44	1.01	0.98	1.04	0.15
pRBC transfusion	1.13	1.06	1.18	<0.001[a]	1.09	1.05	1.13	0.03[a]
Oxygen supplementation	1.00	0.96	1.05	0.84	1.005	0.977	1.035	0.70
Multiple gestation	1.02	0.96	1.08	0.44	1.002	0.965	1.002	0.88
Maternal age	0.99	0.996	1.002	0.70	1.000	0.998	1.041	0.42

[a]Statistically significant. ROP: Retinopathy of prematurity; TOSA: Type 1, severe, or aggressive; pRBC: Received packed red blood cell; CI: Confidence interval.

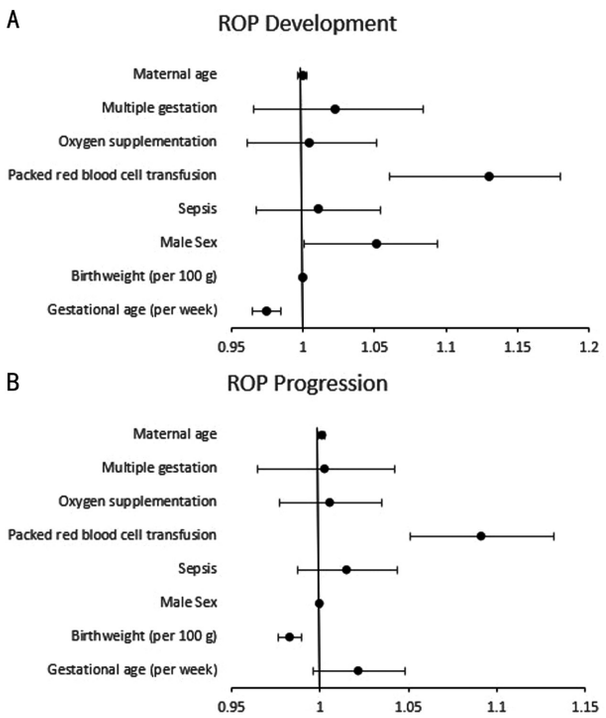

Figure 2 Multivariable associations of neonatal risk factors with development of any ROP (A) and progression to TOSA ROP (B) Lower gestational age, lower birthweight, male sex, transfusion, and oxygen supplementation were significantly associated with ROP development, whereas sepsis was not. For progression, transfusion and oxygen delivery route were significant predictors. ROP: Retinopathy of prematurity; TOSA: Type 1, severe, or aggressive.

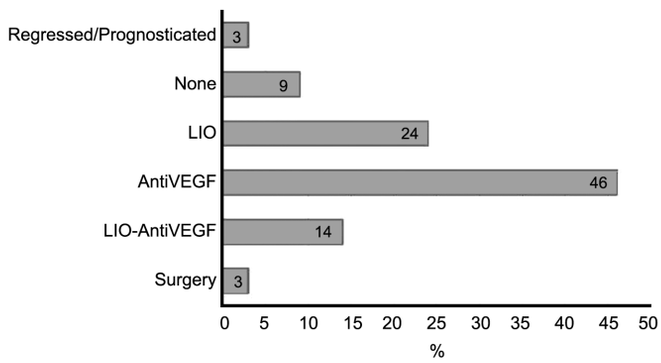

Figure 3 Treatment modalities for infants with all the 177 infants who developed TOSA retinopathy of prematurity Anti-VEGF injection was the most common intervention (81/177, 46%), followed by laser photocoagulation (45/177, 24%). A minority required combined therapy or vitrectomy, while 9% did not receive treatment despite indication. TOSA: Type 1, severe, or aggressive; VEGF: Vascular endothelial growth factor; LIO: Laser indirect ophthalmoscope.

number of pRBC units (OR=1.02, 95%CI: 0.99–1.05, *P*<0.04) were the only risk factors significantly associated with ROP progression.

Treatment One hundred fifty-four (87%) premature infants with TOSA ROP were treated (Figure 3). Almost half (46%) received anti-vascular endothelial growth factor (VEGF) injection only as treatment, followed by 24% who received laser photocoagulation using indirect ophthalmoscope (LIO) only. Sixteen did not receive treatment since they did not follow up during their scheduled procedure. Of the 8 with ROP stage 4, only 4 underwent vitrectomy. One refused surgery. Of the 5 with ROP stage 5, 3 were prognosticated, while one underwent vitrectomy.

Clinical Outcomes For the 177 infants with TOSA ROP, 61 (34%) were treated but last seen without full ROP regression and retinal maturation (Figure 4). For the 306 with type 2 ROP, 220 (72%) were without full ROP regression and retinal maturation on the last follow-up. For the 1417 without ROP, only 812 (57%) reached zone 3 or retinal maturation on the last follow-up.

Comparison of Clinical Profile of Infants Seen in NCR and Outside Areas Premature infants seen in hospitals in NCR had similar GA in those seen in other areas (Table 3). Premature infants seen in the hospital in NCR were significantly lighter than those seen in Region I and Cordillera Administrative Region (*P*<0.006) but heavier than those seen in Region II (*P*<0.001) and VIII (*P*<0.002). Getting treated for sepsis among infants seen in NCR had significantly different proportions to those seen in Region I and CAR (*P*<0.001), V (*P*<0.001), VI (*P*<0.001), and VIII (*P*<0.001).

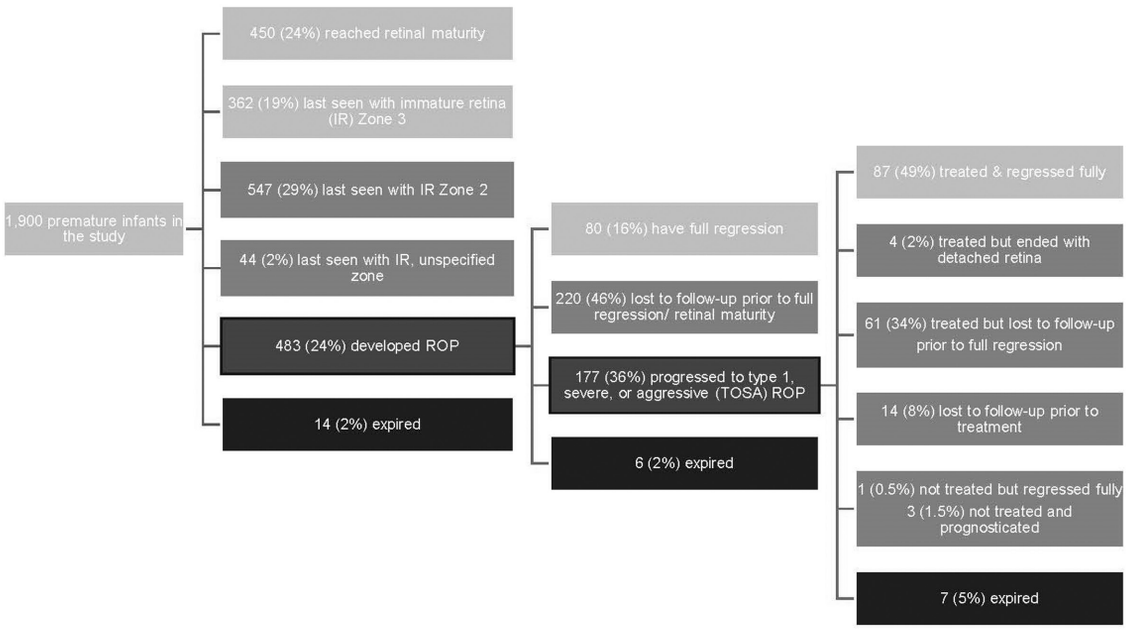

Figure 4 Clinical outcomes of premature infants at last follow-up Among those with TOSA ROP, 34% were treated but remained without full regression or retinal maturity. In the non-TOSA group, 46% were lost to follow-up before full regression. Over half of infants without ROP remained immature at final examination, underscoring the need for strengthened follow-up systems. ROP: Retinopathy of prematurity; TOSA: Type 1, severe, or aggressive; IR: Immature retina.

Receiving pRBC transfusion among infants seen in NCR had significantly different proportions to those seen in other areas, except 8 (P=0.78), and 11 (P=0.66). Receiving oxygen supplementation among infants seen in NCR has significantly different proportions to those seen in Region I and CAR (P<0.001), V (P<0.001), and VI (P<0.001). Aside from Region II (P=0.13), V (P=0.02), and VIII (P=0.02), the rest of the areas had significant differences to NCR in ROP development (ROP). Aside from VIII (P<0.001), there were no significant differences in ROP progression (TOSA ROP) between NCR and other areas. A subgroup was created for Region IV-A from the 29 patients from the region, but were seen in 4 NCR hospitals.

DISCUSSION

This study found that lower GA, lower birthweight, male sex, and pRBC transfusion were significantly associated with ROP development, whereas sepsis and oxygen supplementation were not. Consistent with global literature, lower GA, lower birthweight, and blood transfusion were strongly associated with ROP[11,14]. Oxygen supplementation and sepsis were not likely due to data limitations (*e.g.*, non-culture-proven sepsis, incomplete oxygen dosing records), survivor bias, and evolving NICU practices with tighter oxygen monitoring[11,14-16]. In our cohort, sepsis was defined operationally as having been treated for septicemia, but microbiologic confirmation was not uniformly required. Likewise, improved infection control practices in larger NICUs including antibiotic stewardship programs and neonatal sepsis bundles. Oxygen supplementation was almost universal, and recording did not consistently differentiate between duration, concentration, or whether oxygen blenders were used. Local neonatal practices may have attenuated the expected risks, as many tertiary NICUs in the Philippines have adopted stricter oxygen monitoring protocols and increased availability of pulse oximetry in recent years[17]. Even when oxygen is delivered without a blender in some facilities, target saturations are now more tightly controlled. These may have weakened the contribution relative to GA, birthweight, and transfusion status. Lastly, the sickest infants with prolonged oxygen exposure or severe sepsis are also at the highest risk of early mortality and may not have survived long enough to undergo ophthalmic screening[18-19]. The limited granularity of exposure data may have reduced statistical power to detect significant associations. Similar issues have been described in other LMIC cohorts[20].

When only the GA of <32wk and birthweight of <1500 g, 20% of infants with ROP and 14% of those who progressed to TOSA would have been missed[10]. It is recommended that the criteria on GA be made broader to <35wk and <2000 g in addition to the risk factors enumerated in the consensus statement in 2020, which reduced missed cases to 2%. Similarly, 26 who developed ROP had GA of >32 to 35wk or birthweight of >1500 to 2000 g, with none of the 3 risk factors, and will be missed[21]. Although screening more infants increases costs—approximately USD 272 715 based on analogous economic models—the lifetime societal cost

of blindness far exceeds this amount[22-23]. Also, participating institutions already screened nearly all preterm referrals due to widespread use of STOP criteria, so adopting <35wk and/or <2000 g adds minimal burden while drastically reducing missed cases. Facilities relying only on major criteria may see larger increases in screening, but these remain feasible with modest staffing adjustments, task-sharing, structured scheduling, and tele-ROP[24-25]. The apparent lack of association with oxygen and sepsis likely reflects data quality issues, improved modern NICU practices, and survivor bias. Transfusion remained significant and may act as a proxy for overall illness severity. The Philippines mirrors other LMICs in the third epidemic: ROP occurs in larger and more mature infants than in high-income countries; incidence and care vary widely between institutions and regions; and health-system barriers contribute to preventable blindness[24,26].

Anti-VEGF monotherapy was the most common treatment, contrasting with earlier Philippine series where laser predominated[4,27]. However, because follow-up in this study was short, the true proportion requiring both anti-VEGF and subsequent laser may be underestimated. Literature recommends follow-up to ≥65–70wk postmenstrual age to capture recurrence or persistent avascular retina; most infants in this cohort had not yet reached full regression or retinal maturity[28-30]. Screening and treatment gaps remain significant. Eighty-eight infants were not screened, and 9% of those with TOSA ROP received no treatment. Many infants lost to follow-up still had incomplete vascularization at the last visit, a group known to be at substantially higher risk of developing ROP[28]. Barriers include travel distance, financial constraints, limited NICU capacity, and lack of available ophthalmologists before discharge[24]. Measures such as ROP coordinators, discharge protocols, tele-ophthalmology, and electronic tracking systems can help address these losses[3,25].

Maternal factors also warrant attention. Although maternal age was not statistically associated with ROP, nearly one-quarter of mothers were either <18 or >35 years old, both risk factors for preterm birth. Pregnancy-related hypertension was the most common cause of prematurity, and gaps in prenatal care and institutional delivery remain prevalent, especially among families living far from participating hospitals[31].

Finally, key data gaps underscore the need for a national neonatal ophthalmology registry. Such a system should prospectively capture oxygen monitoring details, microbiologic confirmation of sepsis, transfusion practices, and complete ophthalmologic outcomes. A unified registry would enable stronger causal analyses, real-time quality improvement, benchmarking across regions, and more accurate cost-effectiveness modeling, thereby supporting national policy reforms to prevent ROP-related blindness, similar to other eye diseases[32].

This study also presents the first multiregional cohort of ROP in the Philippines. Nearly one in four premature infants developed ROP, and two in five progressed to TOSA. Incidence of ROP itself varied widely across regions, from 8% in region 1 and CAR to 55% in region 6, reflecting disparities in neonatal care. Higher-incidence regions often had limited NICU capacity, fewer subspecialists, more outborn referrals, and poorer prenatal care, all of which may increase oxygen exposure, transfusion needs, and the prevalence of lower GA and birthweight[33]. Lower-incidence regions likely benefit from better referral patterns or systems such as electronic ROP trackers. These disparities echo the heterogeneity reported within other middle-income countries, where neonatal care varies by geography and hospital type[34]. However, unrepresented areas in Visayas and Mindanao introduce possible selection bias. The national incidence estimate of 25% aligns with previous single-centre reports (14%–43%), confirming that ROP is a nationwide concern[4-7]. This burden resembles that of other middle-income countries experiencing the “third epidemic” of ROP, where improved survival of preterm infants outpaces the availability of consistently high-quality intensive care[3,35]. In contrast, high-income countries report lower rates, typically confined to infants <28wk or <1000 g[36].

This study has limitations. Large regions, including Central Visayas, were not represented, and weighted estimates may not fully correct for selection bias. Data quality was limited for some risk factors, particularly oxygen exposure and sepsis. Follow-up was interim, restricting assessment of long-term outcomes. Nonetheless, the scale, multiregional design, and standardized data collection provide robust national insights.

The main strength of this study is its scale and breadth: 1900 infants from 20 hospitals across 12 regions, encompassing both government and private institutions. This provides the most representative national picture of ROP to date. The use of standardized definitions (ICROP-3)[12] and regression models strengthens internal validity.

Future research in the Philippines should focus on prospective cohorts with microbiologically confirmed sepsis, transfusion thresholds, and oxygen exposure data to clarify risk pathways, on extended follow-up of infants treated with anti-VEGF to 70–80wk postmenstrual age to quantify recurrence and visual outcomes, and on modelling Philippines-specific cost-effectiveness analyses on the incremental costs of broader screening against the long-term costs of blindness, building on the EcROP framework[23].

In conclusion, this study found that lower GA, lower birthweight, male sex, and pRBC transfusion were significantly associated with ROP development, whereas sepsis and oxygen supplementation were not. It also provides the first

multiregional multicenter data on ROP in the Philippines, demonstrating substantial incidence and progression beyond NCR. Current screening criteria may miss a significant proportion of at-risk infants.

ACKNOWLEDGEMENTS

We acknowledge Dr. Milagros H. Arroyo, a leading ROP specialist in the country and a mentor, for reviewing and giving comments for the improvement of our manuscript. We thank the neonatal and ophthalmology staff at all participating hospitals for their dedication to patient care and support for this study. We are grateful to the parents and families of the infants. We acknowledge the Department of Health Single Joint Research Ethics Board for the study approval (2024-04).

Authors' Contributions: Tan RJD conceived the study, coordinated the multicenter network, performed the data analysis, and drafted the initial manuscript. Milante RR, Te AVR, Ereño ECAG, Gonzales RCG, Flores-Anotado JF, Uy CSJ, Macalma KK, Santos-Rayos JJY, Mangahas LJD, Cabrera KR, Agcaoili LR, Ecija CJA, Laddaran TCC, Corpus-Velasquez KD, Jimenez IV JM, Ilagan KS, Daguman IJ, Martinez XDL, Manzano AA, Moreno RJR, Evangelista GS, Taclobao KD, Marcelo-Tan MCT, Castillo CQ, Ibañez IV MBB, Precia MD, Tacata PS, Carbonell RK, Dator DCS, Tiburan JM, Anzures RG, Marohom NED, Lumontod LAE, Quitos ME, Aclan BAA, Uy ATY, Barja CB, Gambalan VA, Ongkeko JMS, and Villanoy GL collected and curated patient data. Tan RJD, Milante RR, and Santos-Rayos JJY contributed to the interpretation of ophthalmic outcomes. All authors critically reviewed the manuscript, approved the final version, and agreed to be accountable for the work. Tan RJD had full access to all data and takes responsibility for the decision to submit for publication.

Data Availability Statement: De-identified participant-level data and statistical code can be made available upon reasonable request to the corresponding author. Data will be shared for research purposes only and subject to standard data use agreements.

Conflicts of Interest: Tan RJD, None; **Milante RR,** None; **Te AVR,** None; **Ereño ECAG,** None; **Gonzales RCG,** None; **Flores-Anotado JF,** None; **Uy CSJ,** None; **Macalma KK,** None; **Santos-Rayos JJY,** None; **Mangahas LJD,** None; **Cabrera KR,** None; **Agcaoili LR,** None; **Ecija CJA,** None; **Laddaran TCC,** None; **Corpus-Velasquez KD,** None; **Jimenez IV JM,** None; **Ilagan KS,** None; **Daguman IJ,** None; **Martinez XDL,** None; **Manzano AA,** None; **Moreno RJR,** None; **Evangelista GS,** None; **Taclobao KD,** None; **Marcelo-Tan MCT,** None; **Castillo CQ,** None; **Ibañez IV MBB,** None; **Precia MD,** None; **Tacata PS,** None; **Carbonell RK,** None; **Dator DCS,** None; **Tiburan JM,** None; **Anzures RG,** None; **Marohom NED,** None; **Lumontod LAE,** None; **Quitos ME,** None; **Aclan BAA,** None; **Uy ATY,** None; **Barja CB,** None; **Gambalan VA,** None; **Ongkeko JMS,** None; **Villanoy GL,** None.

REFERENCES

1 Cayabyab RG, Song A, Ramanathan R, *et al*. Proportion of retinopathy of prematurity that was treated across regions in the United States. *Am J Perinatol* 2021;38(6):581-589.

2 Del Mundo PS, Chua CE. Causes of blindness and severe visual impairment among children enrolled in an early intervention and preschool program of a school for the blind in the Philippines. *Philipp J Ophthalmol* 2015;40:41-46.

3 Al-Khaled T, Valikodath NG, Patel SN, *et al*. Addressing the third epidemic of retinopathy of prematurity through telemedicine and technology: a systematic review. *J Pediatr Ophthalmol Strabismus* 2021;58(4):261-269.

4 Paulino JAT, Santiago APD, Santiago DE. Comparison of the detection rates for retinopathy of prematurity (ROP) of the 2013 Philippine Academy of Ophthalmology (PAO) Revised Philippine Guidelines and the 2005 PAO-Philippine Pediatric Society (PPS) Guidelines for ROP screening in the Philippine General Hospital: a 5-year review. *BMJ Open Ophthalmol* 2020;5(1):e000448.

5 Lazo MS, Corpuz KD. Maternal and infantile risk factor profile of preterm infants screened for retinopathy of prematurity in a tertiary hospital. *Philipp J Ophthalmol* 2018;43:10-14.

6 Chan DFF, Herrera-Arroyo MM. Anatomic outcomes of laser indirect ophthalmoscopy for retinopathy of prematurity in a tertiary referral center in the Philippines. *BMC Res Notes* 2019;12(1):263.

7 Tan RJ. Clinico-epidemiologic profile of preterm infants referred for retinopathy of prematurity screening at the Southern Isabela Medical Center in 2023. *Asian J Public Health Practice* 2023;1:1-8.

8 Department of Health. *Philippine Health Facility Development Plan 2020-2040*. Philippines: Health Facility Development Bureau:2020.

9 Wilkinson DJ, Villanueva-Uy ME, Hayden D, *et al*. Decision-making around resuscitation of extremely preterm infants in the Philippines: a consensus guideline. *J Paediatr Child Health* 2019;55(9):1023-1028.

10 Philippine Pediatric Society, Philippine Society of Newborn Medicine, Philippine Academy of Ophthalmology–Retinopathy of Prematurity Working Group. (2020). Retinopathy of Prematurity Philippine Preventive Care Plan Strategy. A consensus statement of the Philippine Pediatric Society (PPS), Philippine Society of Newborn Medicine (PSNbM) and the Philippine Academy of Ophthalmology–Retinopathy of Prematurity Working Group (PAO-ROPWG). *Philipp J Ophthalmol* 2020;45:58-64.

11 de las Rivas Ramírez N, Luque Aranda G, Rius Díaz F, *et al*. Risk factors associated with Retinopathy of Prematurity development and progression. *Sci Rep* 2022;12:21977.

12 Chiang MF, Quinn GE, Fielder AR, *et al*. International classification of retinopathy of prematurity, third edition. *Ophthalmology* 2021;128(10):e51-e68.

13 Athikarisamy S, Desai S, Patole S, *et al*. The use of postnatal weight gain algorithms to predict severe or type 1 retinopathy of prematurity: a systematic review and meta-analysis. *JAMA Netw Open* 2021;4(11):e2135879.

14 Bahmani T, Karimi A, Rezaei N, *et al*. Retinopathy prematurity: a systematic review and meta-analysis study based on neonatal and maternal risk factors. *J Matern Fetal Neonatal Med* 2022;35(25): 8032-8050.

15 El Emrani S, van der Meeren LE, Jansen EJS, *et al*. Early-onset sepsis as an early predictor for retinopathy of prematurity: a meta-analysis. *Am J Perinatol* 2025;42(3):387-394.

16 Sherief ST, Taye K, Teshome T, *et al*. Retinopathy of prematurity among infants admitted to two neonatal intensive care units in Ethiopia. *BMJ Open Ophthalmol* 2023;8(1):e001257.

17 Zelasko J, Omotayo MO, Berkelhamer SK, *et al*. Neonatal oxygen therapy in low- and middle-income countries: a pragmatic review. *J Glob Health Rep* 2020:4.

18 Thomas R, Bijlsma MW, Gonçalves BP, *et al*. Long-term impact of serious neonatal bacterial infections on neurodevelopment. *Clin Microbiol Infect* 2024;30(1):28-37.

19 Singh M, Alsaleem M, Gray CP. Neonatal Sepsis. In: *StatPearls*. United States of America: StatPearls Publishing:2025.

20 Deb D, Annamalai R, Muthukumar M. Incidence, risk factors, progression, and involution in retinopathy of prematurity at a tertiary care center in South India. *Oman J Ophthalmol* 2023;16(3):452-460.

21 Li L, Gao YL, Chen W, *et al*. Screening for retinopathy of prematurity in North China. *BMC Ophthalmol* 2022;22(1):251.

22 Gyllensten H, Humayun J, Sjöbom U, *et al*. Costs associated with retinopathy of prematurity: a systematic review and meta-analysis. *BMJ Open* 2022;12(11):e057864.

23 Rothschild MI, Russ R, Brennan KA, *et al*. The economic model of retinopathy of prematurity (EcROP) screening and treatment: Mexico and the United States. *Am J Ophthalmol* 2016;168:110-121.

24 Gilbert CE, Todd J. Impact of COVID-19 pandemic on retinopathy of prematurity services in low resource settings. *Eye (Lond)* 2024;38(11):2102-2109.

25 Guo Z, Ma N, Wu YX, *et al*. The safety and feasibility of the screening for retinopathy of prematurity assisted by telemedicine network during COVID-19 pandemic in Wuhan, China. *BMC Ophthalmol* 2021;21(1):258.

26 Bowe BS T, Nyamai MD L, Ademola-Popoola MD D, *et al*. The current state of retinopathy of prematurity in India, Kenya, Mexico, Nigeria, Philippines, Romania, Thailand, and Venezuela. *Digit J Ophthalmol* 2019;25(4):49-58.

27 Dogra MR, Vinekar A. Role of anti-vascular endothelial growth factor (anti-VEGF) in the treatment of retinopathy of prematurity: a narrative review in the context of middle-income countries. *Pediatr Health Med Ther* 2023;14:59-69.

28 Jang JH, Kim YC. Retinal vascular development in an immature retina at 33–34 weeks postmenstrual age predicts retinopathy of prematurity. *Sci Rep* 2020;10:18111.

29 Ünal AC, Akıdan M, Erol MK. A comparation of three different anti-VEGF drugs in development of persistent avascular retina in premature children. *Sci Rep* 2024;14:31097.

30 Hammer JD, Nguyen H, Palmer J, *et al*. Computed analysis of retinal vascular growth after bevacizumab treatment of retinopathy of prematurity until age 3 years. *Clin Ther* 2023;45(1):4-16.

31 Wu ST, Lin CH, Lin YH, *et al*. Maternal risk factors for preterm birth in Taiwan, a nationwide population-based cohort study. *Pediatr Neonatol* 2024;65(1):38-47.

32 Tan RJD, Mercado GJV, Cabrera PE, *et al*. Philippine retinoblastoma initiative multi-eye center study 2010-2020. *Int J Ophthalmol* 2024;17(1):144-156.

33 Albarqi MN. The impact of prenatal care on the prevention of neonatal outcomes: a systematic review and meta-analysis of global health interventions. *Healthcare (Basel)* 2025;13(9):1076.

34 Darlow BA, Gilbert CE, Quiroga AM. Setting up and improving retinopathy of prematurity programs. *Clin Perinatol* 2013;40(2): 215-227.

35 Tawfik S, Mansour A, Selim NL, *et al*. Analysis of a two-year independent screening effort for retinopathy of prematurity in rural Egypt. *BMC Ophthalmol* 2021;21(1):445.

36 Berrocal AM, Fan KC, Al-Khersan H, *et al*. Retinopathy of prematurity: advances in the screening and treatment of retinopathy of prematurity using a single center approach. *Am J Ophthalmol* 2022;233:189-215.