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New developments in retinopathy of prematurity

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New developments in retinopathy of prematurity

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ORIGINAL RESEARCH
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Ten-Year Trend of Retinopathy of Prematurity Among Extremely Preterm Infants in One Neonatal Intensive Care Unit in China

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Background: Extremely preterm (EP) infants are at the highest risk of retinopathy of prematurity (ROP). With more EP infants survived in China, recent data of ROP is lacking. The aim of the study is to report the trend of incidence of ROP among EP infants in a large neonatal intensive care unit in China over the past 10-year period, in relation with the overall survival rate and the change of oxygen saturation targets.

Methods: This retrospective cohort study enrolled all EP infants born before 28 weeks' gestation and admitted to one of the largest tertiary neonatal intensive care units in China from 2010 to 2019. Data were compared between two time periods according to different oxygen saturation targets: 2010–2014 (P1) with low saturation target and 2015–2019 (P2) with higher target.

Results: Of 630 EP infants admitted during the 10 years, 447 (71.0%) infants survived to discharge. The survival rate increased significantly from 61.6% in P1 to 75.8% in P2 ($P < 0.05$). Of the 472 infants who had ROP data, 318 (67.4%) developed ROP of any stage, 67 (14.2%) developed severe ROP, and 44 (9.3%) received treatment. The incidence of any ROP increased significantly from 51.7% in P1 to 74.3% in P2 ($P < 0.05$). The incidence of severe ROP increased from 11.0% in P1 to 15.6% in P2, and ROP treatment increased from 6.9% in P1 to 10.4% in P2, but neither reached statistical significance (both $P > 0.05$).

Conclusions: We observed an increasing trend in the incidence of ROP across the 10-year period in one of the largest neonatal care units in China. The increased survival rate and the use of high-target oxygen saturation in the later period may partly explain this trend. Further investigations are needed to improve the care practices and to reduce the incidence of severe ROP.

Keywords: extremely premature, trend, preterm infant, retinopathy of prematurity, incidence

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INTRODUCTION

The survival rate of extremely preterm (EP, <28 weeks' gestation) infants in China has improved significantly during the last two decades. While with more EP infants survive, the incidences of major morbidities including severe retinopathy of prematurity (ROP) have been increasing (1). Severe ROP is the leading cause of childhood blindness worldwide (2). EP infants are at the highest

risk of severe ROP and ROP requiring treatment. In a Swedish national cohort of EP infants, 9 of 434 (2.1%) were blind and 38 of 434 (8.8%) were visually impaired at 6.5 years, and visual problems were strongly associated with treated ROP (3). EP infants with severe ROP (stage ≥3 or requiring treatment) also have higher risks of cognitive and motor developmental delay, compared with those without severe ROP (4, 5).

ROP is a multifactorial disease, with prematurity and excessive oxygen exposure as the most important risk factors (6). Developed countries have experienced the "first epidemic (in the 1940s and 1950s)" and the "second epidemic (in the 1970s)" of ROP (7), and the incidence of severe ROP in EP infants began to decline or stabilize at a relatively low level (8). However, China, like other developing countries, is in the midst of "the third epidemic" of ROP (since 2000), with increased survival of EP infants and inadequate quality of neonatal care (9–11). Gilbert and colleagues called this "third epidemic" of severe ROP a mixture of first epidemic risk factors (inadequately monitored oxygen) and second epidemic risk factors (extreme prematurity) (7).Since the first guidance on oxygen therapy and the prevention and treatment of ROP issued by the Ministry of Health in 2004 (12), the prevention and management of ROP has improved considerably in China. A national multicenter study from 2010 to 2012 showed that the incidences of ROP and severe ROP in premature infants <34 weeks in China were 15.2 and 1.2%, respectively; and among infants with GA <28 weeks, the incidences of ROP and severe ROP were much higher, at 67.1 and 13.8%, respectively (13). However, during the past decade, there has been evolving targets of oxygen saturations for EP infants, which might influence incidence of ROP. In 2014, a meta-analysis and systematic review of several large trials assessing target oxygen saturation in EP infants showed that higher oxygen saturation targets (91–95% compared with 85–89%) were associated with decreased mortality (14). Based on this, many neonatal intensive care units (NICUs) in China adopted higher oxygen saturation target, though the same meta-analysis also showed increased risk of ROP associated with the higher saturation. Currently, limited data on the temporal trends of ROP incidence among EP infants are available in recent years from China.

The aim of the present study was to determine the trend of incidence and severity of ROP among EP infants in one of the largest NICUs in China during a 10-year period, in relation with the overall survival rate and the change of oxygen saturation targets.

MATERIALS AND METHODS

Study Design, Setting, and Patients

This retrospective cohort study included all infants with gestational age <28 weeks and discharged between January 1, 2010 and December 31, 2019 from a tertiary NICU in Shanghai, China. Our NICU is one of the largest referral center for critical neonates in Shanghai and China with around 1,500 admissions annually. Our hospital is a free-standing children's hospital and all infants admitted to our unit are outborns. The study was approved by the Ethics Committee of the Children's Hospital of Fudan University and performed in agreement with the ethical principles in the Declaration of Helsinki.

From 2010 to 2014, our unit used the saturation target of 85%-89% for EP infants, and the target was changed to 91–95% from 2015. Therefore, the 10-year study period were divided into two phases: 2010–2014 (P1) and 2015–2019 (P2). The incidences and severities of ROP were compared between P1 and P2. Data on maternal and infant characteristics, and NICU treatments related with ROP were collected based on previous report of the study group (2).

Diagnosis of ROP

ROP was assessed by qualified ophthalmologists with RetCam fundus camera. The diagnosis and categorization of ROP was made according to the revised International Classification of Retinopathy of Prematurity (IC-ROP) (15). The first fundus examination was performed at the 4 to 6 weeks after birth according to the national guideline issued in 2004 (12) and updated in 2014 (16). The indication for treatment was Type 1 pre-threshold ROP based on the Early Treatment of Retinopathy of Prematurity Study (ETROP) (17). The features of Type 1 pre-threshold ROP included any stage of ROP in zone 1 with plus, zone 1 stage 3 with or without plus, and zone 2 stage 2 or 3 with plus.

Severe ROP was defined as stage 3 or above or the need for treatment with laser or intravitreal anti-vascular endothelial growth factor (VEGF) therapy.

Definitions

Gestational age was defined, in descending order of preference, from the early prenatal ultrasound result, last menstrual period, or New Ballard Score (18). Small for gestational age (SGA) was defined as birth weight (BW) less than the 10th percentile according to Zhu et al. (19). Antenatal steroid use was defined as any administration prior to birth, regardless of the time interval. Prolonged mechanical ventilation (MV) was defined as >7 days of invasive ventilation.

Statistical Analysis

Results were presented as mean with standard deviation (SD), median with interquartile range (IQR), or numbers with percentage, as appropriate. Infants' characteristics were compared between P1 and P2 using the chi-square test for categorical variables and Student's *t*-test or the Mann-Whitney *U*-test for continuous variables. The trend analysis was performed with a modified Poisson regression model. SPSS statistical software (SPSS 20.0, SPSS Inc., Chicago, IL, USA) was used for analysis of the data. *P*-values were 2-tailed, and $P < 0.05$ was considered statistically significant.

RESULTS

Over the 10 years from 2010 to 2019, a total of 630 infants born before 28 weeks' gestation were admitted to our NICU, with 216 admitted during P1 (2010–2014) and 414 during P2 (2015–2019). Of these, 97 (15.4%) infants died with active treatment, and 86 (13.7%) were taken home by their parents against

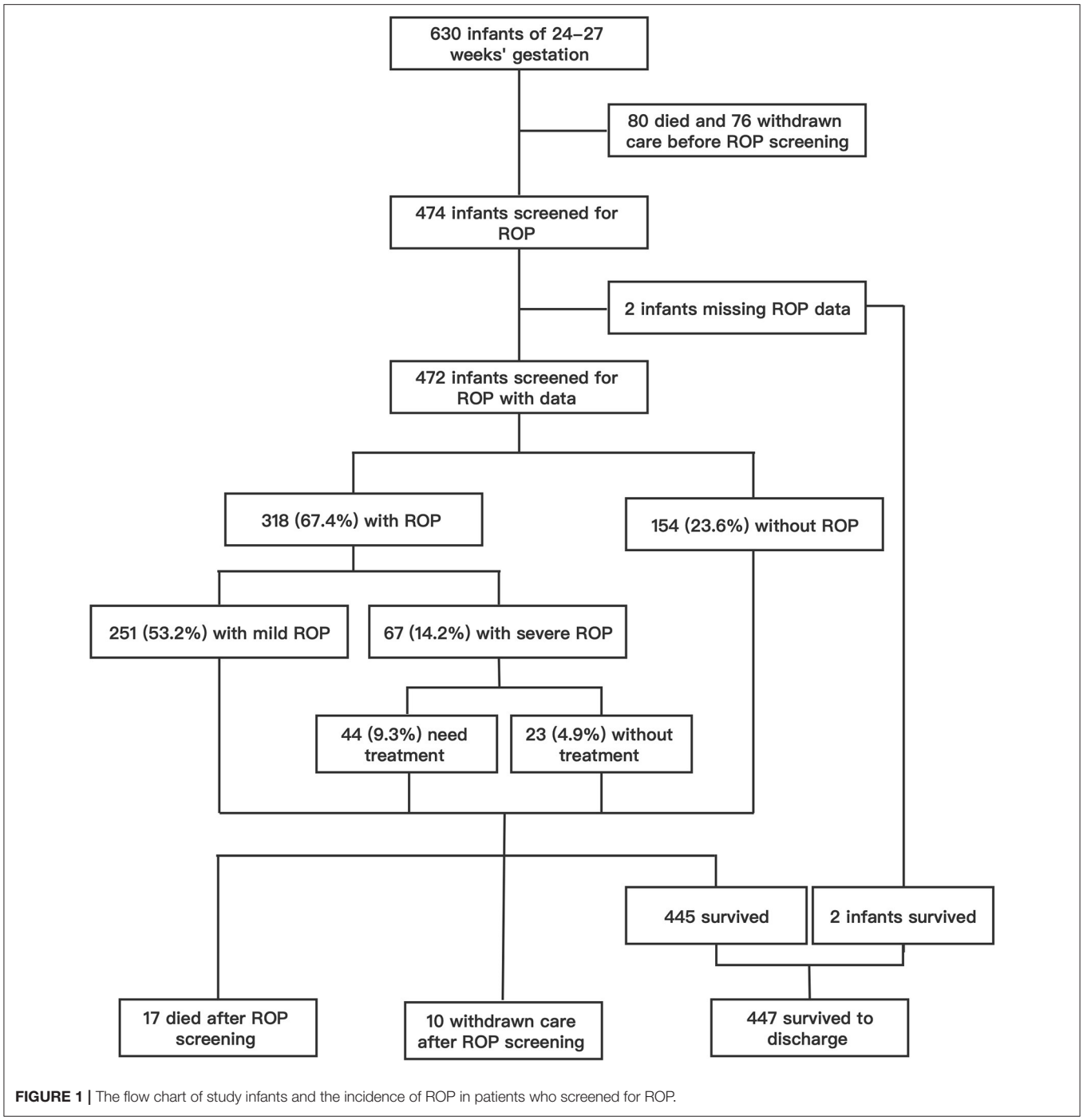

FIGURE 1 | The flow chart of study infants and the incidence of ROP in patients who screened for ROP.

medical advice. A total of 447 infants survived to discharge, with an overall survival rate of 71.0%. A total of 474 (75.2%) survived to the 5th week after birth and met ROP screening criteria and two infants had incomplete ROP data (**Figure 1**). Of the 472 infants with ROP screening and complete ROP data, the mean gestational age was 26.9 (SD 0.8) weeks, and mean birth weight was 1,017 (SD 156) g. ROP was found in 67.4% (318/472) of the infants, and severe ROP in 14.2% (67/472) (**Figure 1**). Overall, 44 (9.3%) received ROP treatment, including 28 infants who underwent laser therapy and 16 infants who were given an anti-VEGF drug (Ranibizumab) via intraocular injections (**Figure 1**).

Mortality, survival, rates of ROP screening and incidences of ROP from 2010 to 2019 are shown in **Table 1** and **Figure 2**. The number of EP infants increased from 34 in 2010 to 100 in 2019. The overall survival rate was 71.0%, and increased from 61.8% in 2010 to 78.0% in 2019 ($P = 0.000$). The number of infants who were screened for ROP increased from 23 in 2010 to 83

TABLE 1 | Rates of mortality, withdrawn care, survival, and ROP in extremely preterm infants from 2010 to 2019[a].

Variable	2010 ($n = 34$)	2011 ($n = 34$)	2012 ($n = 40$)	2013 ($n = 53$)	2014 ($n = 55$)	2015 ($n = 65$)	2016 ($n = 61$)	2017 ($n = 94$)	2018 ($n = 94$)	2019 ($n = 100$)	Total ($n = 630$)	*P*-value[c]
Mortality	10 (29.4)	10 (29.4)	8 (20.0)	13 (24.5)	13 (23.6)	8 (12.3)	7 (11.5)	7 (7.4)	12 (12.8)	9 (9.0)	97 (15.4)	0.000
Withdrawn care	3 (8.8)	8 (23.5)	8 (20.0)	4 (7.5)	6 (10.9)	8 (12.3)	15 (24.6)	9 (9.6)	12 (12.8)	13 (13.0)	86 (13.7)	0.640
Survival	21 (61.8)	16 (47.1)	24 (60.0)	36 (67.9)	36 (65.5)	49 (75.4)	39 (63.9)	78 (83.0)	70 (74.5)	78 (78.0)	447 (71.0)	0.000
Screened for ROP	23 (67.6)	17 (50.0)	25 (62.5)	37 (69.8)	44 (80.0)	50 (76.9)	41 (67.2)	80 (85.1)	73 (77.7)	84 (84.0)	474 (75.2)	0.000
Screened and with data	23 (67.6)	16 (47.1)	25 (62.5)	37 (69.8)	44 (80.0)	50 (76.9)	41 (67.2)	79 (84.0)	73 (77.7)	84 (84.0)	472 (74.9)	0.000
Any ROP[b]	13 (56.5)	5 (31.3)	13 (52.0)	17 (45.9)	27 (61.4)	29 (58.0)	33 (80.5)	63 (79.7)	52 (71.2)	66 (78.6)	318 (67.4)	0.000
Severe ROP[b]	6 (26.1)	1 (6.2)	3 (12.0)	0 (0.0)	6 (13.6)	6 (12.0)	10 (24.4)	13 (16.5)	10 (13.7)	12 (14.3)	67 (14.2)	0.603
ROP treatment[b]	5 (21.7)	1 (6.2)	1 (4.0)	0 (0.0)	3 (6.8)	4 (8.0)	3 (7.3)	8 (10.1)	10 (13.7)	9 (10.7)	44 (9.3)	0.448

ROP, retinopathy of prematurity.

[a]*Data were shown as n (%).*

[b]*Among infants who screened and with ROP data.*

[c]*P-values were determined for trend over the decade using modified Poisson regression models.*

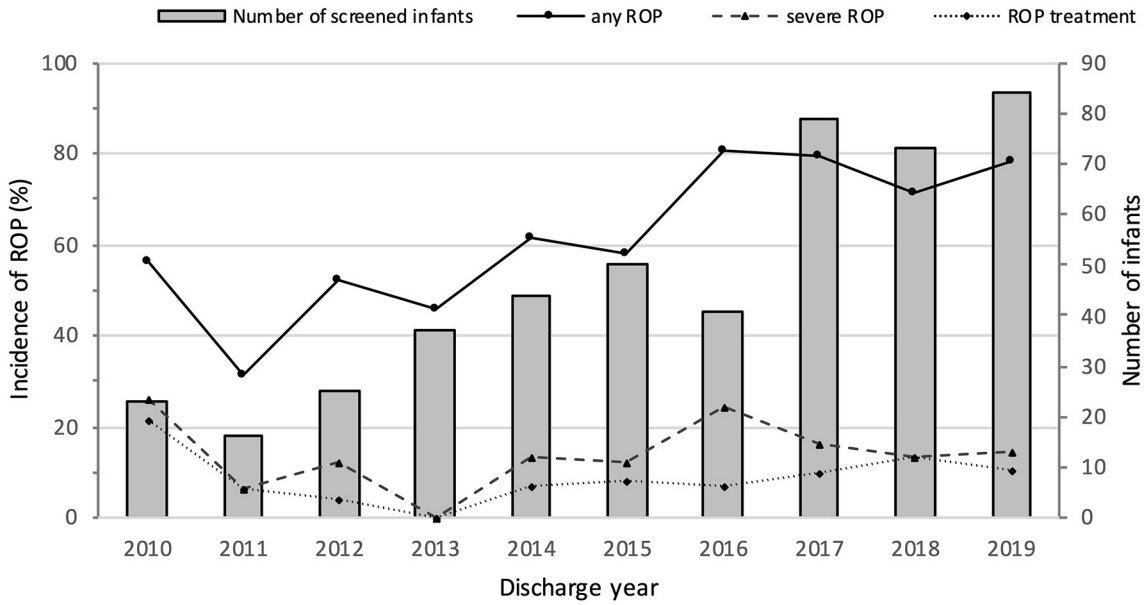

FIGURE 2 | Numbers of screened infants and incidence of ROP in extremely premature infants from 2010 to 2019.

in 2019, with an increasing trend of ROP screening rate ($P = 0.000$). The incidence of any ROP ranged from 56.5% in 2010 to 78.6% in 2019, with a significantly increasing trend over the 10 years ($P = 0.000$). There were no significant trend observed in the incidence of severe ROP or ROP treatment ($P = 0.603$ and $P = 0.448$, respectively).

Table 2 shows the rates of survival, mortality and withdrawal care in two periods by GA. As GA increased, the overall survival rates increased from 45.8% among infants born at 24 weeks to 76.9% among infants born at 27 weeks, and the overall mortality decreased from 50.0 to 11.3% among infants born at 24–27 weeks. In the comparisons of the two periods, the survival rate increased from 61.6% in P1 to 75.8% in P2 ($P < 0.05$). However, when stratified by GA, significant differences were seen only between the 26- and 27-week GA groups.

The incidence of any ROP and severe ROP increased with decreasing GA. The incidence of any ROP was significantly higher in P2 than in P1 (74.3 vs. 51.7%; $P = 0.000$) (**Table 3**, **Figure 3**). However, after GA stratification, differences were seen only between the 26- and 27-week GA groups. The incidence of severe ROP increased from 11.0% in P1 to 15.6% in P2, and ROP treatment increased from 6.9% in P1 to 10.4% in P2, but both increases were not statistically significant ($P > 0.05$) (**Table 3**, **Figure 3**).

Table 4 presents the comparison of the basic characteristics and therapies among the 472 EP infants who completed ROP screening during the two periods. Mean GA and birth weight, proportions of male sex, SGA, and multiple birth remained similar in the two periods. There was no difference in the rates of maternal complications, including gestational diabetes

TABLE 2 | Rates of survival, mortality, and withdrawal care in P1 (2010–2014) and P2 (2015–2019) by gestational weeks, n (%).

	Survival			Mortality			Withdrawal care		
	Total	P1	P2	Total	P1	P2	Total	P1	P2
24 w	11 (45.8)	4 (44.4)	7 (46.7)	12 (50.0)	5 (55.6)	7 (46.7)	1 (4.2)	0 (0.0)	1 (6.7)
25 w	41 (54.7)	13 (56.5)	28 (53.8)	19 (25.3)	6 (26.1)	13 (25.0)	15 (20.0)	4 (17.4)	11 (21.2)
26 w	115 (68.9)	26 (50.0)	89 (77.4)*	25 (15.0)	15 (28.8)	10 (8.7)*	27 (16.2)	11 (21.2)	16 (13.9)
27 w	280 (76.9)	90 (68.2)	190 (81.9)*	41 (11.3)	28 (21.2)	13 (5.6)*	43 (11.8)	14 (10.6)	29 (12.5)
24–27 w	447 (71.0)	133 (61.6)	314 (75.8)*	97 (15.4)	54 (25.0)	36 (10.4)*	86 (13.7)	29 (13.4)	57 (13.8)

**Comparisons between P1 and P2, P < 0.05.*

TABLE 3 | Rates of any ROP, severe ROP, and ROP treatment in 472 extremely preterm infants who completed ROP screening in P1 (2010–2014) and P2 (2015–2019) by gestational weeks, n (%).

	Any ROP			Severe ROP			ROP treatment		
	Total	P1	P2	Total	P1	P2	Total	P1	P2
24 w	11 (91.7)	5 (100.0)	6 (85.7)	5 (41.7)	0 (0.0)	5 (71.4)	3 (25.0)	0 (0.0)	3 (42.9)
25 w	43 (93.5)	12 (85.7)	31 (96.9)	14 (30.4)	4 (28.6)	10 (31.3)	11 (23.9)	3 (21.4)	8 (25.0)
26 w	90 (74.4)	13 (43.3)	77 (84.6)*	23 (19.0)	6 (20.0)	17 (18.7)	16 (13.2)	5 (16.7)	11 (12.1)
27 w	174 (59.4)	45 (46.9)	129 (65.5)*	25 (8.5)	6 (6.3)	19 (9.6)	14 (4.8)	2 (2.1)	12 (6.1)
24–27 w	318 (67.4)	75 (51.7)	243 (74.3)*	67 (14.2)	16 (11.0)	51 (15.6)	44 (9.3)	10 (6.9)	34 (10.4)

**Comparisons between P1 and P2, P < 0.05.*

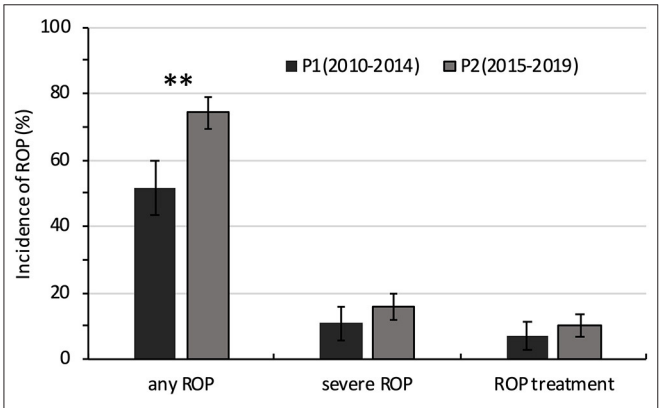

FIGURE 3 | Comparison of the incidence of ROP in extremely premature infants between 2010–2014 (P1) and 2015–2019 (P2). ***P < 0.05.*

mellitus, gestational hypertensive disease and premature rupture of membranes, between P1 and P2. The use of antenatal steroids increased from P1 to P2, as did the percentage of *in vitro* fertilization (IVF) and cesarean deliveries. Additionally, the use of caffeine and exclusive breastmilk significantly increased in the later period. Although there was no difference in the oxygen supplementation days between the two periods, the proportion of infants who required prolonged MV decreased significantly from P1 to P2. There was no significant difference in the proportions of infants who received blood transfusions three times or more in the two periods.

DISCUSSION

Our study analyzed the trend of ROP among EP infants in a tertiary NICU over a 10-year period. During this period, the distribution of gestational age and birth weight remained unchanged. ROP screenings were performed by experienced ophthalmologists using a RetCam fundus camera, and the indication for treatment was consistently based on the ETROP treatment threshold during the whole study period.

The overall incidences of any ROP and severe ROP in EP infants during 2010–2019 in our institute were 67.4 and 14.2%, which were similar to a multicenter study in China in 2010–2012. Compared with recently reported data on short-term outcome of EP infants in Guangdong Province during 2008–2017, the incidence was higher in our NICU for any ROP (67.2 vs. 45.1%), with similar incidences of severe ROP (14.2 vs. 14.6%); however, the survival rate was much higher in our NICU (74.9 vs. 52.5%).

In this 10-year period, we found an increasing trend of any ROP, and the incidence of ROP significantly increased from 51.7% in P1 to 71.3% in P2. The incidences for both severe ROP and treated ROP did not change significantly. However, though statistically unsignificant, the incidence of severe ROP increased by 41.8% from 11.0% in P1 to 15.6% in P2, and the incidence of ROP treatment increased by 50.7% from 6.9% in P1 to 10.4% in P2. Further longitudinal monitoring is required.

The incidence of severe ROP among EP infants in developed countries have been stabilized at a low level or showed decreasing trends. From 2007 to 2013, the overall incidence of ROP treatment in extremely premature infants in 11 International Network for Evaluating Outcomes (iNEO) member countries

TABLE 4 | Comparing basic characteristics and therapies in 472 extremely preterm infants who completed ROP screening in P1 (2010–2014) and P2 (2015–2019).

Variable[a]	Total, *n* = 472	P1, *n* = 145	P2, *n* = 327	*P*-value
GDM	81 (17.2%)	18 (12.4%)	63 (19.3%)	0.069
Maternal hypertension	28 (5.9%)	6 (4.15)	22 (6.7%)	0.272
Antenatal steroid use	252 (53.4%)	53 (36.6%)	199 (60.9%)	0.000
IVF	177 (37.5%)	43 (29.7%)	134 (41.0%)	0.019
PROM	180 (38.1%)	54 (37.2%)	126 (38.5%)	0.79
Birth weight, g	1,017 (156)	1,022 (165)	1,015 (152)	0.659
GA, weeks	26.9 (0.8)	26.9 (0.9)	26.9 (0.8)	0.806
24 weeks GA	12 (2.5%)	5 (3.4%)	7 (2.1%)	0.405
25 weeks GA	46 (9.7%)	14 (9.7%)	32 (9.8%)	0.965
26 weeks GA	121 (25.6%)	30 (20.7%)	91 (27.8%)	0.101
27 weeks GA	293 (62.1%)	96 (66.2%)	197 (60.2%)	0.218
ELBW	200 (42.4%)	63 (43.4%)	137 (41.9%)	0.753
Male sex	288 (61.0%)	87 (60.0%)	201 (61.5%)	0.763
Cesarean delivery	109 (23.1%)	20 (13.8%)	89 (27.2%)	0.001
SGA	13 (2.8%)	6 (4.1%)	7 (2.1%)	0.358
Multiple births	193 (40.9%)	56 (38.6%)	137 (41.9%)	0.504
Blood transfusions ≥3	181 (38.3%)	49 (33.8%)	132 (40.4%)	0.175
Prolonged MV	211 (44.1%)	77 (53.1%)	134 (41.0%)	0.015
Oxygen days[b]	53 (40,72)	52 (41,73)	53 (40,70)	0.843
Exclusive EBM feeding	162 (34.3%)	1 (0.7%)	161 (49.2%)	0.000
Caffeine treatment	315 (66.7%)	13 (9.0%)	302 (92.4%)	0.000

GDM, gestational diabetes mellitus; IVF, in vitro fertilization; PROM, premature rupture of membranes; GA, gestational age; ELBW, extremely low birth weight; SGA, small for gestational age; MV, mechanical ventilation; EBM, expressed breast milk.

[a]*Categorical variables are expressed as n (%) and continuous variables as mean (SD) for normally distributed variables and median (IQR) for non-normally distributed variables.*

[b]*Oxygen days are summed up days from admissions.*

was 19.4% in 2007 and 13.7% in 2013, showing a general decreasing trend (8). In a multicenter study on the outcome of extremely premature infants at 22–28 weeks in the US from 1993 to 2012, ROP of stage 3 or higher increased from 13% of infants (124 of 941) in 1993 to 19% (262 of 1385) in 2003 but decreased to 11% of infants (160 of 1,509) by 2012 (20). These changes can be attributed to a better understanding of the risk factors and pathogenesis of ROP, leading to improvements in perinatal and neonatal care, which improve the primary prevention of severe ROP in EP infants (7). A study conducted by a single center in Hong Kong, China, on the trends in ROP in preterm infants <32 weeks from 2006 to 2015 found a decreasing trend in the incidence of type 1 ROP (severe ROP requiring treatment) for the subgroup with gestational age <28 weeks, although it did not reach statistical significance (21). However, our data indicates an increasing trend in the incidence of severe ROP. One reason for the increasing severe ROP might be that more EP infants survived, similar to the "second epidemic" of severe ROP in developed countries. The EP infants born between 26 and 27 weeks accounted for nearly 90% of the study population, and significant increase of survival rate has been observed among these infants. The overall survival rate of EP infants in our center significantly increased by 17.7% from P1 to P2, and the survival rate in P2 was slightly increased compared with that in the multicenter study in China from 2013–2014 (79 vs. 68.2%). The rising survival rate suggested an improved management of these extremely preterm infants both prenatally, such as an increasing use of antenatal steroids and the postnatal period. In addition, the overall increase in the number of EP infants, which has almost tripled from 34 in 2010 to 100 in 2019, leading more infants screened for ROP, which could also attribute to the increase of ROP incidence in the latter half of the study period.

Moreover, our study showed a higher incidence of ROP treatment for every specific GA stratum than in high-income countries. In Norway, 17 and 9% of preterm infants with a GA of 24 and 25 weeks were treated for ROP, respectively, and none of the infants with a GA > 25 weeks developed ROP requiring treatment in the period from 1999 to 2000 (22). In Switzerland, the incidences of ROP treatment were 14.5, 7.3, 2.7, and 1.1% among infants born at 24, 25, 26, and 27 weeks, respectively, in the 2006–2015 period (23). In our study population, the overall incidence of ROP treatment decreased from 25.0% at 24 weeks to 4.8% at 27 weeks as GA increased; however, it was much higher than the reported incidences in the Norwegian and Switzerland population-based study at each GA.

Efforts have been made in our unit during the past 10 years to improve overall outcomes of EP infants, as well as to reduce ROP.

First, a stricter strategy to use oxygen with blended air and oxygen and monitor oxygen saturation was adopted, although a high-target oxygen saturation (91–95%) has been adopted in this center since 2015. Percutaneous blood oxygen saturation and percutaneous carbon dioxide monitoring were used for EP infants with invasive ventilation to accurately adjust ventilator parameters and avoid excessive fluctuation of blood oxygen saturation, which has been shown in both animal and human clinical studies to increase the risk of severe ROP (24).

Second, the introduction of new non-invasive ventilation strategies in our center since 2015 reduced the proportion of EP infants requiring prolonged MV, which is among the most frequently identified risk factors for ROP. A study conducted in a single center in Spain that included 228 infants with a mean GA of 28.83 ± 2.03 weeks demonstrated that infants with a longer MV time had a higher risk of ROP treatment (an increase in risk of 8.1% for each additional day) (25).

Third, caffeine has been routinely used in EP infants since 2014, which may contributing to early extubation and reduction in severe ROP (26).

Last, the rate of exclusive expressed breastmilk feeding among EP infants increased significantly from 0.7% in P1 to 49.2% in P2 since the establishment of a hospital-based human milk bank in our NICU in 2017. Meta-analyses has shown that human milk is strongly associated with ROP protection (27–29).

Unfortunately, despite of these efforts, the incidence of severe ROP in our center is still on the rise. Except for possible influence from the increasing survival rate of EP infants, practice differences between our unit and developed countries must be examined further in detail and to facilitate targeted quality improvement initiatives.

There are some limitations of our study. First, the retrospective nature of this study inevitably generates inconsistencies in the data, although every effort was made to exclude subjects with incomplete clinical data. Second, our data showed that a significant proportion of infants were taken home by their parents against medical advice. Concerns about adverse outcomes and costs may be the main reason for the negative treatment attitude toward extremely preterm infants. Of these, the vast majority (88.4%, 76 of 86) abandoned care before ROP screening. The infants in this population may survive if treatment was not withdrawn; however, the risk of developing severe ROP needing treatment may be higher. Therefore, the actual incidence of ROP requiring treatment may be underestimated. However, there was no significant difference in the rate of withdrawal care during the 10-year period, which did not affect the trends analysis of ROP incidence. Third, this study was mainly a hospital-based study rather than a population-based study, but our unit is one of the largest NICUs in China. Our study provided information on the trends in ROP incidence in an extremely preterm Chinese population. The results serve as a baseline for future multicenter, prospective trials among Chinese populations.

In conclusion, we observed an increasing trend in the incidence of ROP in EP infants across the 10-year period in one of the largest NICUs in China. The increased survival rate and the use of high-target oxygen saturation in the later period may partly explain this trend, although substantial changes in the NICU protocols and practices have also evolved during this period. More evidence-based management is needed to reduce the incidence of ROP among EP infants.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Children's Hospital of Fudan University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

YD, CC, and SZ: study design. YD, LZ, YZ, and SZ: the collection, analysis, and interpretation of data. YD, LZ, CC, and SZ: manuscript preparation. YD, LZ, YZ, CC, and SZ: final approval.

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Vascular Endothelial Growth Factor Signaling in Models of Oxygen-Induced Retinopathy: Insights Into Mechanisms of Pathology in Retinopathy of Prematurity

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Retinopathy of prematurity (ROP) is a leading cause of blindness in children worldwide. Blindness can occur from retinal detachment caused by pathologic retinal angiogenesis into the vitreous, termed intravitreal neovascularization (IVNV). Although agents that interfere with the bioactivity of vascular endothelial growth factor (VEGF) are now used to treat IVNV, concerns exist regarding the identification of optimal doses of anti-VEGF for individual infants and the effect of broad VEGF inhibition on physiologic angiogenesis in external organs or in the retina of a preterm infant. Therefore, it is important to understand VEGF signaling in both physiologic and pathologic angiogenesis in the retina. In this manuscript, we review the role of receptors that interact with VEGF in oxygen-induced retinopathy (OIR) models that represent features of ROP pathology. Specifically, we discuss our work regarding the regulation of VEGFR2 signaling in retinal endothelial cells to not only reduce severe ROP but also facilitate physiologic retinal vascular and neuronal development.

Keywords: ROP, OIR, VEGF, VEGFRs, VEGF receptors, neuropilins

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INTRODUCTION

Retinopathy of prematurity (ROP) remains a leading cause of blindness in children worldwide despite advances in neonatal care (1). The pathophysiology of ROP is described by a two-phase hypothesis that has been refined with the ability to save extremely premature infants (2). In Phase I ROP, intraretinal vascularization is compromised, and ongoing physiologic vascular development is delayed leading to areas of hypoxic retina. In Phase II ROP, also classified as Stage 3 ROP (3), aberrant retinal angiogenesis grows into the vitreous and is termed intravitreal neovascularization (IVNV). IVNV leads to blindness from retinal detachment that is not, or cannot be, treated (4, 5). Currently, Phase II ROP is treated with methods to ablate the peripheral avascular retina, often with laser (6), or with intravitreal agents that interfere with the bioactivity of vascular endothelial growth factor (VEGF) (7–11). However, broad inhibition of VEGF in preterm infants might interfere with physiologic angiogenesis in external organs or in the developing retina where it can lead to persistent avascular retina and recurrent IVNV (9). Understanding VEGF-mediated molecular

mechanisms involved in IVNV and physiologic vascular development of the peripheral retina is important to identify safe and effective treatment targets.

To understand the role of VEGF in the pathophysiology of ROP, studies were conducted using animal models of oxygen-induced retinopathy (OIR) that recapitulate features of ROP pathology in preterm infants. The most common models were in mouse, rat, and beagle (5). The models differ based on the extent of inner vascular plexus coverage to the ora serrata at the time animals are placed into the model, oxygen levels, duration of exposure to oxygen, the age when animals are placed into the model, and the features of ROP represented by in the model. In the murine OIR model, mice are born and raised in room air until postnatal day (p)7 when intraretinal vascularization of the inner plexus extends to the ora serrata. At p7, mice are placed into 75% oxygen for 5 days, which causes hyperoxia-induced compromise of the developed inner plexus in the central retina surrounding the optic nerve (vaso-obliteration). Mice are returned to room air and develop preretinal neovascular tufts (IVNV) at the junction of the vascular and avascular retina at p17 (Phase II) (12). In the rat model, newborn rat pups with almost no retinal vascular development are exposed to oxygen extremes that fluctuate between 50% and 10% every 24 h for 14 days. At p14, rats have compromised physiologic vascularity and delayed physiologic retinal vascular development (Phase 1). Pups are placed into room air and develop IVNV at p18-20 (Phase II) (13). Although the mouse model is often used for ease of genetic manipulation, the rat OIR model best represents human ROP based on oxygen stresses similar to those in preterm infants (fluctuations in oxygen and changes in extremes of arterial oxygen), similar appearing Phases in ROP (Phase I compromise in physiologic vascularization and delay in physiologic vascular development of the peripheral retina at p14, and Phase II IVNV, vascular tortuosity, and vascular dilation at p18-20), and extrauterine growth restriction (**Figure 1**). In the beagle OIR model, newborn pups at p1 are placed into 100% oxygen for 4 days and, at p5, are returned to room air. The beagle OIR model develops delayed physiologic retinal vascular development and compromised physiologic vascularity (Phase I) and IVNV (Phase II) that have been measured at p15 and observed until p45 (14–16). This OIR model is useful to assess pharmacologic treatments due to increased eye size in beagles compared with rodents.

There are five members of the VEGF family: VEGFA, placental growth factors (PlGFs), VEGFB, VEGFC, and VEGFD (17). Studying the role of VEGF in the murine OIR model is difficult since a single allele knockout of VEGF or VEGF receptors (VEGFRs) is lethal in mice (18–20). Although transgenic mice lacking VEGFB ($Vegfb^{-/-}$) are viable, no difference was observed in IVNV compared with littermate wild-type mice (21). In rat pups raised in OIR compared with room air, retinal VEGFA protein was significantly increased and, mainly, VEGFA splice variant 164 ($VEGFA_{164}$) mRNA at p14 and p18 (22–24). These findings implicated VEGFA in both physiologic retinal vascular development and IVNV. Therefore, broad inhibition of VEGFA was predicted to reduce both. Surprisingly, intravitreal neutralizing antibodies to rat VEGFA compared with IgG significantly reduced IVNV in a dose-dependent manner without interfering with physiologic retinal vascular development at p18 in rat pups. However, IVNV and avascular retina area within the vascularized retina were significantly increased at p25 in rat pups that received an effective dose of anti-VEGFA (25). A VEGF-Trap, which binds VEGFA and PlGFs, was compared with a human Fc control after intravitreal injection at p8 in beagle pups. At p21, both IVNV and physiologic retinal vascular development were reduced at high doses of the VEGF-Trap compared with control. However, the lowest dose (5 μg) of the VEGF-Trap reduced IVNV but not physiologic retinal vascular development (26). Taken together, these studies provide experimental evidence that anti-VEGF agents can interfere with physiologic retinal vascular development, compromise already developed retinal vasculature, and lead to recurrent IVNV at certain doses. Therefore, studies were warranted to refine the dose of anti-VEGF agents that would inhibit IVNV and permit sufficient VEGF expression at a concentration that allows physiologic vascular development of the peripheral retina. In support of this notion, Müller cells or astrocytes in the retina were demonstrated to overproduce VEGFA implicated in the development of IVNV in the murine OIR model (27–29). In rat pups raised in the OIR model, novel approaches to knock down VEGFA or $VEGFA_{164}$ in Müller cells by subretinal introduction of lentiviral vectors that contained a CD44 promoter upstream of an miR-30-based shRNA cassette significantly reduced IVNV at p18 (30, 31) without recurrence at p32 (32). However, lentiviral-mediated knockdown of Müller cell-derived VEGFA thinned the retinal outer nuclear layer compared with knockdown of Müller cell-derived $VEGFA_{164}$ by lentiviral vectors (30). Although the data supported the hypothesis that an optimal anti-VEGF dose will not interfere with physiologic vascular development of the peripheral retina, identifying this dose in infants might be challenging due to variation of pathology among individual infants or eyes (33). Nonetheless, the data support the involvement of VEGFA in the pathophysiology of ROP and physiologic development of retinal vasculature, neurons, and glia. In this article, we discuss VEGFA signaling through different receptors in models of ROP to identify mechanisms involved in the Phases of ROP pathology and provide insights into novel therapeutic approaches for ROP that overcome limitations in identifying optimal doses of antiangiogenic agents for individual infants.

THE ROLE OF VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTORS IN MODELS OF RETINOPATHY OF PREMATURITY

VEGF members bind to VEGF receptors (VEGFRs), which induce receptor homodimerization or heterodimerization and activation through autophosphorylation of the tyrosine residues in the receptor intracellular domains (34). There are three subtypes of VEGFRs, but VEGFA binds VEGFR1 or VEGFR2 to elicit biologic functions (35). Immunohistochemical staining

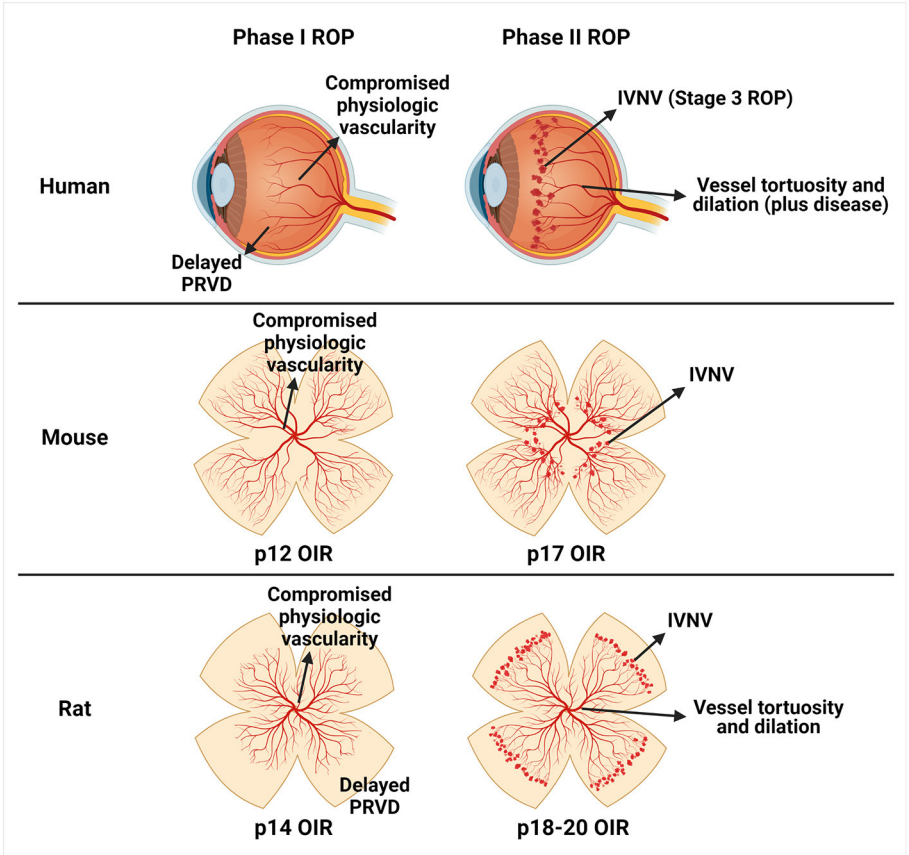

FIGURE 1 | Schematic representation of similarities between human retinopathy of prematurity (ROP) and oxygen-induced retinopathy (OIR) models. Human ROP is described by a two-phase hypothesis (row 1). In Phase I, events surrounding preterm birth (i.e., lack of maternally derived factors, relative hyperoxia, repeated oxygen fluctuations, poor infant growth, etc.) cause a delay in physiologic retinal vascular development (PRVD) and compromise to already developed vessels (compromised physiologic vascularity). In Phase II, the hypoxic avascular retina releases pro-angiogenic factors that promote aberrant retinal angiogenesis into the vitreous termed intravitreal neovascularization (IVNV). The murine OIR model (row 2) recapitulates Phase I compromised physiologic vascularity and has been termed vaso-obliteration at p12, and Phase II IVNV at p17. The rat OIR model (row 3) recapitulates Phase I delay in PRVD to the peripheral retina and compromised physiologic vascularity at p14, and Phase II IVNV and vessel tortuosity and dilation at p18-20. Created with Biorender.com.

of retinal sections from mice in the OIR model demonstrated colocalization of von Willebrand factor-labeled IVNV and VEGFR2, but not VEGFR1, at p19 (36). Retinal lysates from p18 rat pups raised in the OIR model had increased VEGFR2 mRNA, but not VEGFR1 mRNA, compared with p18 pups raised in room air (24). Immunostaining of retinal sections from rats raised in OIR demonstrated immunolabeling of VEGFR1 and VEGFR2 in areas of IVNV at p20 (37). Colocalization of VEGFR2 and von Willebrand factor-stained IVNV was also observed in retinal sections from p15 dogs raised in OIR (16). Specifically, immunostaining of phosphorylated VEGFR2 was reduced in retinal sections from p13 rats that were raised in rat OIR and treated with intravitreal antibodies against VEGFA compared with IgG (23). These findings primarily implicated VEGFR2 in the pathophysiology of ROP; however, this review will summarize studies regarding the role of VEGFR1 and VEGFR2 in models of ROP.

The Role of Vascular Endothelial Growth Factor Receptor 1 in Models of Retinopathy of Prematurity

Intraperitoneal administration of antibodies against VEGFR1 compared with IgG in mice reduced IVNV in mice placed in OIR (38, 39). However, intravitreal PlGF1, a VEGFR1-specific ligand, resulted in no difference in IVNV compared with buffered salt solution control even though previous investigators reported reduced IVNV after intravitreal neutralizing antibody to VEGFR1 (40). The disparity in studies might be because PlGF1 does not bind VEGFR2 monomers (41), and VEGFR2-related signaling is important in IVNV (see *The role of vascular endothelial growth factor receptor 2 in models of retinopathy of prematurity* section). In support of this notion, Zeng et al. observed disordered divisions of mouse embryonic stem cell-derived vessels from VEGFR1 knockout mice ($flt1^{-/-}$) (42). VEGFR1 acts as a decoy receptor, and when knocked

out, it does not bind to VEGF, which permits more VEGF to trigger signaling through VEGFR2 (43). In line with this thinking, rescue of VEGFR1 expression in *flt1*$^{-/-}$ embryonic stem cell-derived vessels, with a transgene that expressed soluble VEGFR1 under the guidance of a PECAM promoter, reduced randomized divisions of endothelial cells and increased ordered divisions (42). Similarly, in the rat OIR model, pups treated with intravitreal anti-VEGFA antibodies had significantly more vascular cell divisions that favored vascular extension rather than widening (44). The studies provided strong evidence that regulation of VEGFR2 is important in orienting dividing endothelial cells and supports the hypothesis that ordered divisions extend peripheral vascular development that occurs in developing retina. The role of VEGFR1 activation in physiologic vascular development of the peripheral retina using a representative model of ROP remains unknown.

The Role of Vascular Endothelial Growth Factor Receptor 2 in Models of Retinopathy of Prematurity

As indicated in the above studies (40, 42), evidence suggested a role for VEGFR2 in ROP. Further support was found in mice with significantly reduced IVNV after gavage with an antagonist to VEGFRs and platelet-derived growth factor receptors (PDGFRs, PTK787) compared with selective PDGFR antagonists (CGP57148 or CGP53716) or vehicle control (45). Similarly, mice treated with a subcutaneous tyrosine kinase inhibitor (SU5416) had significantly reduced IVNV. However, room air-raised mice treated with SU5416 compared with vehicle control had significantly reduced intraretinal vascular extension of the inner plexus to the ora serrata and reduced total retinal thickness of the peripheral retina (46). OIR-raised dogs implanted with a pellet that released antibodies against VEGFR2 into the vitreous had significantly reduced IVNV and delayed physiologic vascular development of the peripheral retina compared with pups implanted with a pellet that released IgG into the vitreous (16). Taken together, the data suggest that inhibition of VEGFR2 affects both physiologic and pathologic retinal angiogenesis and retinal structure. Therefore, this approach might not be a safe therapy for ROP. In an effort to regulate VEGFR2 signaling specifically in retinal endothelial cells, lentiviral vectors that expressed shRNA against VEGFR2 or luciferase control under the guidance of an endothelial-specific promoter, *Cdh5*, were tested in the rat OIR model. Knock down of VEGFR2 in endothelial cells by shRNA significantly reduced IVNV and allowed more physiologic vascular development of the peripheral retina compared with littermate controls at p20. Furthermore, total retinal thickness near the optic nerve head was not thinned after lentiviral delivered *Cdh5*-targeted shRNA against VEGFR2 compared with littermate controls. There was also no difference in a- or b-wave amplitudes assessed by full-field electroretinography in adult rats compared with littermate controls (47). These findings contrasted with earlier studies in which Müller cell-derived VEGFA knockdown by lentiviral vectors in the rat OIR led to retinal thinning, (32) and intravitreal VEGF-Trap delayed physiologic retinal vascular development in the dog OIR model (26) compared with respective controls. Taken together, the data support the thinking that VEGFA signaling is important for neural retinal structure and function, and normal retinal vascularization. Furthermore, regulation of VEGFR2 signaling in retinal endothelial cells accomplishes safe inhibition of IVNV while promoting physiologic retinal vascular development and retinal structure and function. The data also suggest that a certain dose or agent that regulates VEGF-mediated signaling triggered through VEGFR2 in retinal endothelial cells might be a possible therapeutic approach to inhibit IVNV, facilitate physiologic retinal vascular development, and reduce the likelihood of recurrent IVNV in ROP.

THE ROLE OF NEUROPILINS IN MODELS OF RETINOPATHY OF PREMATURITY

Originally identified in *Xenopus* tadpole nervous tissues (48) as receptors for semaphorins (49, 50), neuropilins are cell surface glycoproteins that bind to VEGF family members (51) and form complexes with VEGFRs as co-receptors (52). There are two isoforms of the protein, neuropilin 1 and neuropilin 2, and both have been demonstrated to interact with VEGFRs to trigger signaling induced by VEGFA. Also, $VEGFA_{164}$ has been demonstrated to bind to neuropilin 1 and neuropilin 2 (53). Neuropilin 1 mRNA was increased in retinal lysates from mice placed in OIR compared with room air at p17 (54). Also at p17, retinal sections from mice placed in OIR demonstrated colocalization of neuropilin 1 mRNA with IVNV (55). Specifically, neuropilin 1 (54, 56) or neuropilin 2 (57) protein colocalized with IVNV. Furthermore, Budd et al. found significantly increased neuropilin 1 and neuropilin 2 mRNA in rats raised in OIR compared with room air at p14 and p18 (58).

The Role of Neuropilin 1 in Models of Retinopathy of Prematurity

Neuropilin 1 knockout mice (*Nrp1*$^{-/-}$) are embryonically lethal (59–61). Neutralizing neuropilin 1 with intravitreal antibody significantly reduced IVNV compared with IgG in mouse OIR (55). Compared with littermate control mice that lacked Cre alleles, tamoxifen-inducible knock out of endothelial neuropilin 1 in a Cre-loxP mouse model reduced IVNV in mice in OIR and delayed intraretinal vascular development of the inner plexus in mice raised in room air (62). However, knock out of neuropilin 1 in myeloid lineage cells using *LysM*-Cre did not affect intraretinal vascular development of the inner plexus in room air compared with mice that lacked the floxed *Nrp1* alleles but still expressed *LysM*-Cre (63). These findings implicate endothelial neuropilin 1 not only in the development of IVNV but also in physiologic retinal vascular development.

To understand mechanistically how neuropilin 1 regulates angiogenesis, transgenic mice that expressed a mutant neuropilin 1 that lacked the cytoplasmic domain of the receptor were generated (64). The cytoplasmic domain of neuropilin 1 has been reported to interact with VEGFR2 to enhance VEGFR2-mediated signaling (65–67). Therefore, expression of a mutant neuropilin 1 receptor that lacked the ability to interact with

VEGFR2 to trigger signaling might affect intraretinal vascular development in mice. However, the study reported no difference in intraretinal vascular development of the inner plexus between room air raised mice that expressed a mutant neuropilin 1 and littermate control mice that expressed wild-type neuropilin 1 (64). To determine if VEGFA-binding neuropilin 1 was required for angiogenesis, transgenic mice that expressed a mutant neuropilin 1 with a point mutation in the VEGF-binding b1 domain ($Nrp1^{Y297A/Y297A}$) were generated along with littermate wild-type controls. $Nrp1^{Y297A/Y297A}$ mice raised in room air had significantly reduced intraretinal vascular extension of the inner plexus at p7 and reduced IVNV in OIR at p17 compared with age-controlled littermate wild-type mice (68). Taken together, these observations suggest that VEGF-binding endothelial neuropilin 1, but not the interaction between neuropilin 1 and VEGFR2, was required for intraretinal vascular development. However, further studies are required to determine the role of neuropilin 1 in physiologic vascular development of the peripheral retina and IVNV in translational models of ROP.

The Role of Neuropilin 2 in Models of Retinopathy of Prematurity

Neuropilin 2 knockout mice ($Nrp2^{-/-}$) had significantly reduced IVNV in OIR compared with littermate wild-type mice; however, neuropilin 2 mRNA was expressed in mice raised in room air from p0 to p7 (57). Therefore, it was postulated that $Nrp2^{-/-}$ mice would have reduced intraretinal vascular development compared with littermate controls. However, there was no difference in inner plexus vascular density between $Nrp2^{-/-}$ mice and littermate wild-type mice raised in room air and analyzed at p7 (57). Taken together, the data suggest that neuropilin 2 is involved in IVNV but not required for intraretinal vascular development. Further studies are warranted in OIR models to determine the effect on regrowth after hyperoxia and physiologic vascular development of the peripheral retina before considering neuropilin 2 as a potential therapeutic target for ROP.

DISCUSSION

ROP is the leading cause of blindness and visual impairment in children worldwide. In severe cases of ROP, blindness can occur from retinal detachment caused by IVNV. Studies in OIR models that recapitulate aspects of human ROP have provided insights into VEGF signaling through VEGFRs and neuropilins in specific cell types. Experimental studies support the finding that regulating oversignaling through VEGFR2, especially in retinal endothelial cells, would not only reduce severe ROP but also facilitate normal vascular development. However, there is no suitable way to target endothelial VEGFR2 in premature infants yet. Broad inhibition of VEGF or VEGFR2 using intravitreal neutralizing antibodies or small molecules may affect signaling in other cells in the retina and affect function and structure or potentially leak into the circulation and affect developing organs. However, the use of correct dose or agent suggests that reducing the bioactivity of VEGF may have value to permit some VEGF signaling important in physiologic vascular development of the peripheral retina (10, 69). An appropriate dose of anti-VEGF may regulate overactive VEGFR2 in retinal endothelial cells, which occurs with increased ligand concentration (23, 31), without abolishing VEGFR2 signaling in endothelial or other cells of the retina.

Besides anti-VEGF, alternative approaches are being explored to prevent VEGF-mediated ROP occurrence and progression. Oxidative stresses (i.e., reactive oxygen species) have been implicated in VEGF-mediated IVNV in rodent models of ROP (70). Administration of antioxidants Cu/Zn superoxide dismutase (71) or vitamin E (72) in extremely low gestational age infants reduced the risk of ROP. However, side effects related to vitamin E (73) preclude widespread use. Also, antioxidants may fail to access the intracellular signaling mechanisms leading to pathology or counteract beneficial mechanisms of oxidative signaling. Therapeutic approaches have been considered to regulate hypoxia inducible factors, either stabilization with prolyl hydroxylase inhibitors in phase I (74, 75) or potential inhibition in phase II. It remains to be seen if the phases described in the two-phase hypothesis of ROP can be distinguished sufficiently in an individual human infant. Another treatment approach is carefully monitoring oxygen tension at birth to prevent hyperoxia-induced damage to blood vessels and reduce oxygen fluctuations that slow vascular growth to the peripheral retina (76). Additional experimental studies to regulate semaphorin/neuropilin signaling (77) might lead to future approaches in ROP. Overall, these approaches provide insights into possible therapeutic approaches to regulate VEGF-induced VEGFR2 signaling in ROP.

AUTHOR CONTRIBUTIONS

AR and MEH performed the literature searches and drafted and critically revised the manuscript. MEH provided funding support. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Glaucoma in an Infant With Retinopathy of Prematurity

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Retinopathy of prematurity (ROP) is a leading cause of childhood blindness that occurs due to incomplete development of retinal blood vessels in preterm infants. Glaucoma is an ocular comorbidity in some patients with ROP, and it may be associated with immature anterior chamber development, ROP itself, or the treatment for ROP. There have been a few reports of narrow-angle glaucoma after laser treatment for ROP. In this case report, we describe the course of a female infant born at 24 weeks and 5 days of gestational age with treatment-requiring ROP treated with laser photocoagulation who subsequently developed very elevated intraocular pressure and shallow anterior chambers without pupillary block. The patient required bilateral *ab externo* trabeculotomy for elevated intraocular pressure, which normalized after the procedure. The patient has remained stable at the last follow-up at 51 weeks postmenstrual age. Differing from previous glaucoma presentations in this setting, we illustrate a case of elevated intraocular pressure and anterior chamber narrowing after laser therapy without pupillary block or synechiae. The possible multifactorial etiology of glaucoma in this patient, including incomplete angle development, ischemia, and laser treatment, highlight the need for glaucoma screening in patients with ROP, both in the short and long term.

Keywords: retinopathy of prematurity (ROP), glaucoma, anti-VEGF (vascular endothelial growth factor), laser retinal photocoagulation, myopia, case report

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INTRODUCTION

Retinopathy of prematurity (ROP) is a disorder of incomplete development of retinal blood vessels in preterm infants (1). Although titration of supplemental oxygen, which has been shown to decrease ischemic drive, has decreased the incidence of ROP, this condition remains a leading cause of childhood blindness in the United States (2) and throughout the world (3). The main goals of treatment are to optimize long-term visual outcomes by preventing complications of ROP such as retinal detachment (4). Laser photocoagulation has replaced cryotherapy as the standard of care for treatment-requiring ROP (5, 6), while intravitreal antivascular endothelial growth factor (anti-VEGF) injections are also used with similar efficacy (5), particularly in posterior ROP (6).

Treatment of ROP has known potential complications, including cataract, inflammation, vitreous hemorrhage, choroidal detachment, retinal detachment, and glaucoma (7, 8). Patients with ROP are at increased risk for glaucoma, which can be attributed to retrolental tissue pushing of the lens–iris diaphragm forward (9, 10), as well as pupillary block or neovascularization (11, 12).

The Early Treatment for Retinopathy of Prematurity (ETROP) trial found a 1.67% (12/718) prevalence of glaucoma at 6 years old (9, 10), with 11 out of these 12 children having received laser therapy for high-risk pre-threshold ROP (13). There are few cases reported of narrow angle or angle-closure glaucoma following laser for ROP (14–16).

In this case report, we describe the course of an ex-24-week-old female infant who developed very elevated intraocular pressure and shallow anterior chambers without pupillary block at postmenstrual age of 38 weeks following laser treatment in both eyes for type 1 ROP (zone 2 stage 3 with plus disease). Examination was remarkable for corneal haze that precluded gonioscopy and shallow anterior chambers without pupillary block or neovascularization. Genetic testing for the most common causes of congenital glaucoma was negative. There was significant improvement in the anterior chamber (AC) depth with cycloplegia; however, the patient ultimately required bilateral *ab externo* trabeculotomy for adequate intraocular pressure control. This case highlights that glaucoma in the setting of ROP may be multifactorial and should be regularly screened for in any at-risk infant.

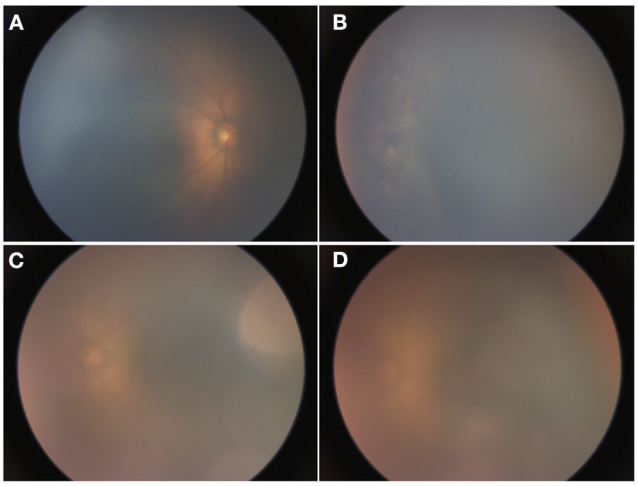

FIGURE 1 | RetCam images taken at 37 weeks of postmenstrual age (PMA). **(A)** Right eye with zone 2, stage 3 retinopathy of prematurity (ROP), **(B)** limited view of laser scars in the periphery of the right eye, and **(C,D)** left eye with zone 2, stage 3 ROP.

CASE

A 450-g female infant was born at 24 weeks and 5 days of gestational age by normal spontaneous vaginal delivery at an outside hospital and transferred to our institution at a postmenstrual age (PMA) of 33 weeks and 2 days for patent ductus arteriosus ligation. At our institution, she underwent an initial ROP screening, which showed stage 0 immature vessels in zone 2 of both eyes. There were clear views of the fundus in both eyes. The patient was then transferred back to the home referring hospital where she underwent two sessions of diode laser in both eyes at 36 and 37 weeks of PMA for treatment-requiring ROP. Due to concern for inadequate laser and poor fundus view with corneal haze, she was re-referred to our institution. Upon reevaluation, she was noted to have cloudy corneas, intraocular pressure (IOP) of 40–45 mmHg, and persistent zone 2, stage 3 ROP, with peripheral laser scars in both eyes (**Figure 1**).

On exam and diagnostic imaging with B-scan ultrasound, there was no rubeosis, and no choroidal or retinal detachments were noted (**Figure 2**). Clinical examination and ultrasound biomicroscopy (UBM) revealed significant anterior chamber shallowing without pupillary block or synechiae, which improved significantly with topical cycloplegia with cyclopentolate 0.5% (**Figure 3**). With oral acetazolamide and topical IOP-lowering eyedrops, her pressures improved but were still elevated to the 30- to 35-mmHg range, and the corneal clouding still prevented adequate gonioscopic visualization of angle anatomy. Fundus examination revealed persistent stage 3 ROP with inadequate laser, particularly nasally; however, the view was still somewhat limited for additional laser photocoagulation (**Figure 1**). She underwent intravitreal injection of bevacizumab 0.625 mg in both eyes at 39 weeks of PMA. In both eyes, regression of ROP after laser and intravitreal bevacizumab was noted by 41 weeks of PMA (2 weeks after injections). Despite moderate improvement in the anterior chamber depth (**Figure 3**) and IOP, medical treatments were ultimately determined to be inadequate, and the patient required *ab externo* trabeculotomy in the right eye at 42 weeks of PMA and left eye at 44 weeks of PMA. With parental consent, genetic screening for congenital glaucoma through the Prevention Genetics Glaucoma Panel was obtained and found to be negative.

The intraocular pressures normalized to under 20 mmHg by postoperative week 2 after trabeculotomy in both eyes. The patient has remained stable from both a retina and glaucoma perspective at the last follow-up at 51 weeks of PMA in the office. Of note, cycloplegic refraction revealed −8.00 and −2.00 D myopia in the right and left eyes, respectively, for which she was prescribed spectacle correction. The timeline of clinical findings and management of this patient are presented (**Figure 4**). Written informed consent was obtained from the legal guardian of the minor for the publication of any potentially identifiable images or data included in this article.

DISCUSSION

The pathogenesis of glaucoma in ROP has various proposed mechanisms including incomplete development of the anterior segment and secondary angle closure from ROP or the treatment of ROP. Given the presentation and exam findings of our patient, it is possible that underlying incomplete development of her anterior segment structure, as well as ROP, may have put her at increased risk for glaucoma that was further exacerbated by ROP laser treatment though no effusions or clear sequelae of this were observed.

There are few cases in the literature describing glaucoma in the short-term postoperative period after ROP laser (14–16). The cases requiring surgical intervention presented with shallow or

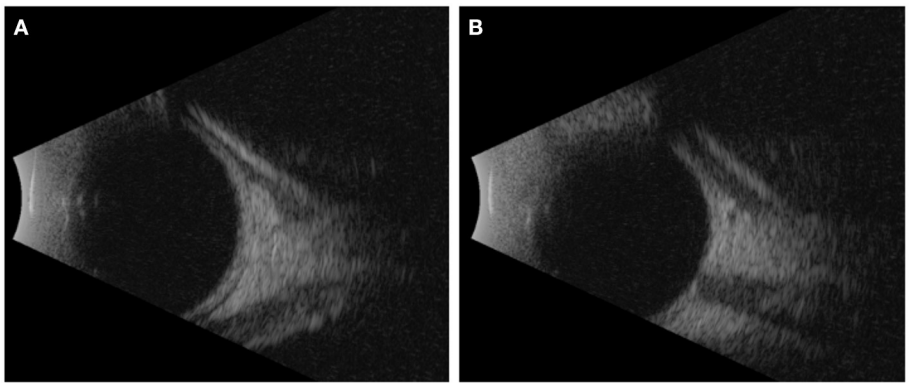

FIGURE 2 | B-scan ultrasound images taken at 40 weeks of PMA. **(A)** Right eye and **(B)** left eye.

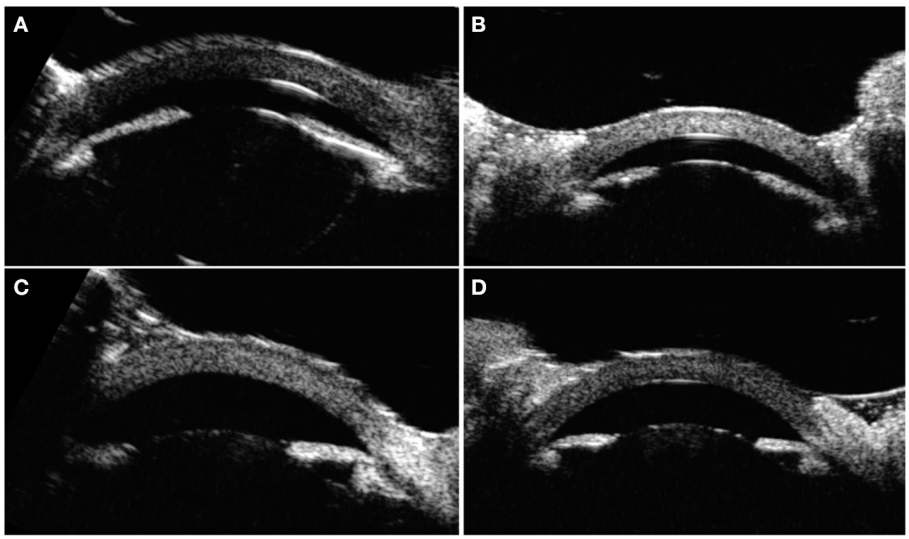

FIGURE 3 | Ultrasound biomicroscopy images taken at 40 and 41 weeks of PMA. **(A)** Right eye before cyclopegia. **(B)** Left eye before cyclopegia. **(C)** Right eye after cyclopegia. **(D)** Left eye after cyclopegia.

flat AC depth and had documented posterior synechiae with pupillary block in infants with gestational ages ranging from 24 to 29 weeks (14). A report from Australia described the case of a male infant of 24 weeks of gestational age receiving laser therapy for stage 2 zone 3 ROP who was later found to have pupillary block and angle closure in the right eye as well as anatomic narrow angle in the left eye (15). A third report described a female infant of 25 weeks of gestational age who received laser photocoagulation for ROP in both eyes (stage 2, zone 2 with plus disease), after which she developed total posterior synechiae and shallow ACs (16).

In our case, the initial treatment with topical cycloplegia and IOP-lowering topical and oral medications led to deepening of the anterior chamber as well as moderate, though ultimately insufficient, improvement of the IOP. Normalization of IOP was achieved after *ab externo* trabeculotomy in both eyes. This points to a possible mixed mechanism of glaucoma in infants with ROP after laser therapy: (1) abnormal angle anatomy from prematurity or underlying genetic predisposition, and (2) ciliary body rotation, possibly exacerbated by laser. In contrast to the previously described cases in the literature (14–16), our case illustrates a presentation of elevated IOP and anterior chamber narrowing after laser therapy without pupillary block or synechiae.

Prematurity itself introduces some structural risks that may contribute to glaucoma. Development of the trabecular meshwork is not complete until late in gestation, after at least 25 weeks, which makes the angle anatomy susceptible to many factors that can potentially influence risk of angle-closure glaucoma (17). Other predisposing anterior segment abnormalities observed in premature children, with and without ROP, include steep corneal curvature, decreased anterior chamber depth, anteriorly displaced iris planes, and increased lens thickness (10, 18–22). Eyes with ROP not requiring

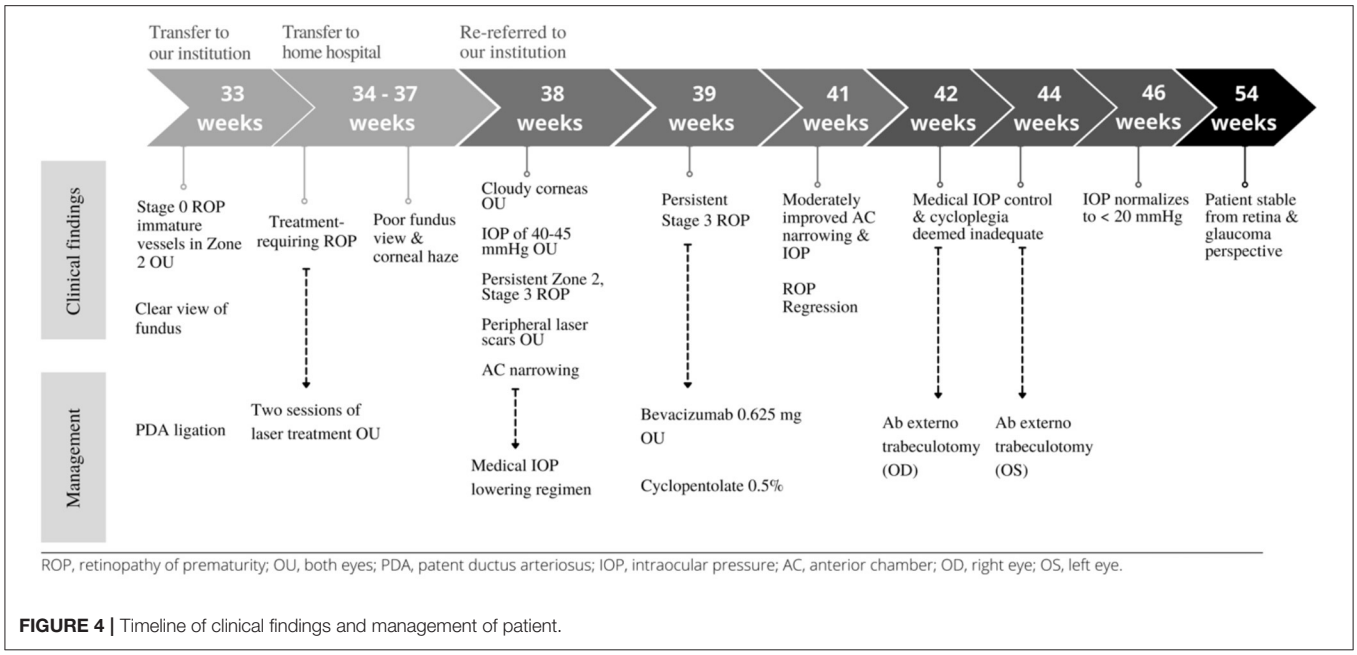

FIGURE 4 | Timeline of clinical findings and management of patient.

treatment as well as ROP-treated eyes have been found to have narrower anterior chamber angles (ACA) than full-term children (22) or preterm monitored eyes (23). These changes may also explain the high prevalence and magnitude of myopia in preterm children (24), and the even higher apparent risk in those with laser-treated ROP (21). It is notable that our patient demonstrated a high degree of myopia in right eye and a moderate degree of myopia in the left eye at just 11 months of PMA.

Premature infants with ROP likely acquire other additional pathologic features that put them at additional risk of glaucoma. The anterior segment changes observed in premature infants with ROP could be further exacerbated by an arrested state of retinal development, such that the local growth signals involved in anterior segment development are altered (24). Additionally, laser treatment is considered to contribute significantly to the development of narrow angles and anterior segment defects in children with ROP (23, 24). More specifically, laser-induced mechanical changes may impair development of the angle by affecting the posterior ciliary nerve, artery, or pars plana (23). While anterior chamber narrowing without closure has been previously described after laser for other conditions, the laser-induced anterior shifting and inward rotation of the ciliary body is typically short lived in older children and adults (25). In a case series of secondary glaucoma in children with ROP, all of the patients had shallow anterior chambers before the onset of glaucoma symptoms, so these patients might have had an initial anatomic compromise of the aqueous outflow subsequently exacerbated by other factors leading to high intraocular pressures (26). Likewise, in another study, shallow anterior chambers were noted to be a feature of most stage 3 ROP eyes, as a result of arrested development of the anterior segment, but with notable higher and more significant prevalence in laser-treated eyes (27). Given the presentation and exam findings of our patient, it is possible that underlying developmental anterior segment abnormalities, as well as ROP, may have put her at increased risk for glaucoma that was further exacerbated after ROP laser treatment. A potential future avenue for research would be to investigate the use of anti-VEGF injections as an alternative to laser in infants with significant narrow-angle glaucoma or anterior segment narrowing.

Laser treatment may induce structural anterior segment changes in infants with ROP and increase their vulnerability to complications, such as secondary glaucoma. Careful anterior segment examination in ROP infants should be undertaken to exclude glaucoma risk factors, such as shallow anterior chambers, rubeosis, and ocular hypertension. In particular, shallow anterior chambers are challenging to assess in premature eyes and can be overlooked unless accompanied by more obvious clinical signs of glaucoma like corneal clouding, enlarged corneal diameters, and blepharospasm (14). Glaucoma poses a vision-threatening risk in infants with ROP, due to premature development of the eye, as well as direct consequences of ROP and ROP treatment. While congenital glaucoma is a possible etiology in any infant with elevated intraocular pressure and cloudy corneas, this case highlights other contributory factors, such as prematurity itself, as well as laser for ROP, that should be considered.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the minors' legal guardian for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

TL, NL, and AO contributed to the conception and design of the report. TL, AO, VR, KK, and SV participated in the patient's care. TL and NL wrote the first draft of the manuscript. VR, KK, SV, and AO wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Cost–Utility Analysis of Wide-Field Imaging as an Auxiliary Technology for Retinopathy of Prematurity Care in Brazil

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Purpose: To evaluate the cost–utility of wide-field imaging (WFI) as a complementary technology for retinopathy of prematurity (ROP) screening from the Brazilian Unified Health System's perspective.

Introduction: ROP is one of the leading causes of avoidable childhood blindness worldwide, especially in middle-income countries. The current ROP screening involves indirect binocular ophthalmoscopy (IBO) by ROP expert ophthalmologists. However, there is still insufficient ROP screening coverage. An alternative screening strategy is the combination of WFI with IBO.

Methods: A cost–utility analysis was performed using a deterministic decision-tree simulation model to estimate incremental cost–utility for ROP care. Two screening strategies were compared: (1) IBO and (2) combination of WFI of all eligible preterm infants and IBO for type 2 ROP or worse and for non-readable images. Eligible population included preterm infants <32 weeks of gestational age or birth weight equal to or <1,500 g. The temporal horizon was lifetime. Visual outcome data was converted to utility, and the health benefits were estimated on quality-adjusted life-years (QALY). Incremental cost per QALY gained was calculated from the health system perspective. Costs were estimated considering equipment, maintenance, consumables, and staff. A micro-costing approach was used for WFI. Two technician nurses were trained for imaging execution and had their time evaluated. Two ROP expert ophthalmologists had their time evaluated for imaging reading. One-way sensitivity analysis and probabilistic sensitivity analysis were performed.

Results: Combined screening strategy resulted in a cost-effective program considering 90% ROP screening coverage. Costs per examination: (1) screening with IBO: US dollar (US $) 34.36; (2) screening with combination: US $58.20; (3) laser treatment: US $642.09; (4) long-term follow-up: ranged from US $69.33 to 286.91, based on the infant's visual function. Incremental cost per QALY gained was US $1,746.99/QALY per infant screened with the combination strategy. One-way sensitivity analysis resulted in cost-effectiveness for all parameters. Probabilistic sensitivity analyses yielded a 100%

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probability of combination being cost-effective in a willingness-to-pay threshold of US $1,800/QALY.

Conclusion: The combined strategy for ROP screening was cost-effective. It enhances access for appropriate ROP care in middle-income countries and dminishes opportunity costs for ophthalmologists.

Keywords: retinopathy of prematurity, neonatal screening, diagnosis, healthcare economics, costs and cost analysis, quality-adjusted life years (QALY), telemedicine, Brazil

INTRODUCTION

Retinopathy of prematurity (ROP) remains a leading cause of avoidable childhood blindness in middle-income economies, such as Brazil (1, 2). The combination of (1) high preterm birth rate, (2) improvement of neonatal care quality (leading to better survival rates), and (3) insufficient access to ROP screening and treatment are the main causes of the third ROP epidemic faced in countries such as Brazil (1, 3, 4). The effectiveness and affordability of ROP screening, diagnosis, and treatment have been well-documented (5–10).

The current screening of infants at risk of ROP, usually determined by gestational age (GA) and birth weight (BW) criteria, requires carefully timed retinal examinations by a skilled ophthalmologist. Noteworthy, fewer than 10% of infants screened for ROP in Brazil will develop type 1 disease and should be submitted to treatment within 72 h (6). However, only 52% of at-risk preterm infants are estimated to have access to ROP examinations, and probably fewer infants have access to treatment in Brazil (6, 11).

It is estimated that the Brazilian Unified Health System (SUS) provides 76% of neonatal care in the country (12). According to official data, 37,000 infants were born with BW <1,500 g in 2017 (13). Therefore, each year, ∼20,000 infants would survive to 4 weeks requiring eye examinations, and ∼1,600 would need laser treatment for severe ROP (6, 11, 14). If 50% of them had access to appropriate management, 800 infants would be at risk of severe visual impairment throughout their lives every year. In 10 years, this number would rise to 8,000 visually impaired infants due to ROP.

The main obstacles for a comprehensive and effective ROP screening in Brazil, and probably in other middle-income countries, are the lack of skilled ophthalmologists to provide ROP care, the uneven distribution of these professionals among units, and the unequal access to appropriate quality neonatal care (11, 15–17). An alternative to improve accessibility and quality ROP care is the use of wide-field imaging (16, 17). Several authors reported good mean diagnostic accuracy for ROP type 2 or worse, feasibility, and cost-effectiveness of wide-filed imaging compared with screening with indirect binocular ophthalmoscopy (17–20).

However, wide-field imaging is not adopted for ROP screening in Brazil. The aim of this study was to perform a cost–utility analysis to compare two ROP screening strategies (indirect binocular ophthalmoscopy and combination of wide-field imaging with indirect binocular ophthalmoscopy) under the SUS's perspective. To the best of our knowledge, this is the first cost–utility analysis for ROP care, using the combination of wide-filed imaging and indirect ophthalmoscopy, from a governmental health system perspective of a middle-income country and with a long-term (lifetime) follow-up.

METHODS

Setting and Population

Brazil, a middle-income country with a large universal governmental health system, has one of the highest numbers of infant survivors with severe visual impairment or blindness due to ROP (1, 21). The Brazilian guideline for ROP appropriate screening and timely treatment was published in 2007 (22). The governmental ROP screening care provides diagnosis and treatment at no cost to infants at risk for ROP. However, current ROP screening care has an estimate coverage of only 52% in Brazil (6, 11).

The eligible population included preterm infants with GA <32 weeks or BW ≤1,500 g born in governmental maternities in Brazil. Twenty-two governmental maternities from the city of Rio de Janeiro, Brazil, were used as a proxy to estimate the target population. The number of at-risk ROP infants (983) in these 22 maternities was estimated according to official (13). Non-treated and treated preterm infants needed a mean of 3 and 9 examinations, respectively, before discharge, resulting in a total of 3,254 annual examinations in Rio de Janeiro (11).

Model Structure and Assumptions

A decision analytical model for ROP care (screening, treatment, and long-term follow-up) was created simulating a cohort of preterm infants for a lifetime time horizon and from the SUS's perspective (**Figure 1**). The decision tree was used to represent the probability of the eligible population's possible health events and visual function outcomes in terms of cost and utility.

Three different visual acuities were defined: (1) good visual function in treated and non-treated infants was defined as 0.5 decimal visual acuity, because the eligible population usually has other morbidities that can affect the maximum potential visual acuity (1.0 decimal visual acuity). (2) Poor visual function in infants with severe ROP not treated was defined as 0.0 decimal visual acuity (23). (3) Poor visual function in treated infants with unfavorable outcome was defined as 0.05 decimal visual acuity (5).

The gold standard strategy is indirect binocular ophthalmoscopy performed by an ROP expert ophthalmologist. Eligible preterm infants can have access to gold standard ROP

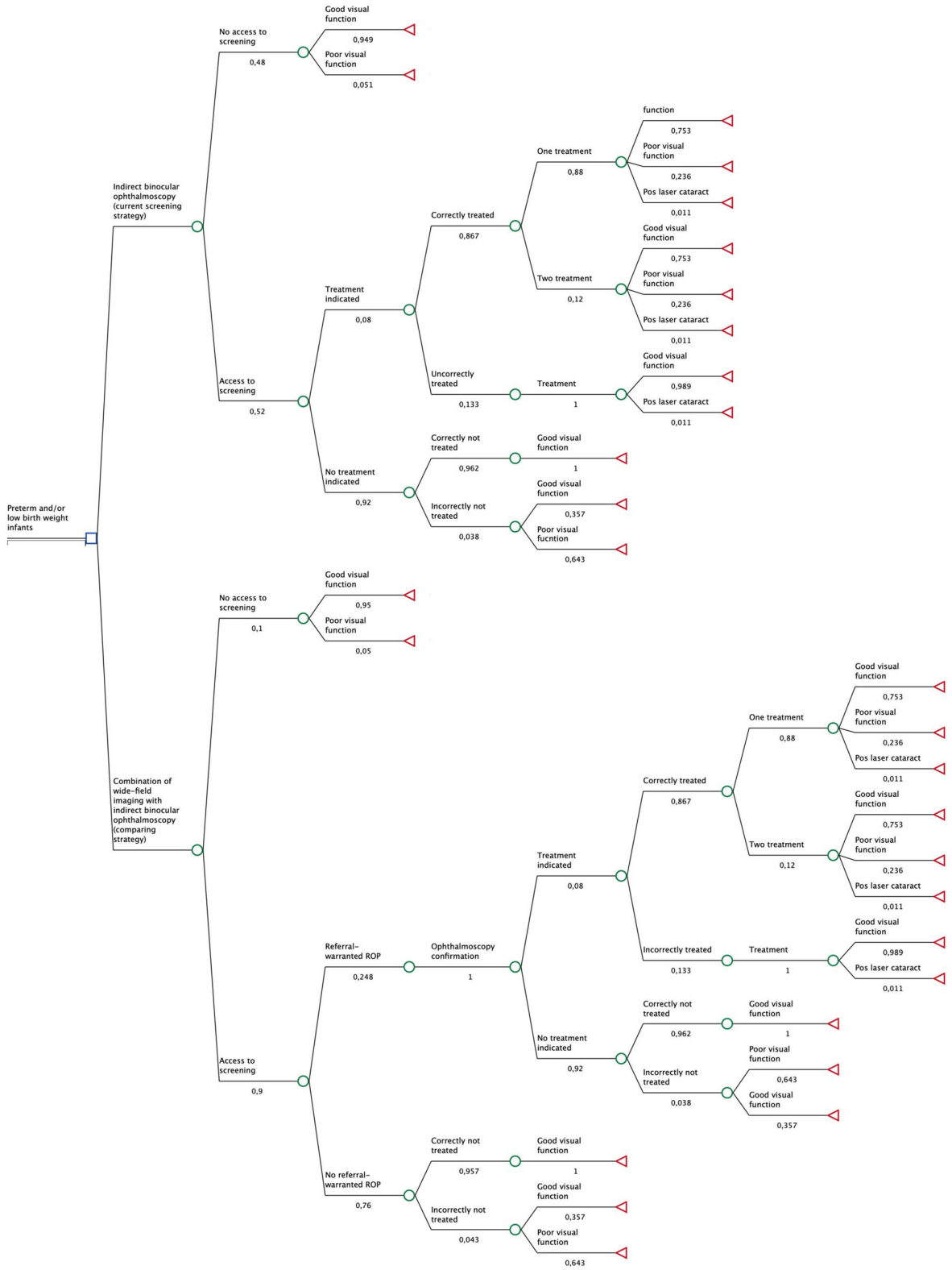

FIGURE 1 | Decision analytic model for ROP care in preterm and/or low birth weight infants with two strategies: the current stratagy, indirect binocular ophthalmoscopy, and the comparing strategy, combination of wide-field imaging with indirect binocular ophthalmoscopy. The number under the branches of the decision tree represents the probability of each parameter branch to happen.

screening or not. Infants with no access to care can develop good or poor visual function, according to ROP's clinical course. Infants with access to care may need treatment or not. Infants submitted to one or two treatments may be correctly or incorrectly treated. They may develop good or poor visual function according to ROP's clinical course or, rarely, due to post-laser cataract. Infants not submitted to treatment can have severe ROP or not and therefore develop good or poor visual function.

The combined strategy considered the performance of wide-field imaging by non-ophthalmologists and remote reading by ROP expert ophthalmologist together with standard indirect binocular ophthalmoscopy of suspected (ROP type 2 or worse) or non-readable images. Eligible preterm infants can have access to the combined screening strategy or not. Infants with no access to care can develop good or poor visual function, according to ROP's clinical course. Infants with access to care are submitted to wide-field imaging. Suspected and unreadable images are referred to ophthalmoscopy and follow the aforementioned model. Infants with non-suspected images will not be referred. If this image reading is correct, they do not have ROP and will develop good visual function. However, if the image is misread and they have any ROP, they, incorrectly, will not be referred and can develop good or poor visual function, according to ROP's clinical course.

Assumptions were required to develop the screening model. All screened infants survived hospitalization. The treatment criteria followed the Early Treatment for Retinopathy of Prematurity Study (5), and all infants requiring treatment had bilateral laser treatment. Cataract was the only complication from laser treatment, and those infants developed low vision and intermediate utility. Non-readable images were referred to ophthalmoscopic examination. Final vision function in non-treated 15-year-old patients (23) and in treated 6-year-old patients (5) remained stable for life. All patients had an average life expectancy of 75 years. Anesthesia and additional hospitalization costs were not included.

The outcome was the incremental cost–utility ratio (ICUR), which was calculated as incremental cost per quality-adjusted life-years (QALY) gained per infant for ROP screening with the combined strategy compared with standard strategy, discounting future costs and QALYs at 5% per year (24).

TreeAge Pro 2011 was used to run the model (TreeAge Software, Inc., Williamstown, MA, USA).

Model Parameters

Effectiveness Data

Sensitivity and specificity used for indirect binocular ophthalmoscopic diagnosis of ROP requiring treatment were, respectively, 0.867 and 0.962 (10, 25). Sensitivity and specificity for imaging reading of type 2 ROP or worse were, respectively, 0.768 and 0.957 (10, 25).

Utility Data

Utility valuations were based on decimal visual acuity following the formula: utility $= 0.374. x + 0.514$ (26), with x representing decimal visual acuity in better-seeing eye. Utility for good visual function in treated and non-treated infants was estimated as 0.701 (0.5 decimal visual acuity). Utility for poor visual function infants with severe ROP not treated was estimated as 0.514 (0.0 decimal visual acuity) (23), and utility for poor visual function in treated infants with unfavorable outcome was estimated as 0.5327 (0.05 decimal visual acuity) (5).

Cost Data

Wide-Field Imaging Cost

Wide-field imaging cost was calculated using a micro-costing approach as this procedure is not provided by SUS. The following items were considered: equipment kit (portable digital retinography, 130° lens, extra pedal, annual security contract, and maintenance), consumables (anesthetic and mydriatic eye drops, ophthalmic gel, lid speculum, gauze, glucose solution, antiseptic product, 20 diopter lens and gas), and staff (professional, training, traveling, and uploading images time). The equipment kit cost was based on market value provided by the manufacturer. The costs of consumables were obtained from official data (27). Costs were annualized using a standard discount rate of 5% (24) and an estimated equipment lifespan of 5 years and pedal lifespan of 2 years (6).

Staff costs were calculated by a time and motion study undertaken at two separate time points in order to assess the learning curve of nurse technicians trained by ophthalmologists. The first time point included 20 patients (40 eyes), and the second, 1 month later, 16 patients (32 eyes) (28). The second time point was considered in the calculation of staff costs. A mean of 10 min between each retinography was given to include dietary time or examination by other neonatal intensive care unit specialties. Training included equipment setup, image capturing, uploading, and equipment dismantling. Two ROP specialist ophthalmologists also had their mean time calculated for remote imaging reading (20 images). A mean of 5 min was given between each reading. Mean time spent per examination was used for estimating staff cost per examination and the number of professionals needed to cover the hypothetical screening program.

Wide-field imaging unit cost was calculated dividing the total cost of equipment, maintenance, consumables, and staff by the number of examinations.

Indirect Binocular Ophthalmoscopy and Treatment Costs

Indirect binocular ophthalmoscopy and treatment unit costs were based on published and updated data (6). The following items were considered: equipment kit (indirect binocular ophthalmoscopy, 20-diopter lens), consumables (anesthetic and mydriatic eye drops, lid speculum, depressor, gauze, glucose solution, and antiseptic product), and professional and training staff. Costs were annualized using a standard discount rate of 5% (24) and an estimated equipment life of 10 years (6).

Combination of Wide-Field Imaging and Indirect Binocular Ophthalmoscopy Cost

The combination's unit cost was estimated assuming 100% of infants would need wide-field imaging and 25.8% of them would be referred to ophthalmoscopy. Infants referred to

ophthalmoscopy include 20.8% of ROP type 2 or worse and 5% of non-readable images (10).

Follow-Up Cost

Follow-up costs were split into three categories of eye care needs: (1) non-treated infants with good visual function; (2) treated infants with good visual function; (3) treated or non-treated infants with poor visual function. Costs were estimated according to an expert opinion based on frequency of ophthalmological and occupational therapy visits and on recommended complementary examinations (examination under anesthesia and Teller Visual Acuity Cards). The National Reimbursement Table underestimates true health procedures cost, and therefore, values were adjusted by 3.51 for follow-up estimated cost (29).

In 2019, costs were presented in Brazilian reais (R $) and then converted to US dollars (US $) (at the rate of US $1 = R $3.94 considering the mean rate from March to July 2019). Societal costs (indirect costs, loss of productivity, or cost of death) were not included.

Sensibility Analysis

One-way sensitivity analysis was performed on all parameters of the model. Probabilities and utility ranges were obtained from literature. Costs ranged from −30% to + 30% (9) for ophthalmoscopy and treatment, from −30% to +60% for wide-field imaging, and from 0% to 10% discount rate for follow-up. The Monte Carlo probabilistic simulation, running 1,000 iterations samples, was performed to determine the probability of key parameters impacting the results. Beta, gamma, and lognormal probability distributions were applied for utilities, costs, and clinical parameters, respectively.

Brazil does not have a willingness-to-pay threshold to support healthcare technologies' adoption by SUS. A cost-effectiveness acceptability curve was constructed considering threshold values proposed for Brazil based on a range below US $7,544/QALY (30).

Correlation Between QALY and Visual Acuity

The difference between normal (0.5) and abnormal (0) decimal visual acuity in the model was correlated with the difference between QALY in good (13.66) and poor visual function (10.01), respectively.

Ethics Statement

The study was approved by the Ethical Review Board of Instituto Nacional de Saúde da Mulher, da Criança e do Adolescente Fernandes Figueira, Fundação Oswaldo Cruz, in Rio de Janeiro, Brazil.

RESULTS

The model parameters and range values are shown in **Table 1**. The ICUR of combined screening strategy (wide-field imaging in all at-risk ROP infants and indirect binocular ophthalmoscopy in referral cases) was US $1,746.99/QALY. Costs per examination by each screening strategy, treatment, and follow-up are shown in **Table 1**.

Nurse technicians' learning curve to perform anterior and posterior retinography resulted in an efficiency gain of 45% (from 22 to 13 min per examination), and to set up and dismantle equipment, of 12% (from 13 to 12 min). The performance training lasted 500 min. In a 6-h shift, each team would be able to perform 10 to 13 examinations per day, that is, 250 to 325 examinations per month (150 h). Mean time spent for remote imaging reading by ROP specialists was 5 min per image. On average, 12 images were read per hour, that is, 1,200 images per month (100 h).

The model showed that the probability of infants developing severe visual impairment due to ROP was 5% in ophthalmoscopy strategy and 3.2% in combined strategy. The tornado diagram demonstrates the impact of that variation in each parameter (**Figure 2**). The Monte Carlo probabilistic simulation yielded a 100% probability of combination strategy being cost-effective in a willingness-to-pay threshold of approximately US $1,800/QALY (**Figure 3**) (30).

A correlation was established between the gain in QALY and the gain in visual acuity. Every 1.2 QALY gained represented five lines gained in the decimal visual acuity chart (**Table 2**).

DISCUSSION

Portable wide-field imaging has been available since early 2000, and as such, it is not a new screening technology (31). However, its high cost has been a barrier for its widespread use, especially in low- and middle-income countries. The results of this study suggest that the screening strategy combining wide-field imaging by nurses with indirect binocular ophthalmoscopy for ROP care (screening, treatment, and follow-up) costs approximately US $1,700/QALY gained when compared with standard indirect binocular ophthalmoscopy alone.

More importantly, the combination could enhance ROP screening coverage, particularly in marginalized areas that lack ROP experts. In our model, 5% of infants screened with the ophthalmoscopy strategy developed visual impairment, in contrast to 3.2% with the combination strategy, meaning a reduction in 36%. In Brazil, considering that there are 37,000 infants at risk of ROP, 76% of them depend on governmental maternities, 90% of them could have access to the combined strategy, and that the difference of developing visual impairment between the two strategies is 1.8%, ∼455 visually impaired children due to ROP could be avoided every year in Brazil (37,000 × 0.76 × 0.9 × 0.018). In other words, we would need to screen 55 children to avoid 1 visually impaired child. If they have a mean life expectancy of 75 years, this could prevent 34,000 blind-years (blind children × life expectancy) (32).

The combined strategy could also enhance ROP screening efficiency by reducing the opportunity cost of ROP expert ophthalmologists. Opportunity cost is the cost of the second-best option or the not-chosen option. Currently, an experienced professional screens 100% of at-risk infants and treats <10%, but

TABLE 1 | Parameter estimates used in the model divided by screening, treatment, and follow-up categories.

Parameters estimate	Baseline	Range (low–high)	Source	PSA
Screening				
Access to ophthalmoscopy	0.52	0.20–0.80	(6) Assumption	Lognormal
Access to combination	0.90	0.52–0.95	Assumption	Lognormal
Ophthalmoscopy sensitivity	0.867	0.70–0.90	(10, 25), assumption	Lognormal
Ophthalmoscopy specificity	0.962	0.70–0.97	(10, 25), assumption	Lognormal
Wide-field imaging sensitivity	0.933	0.455–0.952	(10, 17)	Lognormal
Wide-field imaging specificity	0.962	0.617–0.98	(10, 17), Assumption	Lognormal
Good-quality imaging	0.95	0.90–0.98	(25), Assumption, (19)	Lognormal
ROP type 2 or worse	0.208	0.05–0.25	(10, 17, 37)	Lognormal
No. of examinations in infants not requiring laser treatment	(3)	1–13	Unit observation from 2006 to 2019	Lognormal
No. of examinations in infants requiring laser treatment	(9)	2–15	Unit observation from 2006 to 2019	Lognormal
Treatment				
ROP needing treatment	0.08	0.07–0.10	(6)	Lognormal
Two treatments needed	0,12	0.11–0.20	Unit observation from 2006 to 2019, (20), assumption	Lognormal
Facectomy (cataract surgery)	0.0109	0.005–0.05	(38), Assumption	Lognormal
Good visual function after treatment	0.753	0.60–0.857	(5), Assumption, (39)	Lognormal
Poor visual function when treatment is indicated and not performed	0.643	0.50–0.80	(23), assumption	Lognormal
Utility/QALY estimates				
Good visual function	0.701/13.65	7.0–66.6	(20, 26), discount rate 0–10%	Beta
Poor visual function				
Blindness	0.514/10.01	4.79–38.55	(20, 23, 26), discount rate 10–0%	Beta
Visual impairment	0.5327/10.38	5.32–39.95	(5, 26), discount rate 0–10%	Beta
Costs estimate (US $)				
Ophthalmoscopy	34.36	24.05–44.66	(6), −30% +30%	Gamma
Equipment	3.16		(27)	
Inputs	0.87		(27)	
Human resources (professional + training)	30.32 (23.43+6.89*[1])		(6, 40, 41)	
Wide-field imaging	64.35	42.05–102.97	−30%, +60%	Gamma
Equipment	35.02		Market value	
Inputs	1.13		(27)	
Human resources (professional + training)	28.15 (28.04+0.11*[2])		(40–44)	
Combination	58.20*[3]	40.74–93.12	−30%, +60%	Gamma
Laser treatment	642.09	449.46–834.72	(6), −30% +30%	Gamma
Equipment	502.92		(27)	
Inputs	0.87		(27)	
Human resources (professional + training)	134.26 (72.22+62.04*[4])		(6, 40, 41)	
Cataract surgery (facectomy)	795.20	556.64–1,033.75	(45), −30% +30%	Gamma
Follow-up				
Good visual function in non-treated infants	69.33*[5]	44.17–230.96	(45), Discount rate range 10–0%	Gamma
Good visual function in treated infants	190.63*[5]	106.53–675.13	(45), Discount rate range 10–0%	Gamma
Poor visual function	286.91*[5]	195.04–781.16	(45), Discount rate range 10–0%	Gamma

Parameters included clinical, epidemiological, utility and costs data and are presented as baseline and ranges values (high and low) with sources. Distribution of logarithmical probabilistic sensitivity (PSA) are presented for each parameter.

QALY, quality-adjusted life-years; ROP, retinopathy of pre-maturity; US $, US dollar.

[1] Ophthalmoscopy training 33 h(6).

[2] Wide-field imaging training 500 min.

[3] 100% wide-filed imaging and 25.8% ophthalmoscopy.

[4] Treatment training 33 h(6).

[5] Discount rate 5%.

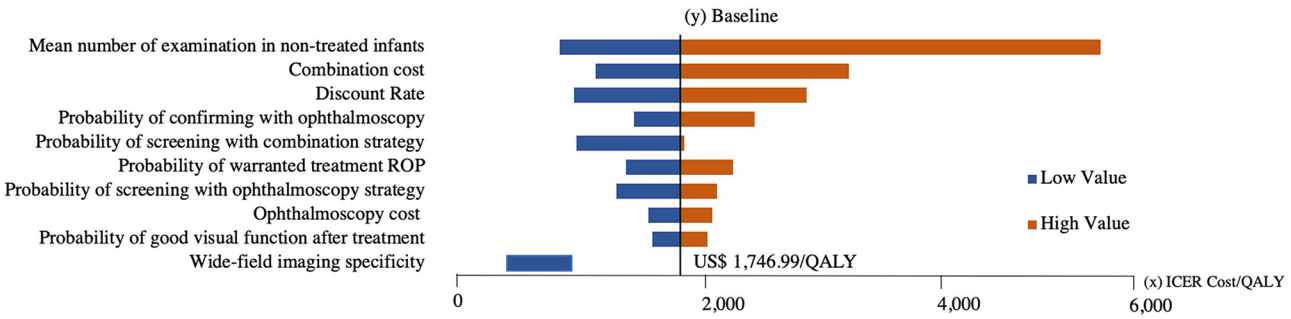

FIGURE 2 | Tornado diagram of the 10 parameters that most impacted the incremental cost–utility ratio (ICUR). *X* axis represents the impact on the ICUR in US dollars (USD) cost per quality-adjusted life-years (QALY) of each parameter variation, and *Y* axis represents baseline parameters with an ICUR of USD 1,746,99/QALY. Orange and blue bands show each parameter high and low values, respectively.

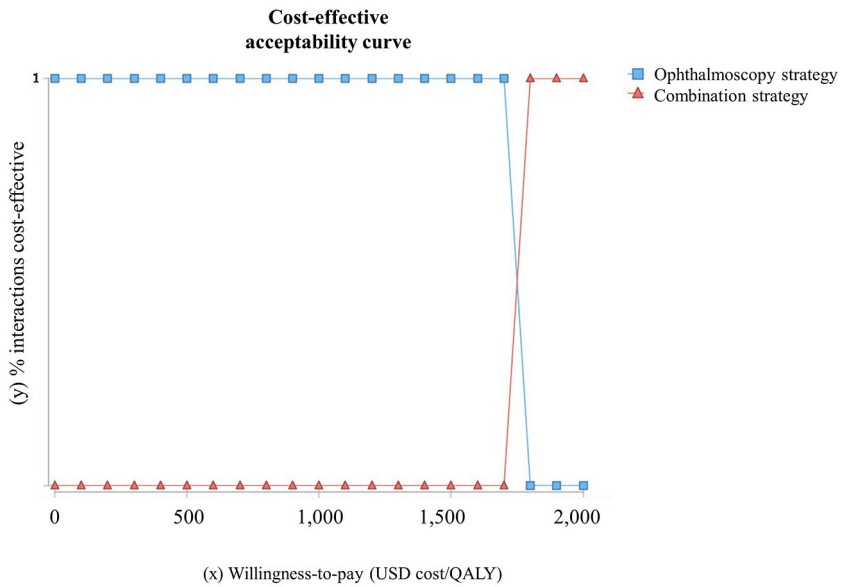

FIGURE 3 | Monte Carlo probabilistic cost-effective acceptability curve. Interactions cost-effective percentages (*y*) between combination strategy (blue square) and ophthalmoscopy strategy (red triangle) by willingness-to-pay (WTP) (*x*) ranging from 0 to USD 2,000/QALY. Above USD 1,800/QALY combination strategy is 100% cost-effective.

with the combination, he/she could examine 26% of infants at high risk of severe ROP and use almost 75% of the remaining time to teach and train younger professionals, perform other surgeries, and do scientific research (17, 20, 33).

In addition, eye examination documentation is precise and objective with wide-field imaging. It enables exchanging clinical cases by ROP experts and in-training ophthalmologists and favors medical liability management (25, 33). Besides, it could facilitate the family's understanding of the disease and enhance follow-up adherence (16). Documentation could also be an opportunity for creating an online eye examination database accessible to families and healthcare professionals involved in the infant's care follow-up. Eye examination documentation with indirect ophthalmoscopy is also possible, and its cost has been estimated (34). However, the learning curve of a non-ophthalmologist to perform indirect ophthalmoscopy should be longer as it is a diagnostic examination learned during medical residency in ophthalmology.

Previous economic modeling studies have included the cost-effectiveness of ROP screening, treatment, and follow-up (7–9, 20, 25, 34). Regarding wide-field imaging, one study of cost–utility analysis for ROP management adopted a third-party-payer perspective from the US Current Procedural Terminology with a 3-month post-operative follow-up (25), and another study adopted the UK National Health System's perspective with a 10-year follow-up (20). However, our study included a lifetime perspective and the cost of cataract surgery as a complication following laser treatment unlike these other authors (20, 25).

TABLE 2 | Correlation between decimal visual acuity and quality-adjusted life-years (QALY) gained by infants with good and poor visual functions.

Decimal visual acuity	QALY	Correlation of decimal visual acuity/QALY
0	0	
0.00625	0.261	
0.0125	0.521	5 lines/1.2 QALY
0.025	0.782	
0.05	1.043	
0.06	1.304	
0.08	1.564	
0.1	1.825	5 lines/1.2 QALY
0.13	2.086	
0.16	2.346	
0.2	2.607	
0.25	2.868	
0.32	3.129	5 lines/1.2 QALY
0.4	3.389	
0.5	3.65	

This study adopted three visual acuity levels to estimate three utility values and projected a very low incremental utility (0.044), similar to Jackson et al. (25) (0.0375). Using Castillo-Riquelme's utility values in the sensitivity analysis, which were higher for good visual function and lower for poor visual function than ours, there was also a low incremental utility value (0.088) (20). This low incremental utility reinforces the effectiveness of both screening strategies (ophthalmoscopy and combination). Therefore, wide-field imaging does not replace standard ophthalmoscopy, but it can have a crucial role in creating an ROP care program to enhance both: screening coverage and healthcare system efficiency.

Our group estimated that the gain of a single QALY represents an improvement of five lines in visual acuity chart. This estimate does have flaws due to the elasticity concept as the utility gained by a blind child is higher than the utility gained by a low vision patient. However, this estimate enables specialists who are not familiarized with the term "utility," to better understand the enormous QALY gained in terms of lines of visual acuity with this screening combination.

Wide-field imaging for ROP is currently not available within SUS; therefore, a micro-costing approach was executed to estimate its cost. Regarding this, the study's major strengths were training non-ophthalmologists for bedside wide-field imaging, which resulted in an efficiency gain of 32%. Nurse technicians improved more in performing wide-field imaging (45% improvement), which is a more difficult step, than in setting up and dismantling the equipment (12%). The improvement was better in anterior segment imaging (73%) and good-quality imaging selection steps (44%). The efficiency level will increase as the learning curve was compared after only 1 month of learning.

Another major point was measuring reading time per image by ROP expert ophthalmologists. Measuring the time spent per examination for retinography and for image reading enabled us to estimate precisely wide-filed imaging cost and learning curve, which was not seen in other studies (20, 25, 34). Also, this measure allowed for planning a logistic and feasible ROP care program in Rio de Janeiro, as seen in other regions (19, 35).

Castillo-Riquelme et al. also performed a micro-costing approach to estimate the wide-field imaging cost in four scenarios (20). In the scenario like ours, where a specialized nurse visits the neonatal unit care for image capture and the ophthalmologist is the reader, the estimated cost per examination was 28 pounds. Our wide-field screening cost per examination was 35% higher than theirs [45.28 pounds (at the rate of 1 pound = R $5.60)]. This can probably be explained by difference in equipment and staff costs (20).

Our equipment cost per examination (24.64 pounds) represents 58% and staff cost (19.80 pounds) 40% of the total wide-field imaging cost. Conversely, in Castillo-Riquelme's study, the equipment cost represents 29% (8 pounds) and the staff cost 71% (20 pounds) (20). The Brazilian equipment cost per examination is three times the cost in the United Kingdom, according to our estimates. There may be two reasons to explain this: first, the exchange rate for acquiring the equipment in Brazil; second, the National Sanitary Vigilance Agency currently allows commercialization of only one equipment supplier. New suppliers could make the price more competitive.

The tornado diagram showed the parameters that most affected the ICUR were number of examinations in non-treated infants, combination strategy cost, and discount rate. The first can be explained because infants not treated represent 90% of all screened infants; therefore, the higher the number of their examinations during screening, the higher the total cost. However, the frequency of the upper limit of 10 examinations, in our experience, occurs in only 2% of the cases, whereas the frequencies of 2 and 3 examinations occur in 67 and 44%, respectively. The second parameter, combination strategy cost, also affected the model as when the cost is 60% higher, the ICUR doubles (US $3,849.15/QALY), and when the cost is 30% lower, the ICUR diminishes 60% (US $697.62/QALY). Moreover, the discount rate ranging from 0 to 10% also impacted the ICUR because the higher the discount rate, the lower the expected present value, especially in a lifetime time horizon.

Probabilistic analysis yielded a 100% likelihood of the combination strategy being cost-effective with a willingness-to-pay threshold of US $1,800. Brazil does not have a cost per QALY threshold for healthcare technology incorporation such as the United Kingdom, Canada, Chile, Colombia, or Mexico. The establishment of a threshold could facilitate healthcare technology evaluation interpretation and decision making (29).

Following the emergent concept of universal eye screening, where wide-field imaging is proposed to screen all term and preterm newborns (36), combination cost could be diminished because of the efficiency gain in screening all living infants with a low marginal cost. In other words, combination cost could be lower in a universal eye screening scenario, compared with an ROP screening scenario. Nevertheless, screening all

living infants may raise concern regarding many unnecessary examinations performed in healthy infants or in infants with benign and transient alterations, such as retinal hemorrhage after vaginal delivery, which are the most common ocular alterations found (36).

Our study has some limitations that should be mentioned. First is the use of a mathematical formula to estimate the utility, for lack of better measurements, in visually impaired children. However, we found a similar low incremental utility (0.088) using more extreme utility values (high and low intervals) in the sensitivity analysis based on another study (20), which supports that the formula can be a reasonable and available option. Nevertheless, specific questionnaires for visual impairment in children are needed for a better utility estimate. Second, using assumptions in the model can cause some shortcomings in the results. However, we used assumptions for both strategies compared, minimizing these shortcomings. Third, costs of anesthesia and hospitalization, performed in both screening strategies, were not included, so the incremental cost should have the same magnitude. Fourth, costs for image printing were not included, although it is possible to create a sustainable program where images could be sent to a cellphone or by e-mail.

Some challenges remain for implementing the combined strategy. Because of the ever-developing nature of wide-field imaging, equipment leasing from the manufacturer, instead of its purchase, could result in a considerable benefit. This would allow not only a decrease in expense but also the adoption of more modern equipment as it becomes available. Another interesting challenge would be the implementation of a centralized imaging center that could receive, organize, and send the images to expert readers, as estimated by Mohammadi et al. (34). This center could even be responsible for training professionals and for the follow-up of infants after their discharge. In this scenario, other direct costs (infrastructure, staff, input) would have to be included.

More studies showing wide-field imaging accuracy for other eye diseases in infants could make it more efficient and facilitate its widespread use under the emergent concept of universal eye screening at birth. In addition, further studies focusing on the economic burden of this disease are also crucial to address the problem. Including indirect costs of visual impairment in childhood (as loss of productivity or governmental subsidies) and using the societal perspective could make the combination strategy even more affordable. Finally, our model has a long-life expectancy with low prospects of infants in need of treatment and of infants at risk of visual impairment. The use of another model considering the infant's coverage as the outcome could also enhance the analysis.

In conclusion, we have presented that the combination of wide-field imaging with binocular indirect ophthalmoscopy in specific referral cases is feasible and cost-effective for ROP screening from a middle-income country's perspective. It could also be a cost-saving strategy if the screening includes all living newborns. Moreover, the combination could enhance ROP screening coverage and health efficiency in middle-income countries, reducing the leading cause of childhood visual impairment in these countries.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Instituto Nacional de Saúde da Mulher, da Criança e do Adolescente Fernandes Figueira, Fundação Oswaldo Cruz, Rio de Janeiro, RJ, Brazil. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AAZ, ZFMV, and MP: conceptualization. LMN, LMH, AAZ, and MP: methodology. LMN, LMH, AAZ, and MP: validation. LMN, LMH, AAZ, RES, ZFMV, and MP: formal analysis. LMN, LMH, AAZ, and MP: resources. LMN, LM, AAZ, and MP: data curation. LMN, LMH, AAZ, and MP: writing original draft and preparation. LMN, LMH, AAZ, RES, ZFMV, and MP: writing, review, and editing. AAZ and MP: supervision. AAZ and MP: project administration. All authors have read and agreed to the published version of the manuscript.

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Advantages of Widefield Optical Coherence Tomography in the Diagnosis of Retinopathy of Prematurity

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Recent advances in portable optical coherence tomography (OCT) and OCT angiography (OCTA) have resulted in wider fields of view (FOV) and shorter capture times, further expanding the potential clinical role of OCT technology in the diagnosis and management of retinopathy of prematurity (ROP). Using a prototype, handheld OCT device, retinal imaging was obtained in non-sedated infants in the neonatal intensive care unit (NICU) as well as sedated infants in the operating room of Oregon Health & Science University (OHSU) Hospital. In this observational study, we provide an overview of potential advantages of OCT-based disease assessment in ROP. We observed that next-generation OCT imaging (a) may be sufficient for objective diagnosis and zone/stage/plus disease categorization, (b) allows for minimally-invasive longitudinal monitoring of disease progression and post-treatment course, (c) provides three-dimensional mapping of the vitreoretinal interface, and (d) with OCTA, enables dye-free visualization of normal and pathologic vascular development.

Keywords: retinopathy of prematurity, pediatric retina, optical coherence tomography, handheld optical coherence tomography, optical coherence tomography with angiography

INTRODUCTION

Optical coherence tomography (OCT) and OCT angiography (OCTA) are widely used to evaluate patients with diseases of the macula and vitreoretinal interface. Over the last two decades, the diagnosis and management of both leading causes of blindness in adults (diabetic retinopathy and age-related macular degeneration) have incorporated OCT into the standard of care. Applications in pediatric retinal diseases, such as retinopathy of prematurity (ROP), have been more challenging due to the difficulty of imaging children using devices designed for adults, both in terms of positioning requirements of adult table-mounted devices as well as the need for patient cooperation to prevent motion artifacts. Recent advancements in OCT technology have made image acquisition feasible for use in awake infants and have the potential to improve our management of many diseases in pediatric retina, including ROP, by allowing for objective diagnosis and sensitive detection of anatomical changes.

Previous ROP studies incorporating OCT technology have largely directed attention at the diagnostic value of macular and posterior retinal changes due to practical FOV limitations. These efforts have broadly fallen into two categories: detection of subclinical pathology and evaluating objective biomarkers of disease. We have learned that OCT can demonstrate retinoschisis (1) and early vitreoretinal traction (2) better than our eyes can appreciate during the clinical examination, that cystoid macular changes can occur in ROP (3, 4) as in other retinal vascular diseases, and that the changes associated with plus disease cause three-dimensional architectural changes in the retina (5), including at the vascular-avascular border (6, 7). There has also been increased attention on the sequelae of blood retinal barrier disruption, with an increase in vitreous opacities seen in more severe ROP (8). Recent papers have focused on normal and abnormal foveal development in prematurity (9, 10), previously impossible to evaluate *in vivo*, as well as the repeatability and reproducibility of measurements taken with a handheld OCT device (11).

Over the last 10 years there has been a transition toward faster laser speeds using swept-source (SS-OCT) designs in handheld OCT prototypes, which has enabled faster image acquisition and OCTA (12–14). With OCT in general, there is a tradeoff between signal quality, imaging speed, and FOV. In the pediatric population, since imaging non-sedated infants necessitates fast imaging speed to prevent motion artifacts, the tradeoff is between signal quality and FOV. For OCTA, this reality means that given current imaging speeds, OCTA can be obtained at small FOVs but motion artifact becomes significant as FOV is expanded. Image segmentation also remains a challenging barrier, especially given motion artifact, and has thus far prevented validation of quantitative OCTA biomarkers in neonates.

We previously described a widefield, handheld SS-OCT device with a $>55^\circ$ FOV, that was capable of visualizing peripheral pathology when coupled with scleral depression (15). Subsequently, we have re-engineered the FOV to approximately 105° in a new design, which can provide real-time *en face* visualization that can be used to optimize the image quality and orientation prior to image acquisition, which takes 1.5 s. (16) Our experience operating this device in the NICU has provided a number of observations as to how advances in OCT technology may provide value to patient care in the future. In this paper, we review the potential advantages of using widefield OCT in the diagnosis and management of ROP.

METHODS

This study was approved by the Institutional Review Board (IRB) at Oregon Health & Science University (OHSU) and adheres to all tenets of the Declaration of Helsinki. Infants were eligible for recruitment if they met criteria for ROP screening (birthweight $\leq$ 1,500 g or gestational age $\leq$ 30 weeks). Exams were performed at the bedside with an eyelid speculum, after administration of cyclomydril and proparacaine. Consent for imaging was obtained from parents. Between March and November 2021, we performed more than 200 eye examinations with OCT. Infants were imaged with a 400-kHz portable handheld SS-OCT system with a modular lens system as shown in **Figure 1**, providing up to a 105° FOV. The camera was held by the examining ophthalmologist and a second person controls the software.

FIGURE 1 | Portable handheld OCT device. Upper-left image shows the prototype device with OCT module and computer. Upper-right image shows a close-up of the probe with a 5.5-inch display capable of real-time *en face* visualization. Bottom image shows the imaging process of an infant in the neonatal intensive care unit.

Our investigational system features real-time *en face* visualization to allow the operator visual feedback of the scanning region. OCT volumes were averaged in linear scale, and processed using custom software to create mean-intensity *en face* projections. B-scans were processed using an image registration algorithm. This enables the OCT to be used as a fundus camera for visualization of peripheral ROP stage even prior to acquisition of the OCT volumes. Image acquisition takes 1.5 s.

In post-processing, three-dimensional rendering was completed in the Volume Viewer plugin of Fiji, a distribution of ImageJ (17). Segmentation of OCT volumes was performed manually with the Insight Toolkit (18), then interpolated and applied to volumes using custom software coded in MATLAB (19). OCTA images were generated using a novel phase-stabilized complex-decorrelation methodology (20), with automated segmentation performed using a guided bidirectional graph search method (21), both of which were designed specifically for use in swept-source, widefield applications.

RESULTS

Objective Diagnosis/Documentation

We found that real-time *en face* visualization allows handheld OCT to be used much like an ophthalmoscope, with a

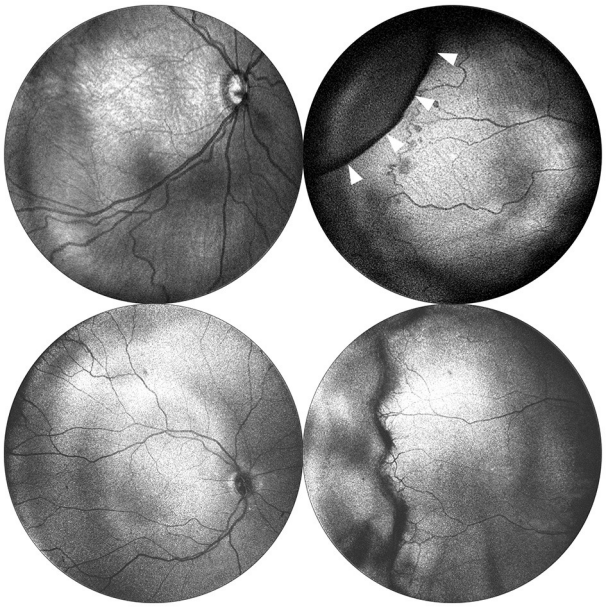

FIGURE 2 | Posterior and peripheral *en face* images obtained via portable 55° and 105° FOV OCT. Images in the top row were obtained using a 55° FOV system from a baby born at 24 weeks gestation (770 grams) and imaged at 33 weeks postmenstrual age. The images in the bottom row were obtained using a 105° FOV system from a baby born at 30 weeks gestation (1,390 g), and imaged at 40 weeks postmenstrual age. Posterior images are shown in the left column and demonstrate the expanded FOV. Peripheral images are shown in the right column and were obtained with the aid of scleral depression using the 55° system. White arrows indicate the indentation of the scleral depressor.

comparable FOV and improved contrast when visualizing the border between vascular and avascular retina. Since visualization of peripheral stage typically requires scleral depression, we evaluated whether scleral depression, coupled with the handheld OCT could detect and visualize peripheral stage. **Figure 2** demonstrates posterior and peripheral images obtained using this method, using both 55° and 105° FOV devices. In most cases, it was possible to objectively assess the degree of peripheral stage. The cases where we were unable to visualize the retinal periphery using OCT were also the most challenging to examine ophthalmoscopically. These included babies with swollen eyelids due to continuous positive airway pressure (CPAP), and those who were unstable clinically, where we prioritized the clinical standard ophthalmoscopic examination to rule out clinically significant disease but otherwise kept the examination as brief as possible to minimize any added stress and risk from research imaging. That said, in those most challenging cases where we were able to obtain OCT imaging, we often found that *en face* OCT provided better sensitivity for detection of subtle changes at the vascular-avascular border, although this was not performed in a masked fashion.

Monitoring of Disease Progression and Regression

Serial evaluation of fundus photos has demonstrated value in detecting signs of disease progression (22). We found that *en face* visualization provided sufficient detail to assess relative changes in disease severity across time (**Figure 3A**) by direct comparison to prior images. Additionally, when evaluating the effect of treatment with intravitreal bevacizumab, we found that direct comparison of the *en face* OCT of the posterior pole and retinal periphery demonstrated reduction in the stage and extent of peripheral disease as well as the degree of plus disease (**Figure 3B**).

Vitreoretinal Interface and Retinal Detachment

A major advantage of OCT over the ophthalmoscopic examination in vitreoretinal disease management is the ability to determine three-dimensional relationships between the vitreous, the retina, and extraretinal membranes. While these relationships are visible with smaller FOV systems, it takes far more time to visualize the entire periphery with multiple scans. With the 105° FOV system, we can capture both the posterior pole and retinal mid-periphery in a single image, allowing for three-dimensional reconstruction of the topographical anatomy of the retina and vitreous. **Figure 4A** demonstrates how these three-dimensional relationships can be visualized in the setting of a retinal detachment using cross-sectional B-scans. Additionally, three-dimensional rendering provides another means of interactive visualization, which may aid surgical planning (**Figure 4B**).

Using the 55° and 105° FOV systems, we imaged patients with a broad range of peripheral stage, as shown in **Figures 3**, **5**. Note that eyes can have differences both in the degree and extent of peripheral stage as well as the degree of dilation and tortuosity of the posterior retinal vessels. B-scans drawn along the length of the vascular-avascular junction demonstrate three-dimensional retinal changes (**Figure 5A**) and could one day be a more precise and continuous biomarker for disease severity in an eye than "maximum stage," which the current classification system recommends. OCT also aids in the diagnosis of popcorn neovascularization, considered in the spectrum of stage 2 ROP, and can show how extraretinal fibrovascular proliferation coalesces into the typical stage 3 lesion appearance (**Figures 3**, **5**).

Optical Coherence Tomography Angiography

Figure 6 shows OCTA *en face* projections obtained with the widefield OCT device. With OCTA, there is a tradeoff between FOV and motion artifact as seen in the example. In the future, this may be reduced by using a smaller FOV, with a faster laser, or with improved software. Nonetheless, these results demonstrate the potential for non-invasive angiographic visualization of non-perfusion and neovascularization, both of which may be quantifiable biomarkers in the future.

DISCUSSION

Advances in the speed and optical engineering of OCT devices have made the incorporation of OCT into ROP diagnosis

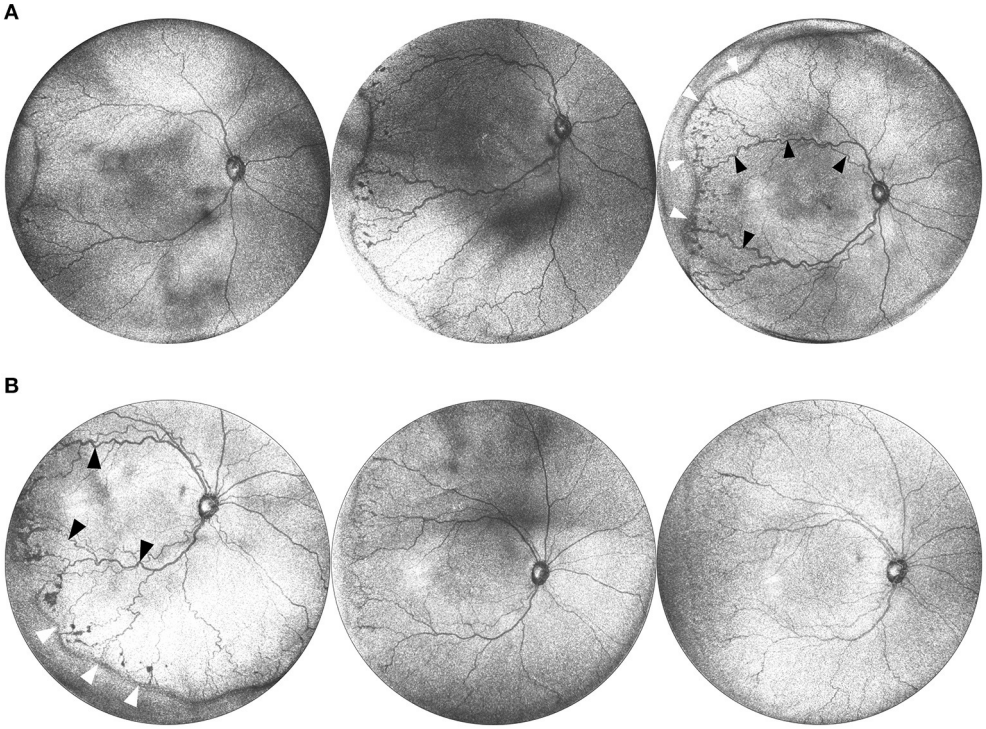

FIGURE 3 | (A) Serial widefield OCT images taken on three successive weeks. These images are from a baby born at 25 weeks gestation (449 g) and imaged at 36, 37, and 38 weeks postmenstrual age. Serial imaging shows the posterior and peripheral retina in one image, and tracks the progression of arterial and venous tortuosity and fibrovascular proliferation. Black arrows highlight areas of increased dilation and tortuosity. White arrows indicate the peripheral ridge which has increased over the time period, along with popcorn neovascularization posterior to the ridge. **(B)** Serial images pre and post treatment. This is the same infant from **(A)** at postmenstrual age 38, 39, and 40 weeks. The leftmost image shows a posterior *en face* view taken immediately prior to treatment with 0.625 mg intravitreal bevacizumab. Middle image shows regression of disease 1 week after treatment, and rightmost image shows further regression 2 weeks after treatment. Black arrows indicate areas of vascular tortuosity pre-treatment that improve post-treatment. White arrows indicate areas of pathologic neovascularization that appears less dense post-treatment.

more practical. In this paper, we describe key potential advantages of widefield OCT in the diagnosis and management of ROP.

Widefield imaging using OCT has the potential to provide quantitative and objective assessment of each of the components of ROP classification. The diagnosis of ROP has always been subjective and qualitative, with the clinician responsible for determining the zone, stage, and presence of plus disease. Yet each of these components represents an ordinal categorization of a continuous spectrum that could be measured more discretely using OCT. Zone represents the area of vascularized retina, which could in theory be measured as an area using *en face* OCT given the high contrast possible on OCT images. As shown in **Figure 3A**, stage represents a continuous spectrum that slowly evolves over time until it is eventually treated, or spontaneously regresses (23). In the future, it may be feasible to automatically segment the peripheral vascular-avascular junction and quantify thickness to create objective cutoffs for stage that correlate with population-derived treatment thresholds. Finally, the spectrum of plus disease has been well-described, and may be more objectively quantified using artificial intelligence-derived metrics (24).

Previous work has demonstrated that there is a relationship between plus disease severity on a posterior pole photograph, the zone of disease, and the degree and number of clock hours of peripheral stage in an eye on ophthalmoscopy (24). Widefield OCT has the potential to directly visualize these relationships and provide rapid, non-invasive assessment of ROP severity. Each of these biomarkers may be followed over time to directly assess disease progression (25) or regression (23). This has implications not only for improved clinical care, but also for research as it has not previously been possible to directly measure the continued growth of the retinal vasculature *in vivo,* and the changes associated with the development of pathologic neovascularization. The natural course and response to treatment of ROP can be followed longitudinally with more frequent imaging, which may allow for earlier detection of changes and correspondingly reduce the time to treatment.

The advantage of widefield OCT over fundus photography is even greater for eyes with moderate or severe ROP where

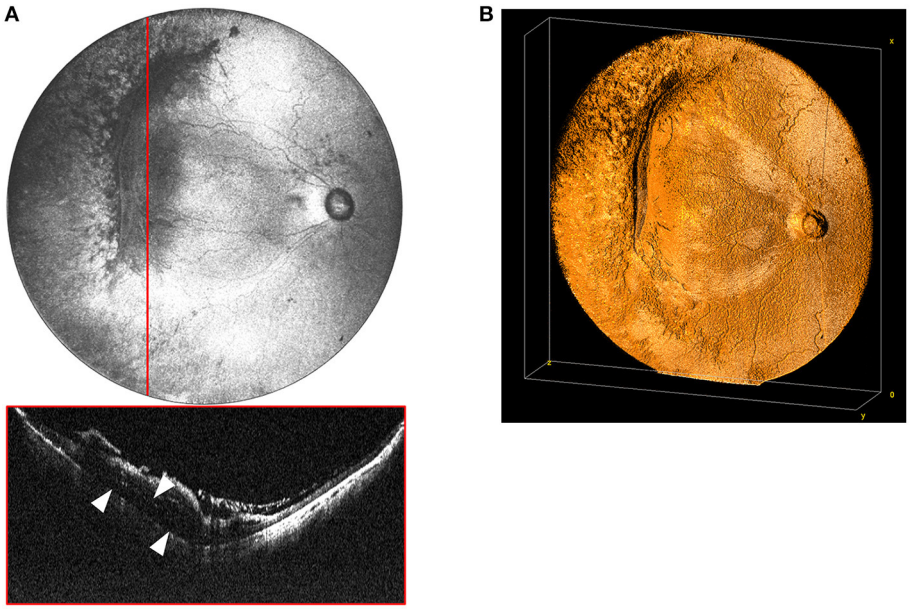

FIGURE 4 | (A) Widefield *en face* OCT image of a stage 4A tractional retinal detachment secondary to ROP. These images are from a baby born at 25 weeks gestation (571 g) and imaged at 50 weeks postmenstrual age. Red horizontal line indicates location of the corresponding cross-sectional B-scan. White arrows designate area of retinal detachment with subretinal fluid. **(B)** Volumetric rendering of retinal detachment shown in 4A. This visualization enables topographic representation of the three-dimensional relationships in severe retinopathy of prematurity, including highlighting the elevation of the blood vessels and fibrovascular proliferation causing the retinal detachment.

the topographic changes in the vitreoretinal interface are more dramatic. In our experience, these changes are easier to appreciate using OCT, especially as stage 2 with popcorn neovascularization develops. These lesions often coalesce into typical stage 3 appearance (as in **Figures 3**, **5**). Technically, the distinction between stage 2 and stage 3 is when "extraretinal" neovascularization develops, but practically, the diagnosis is clinical and based on the ophthalmoscopic appearance, since popcorn neovascularization represents extraretinal neovascularization. This is a great example of how OCT and OCTA could lead to more precise classifications of ROP stage in the future, since the transition when neovascularization breaks through the inner limiting membrane (ILM), which can be observed *ex vivo* on histology (6), but not *in vivo*, is a critical turning point in the risk of retinal detachment and blindness. Previous work has highlighted the significance of vitreous opacities, which are presumably signs of exudation from breakdown of the blood-retinal barrier secondary to vascular endothelial cell dysfunction (8). Being able to directly evaluate the three-dimensional anatomy of the peripheral retina, as well as the vitreous, may help determine whether these findings are simply a surrogate marker of ROP severity, or independent prognostically. Finally, the use of OCT for early detection and diagnosis of retinal detachment could dramatically reduce the likelihood of blindness. Since OCT is far more sensitive for the detection of early vitreoretinal traction, it is hard to imagine that with appropriate follow-up, extensive stage 3 and early stage 4 ROP would be missed.

As OCTA technology advances, additional biomarkers relating to avascular zones or neovascular flow may be discovered and incorporated into clinical care. Fluorescein angiography (FA) has been shown to increase sensitivity of ROP screening and improve inter-observer agreement regarding classification (26). OCTA provides an alternative to FA that does not require intravenous contrast. Perhaps the most significant impact of widefield OCT in the evaluation of premature babies is what we have yet to discover. In adults, OCT is increasingly being used to predict the presence of systemic disease, in particular neurological and cardiovascular disease. ROP exists in a larger collection of comorbid diseases with similar etiology, with hyperoxia induced vascular injury in capillary beds throughout the body. Clinically, this is most relevant in the brain, lung, gastrointestinal tract, and kidneys, and it may be that microvascular or structural alterations in the eye, detectable with OCT or OCTA, indicate the presence of comorbid brain or lung disease. Indeed, there is already some indication that this is the case, with recent work demonstrating abnormalities in retinal thickness associated with birthweight, and prior history of sepsis and necrotizing enterocolitis (27).

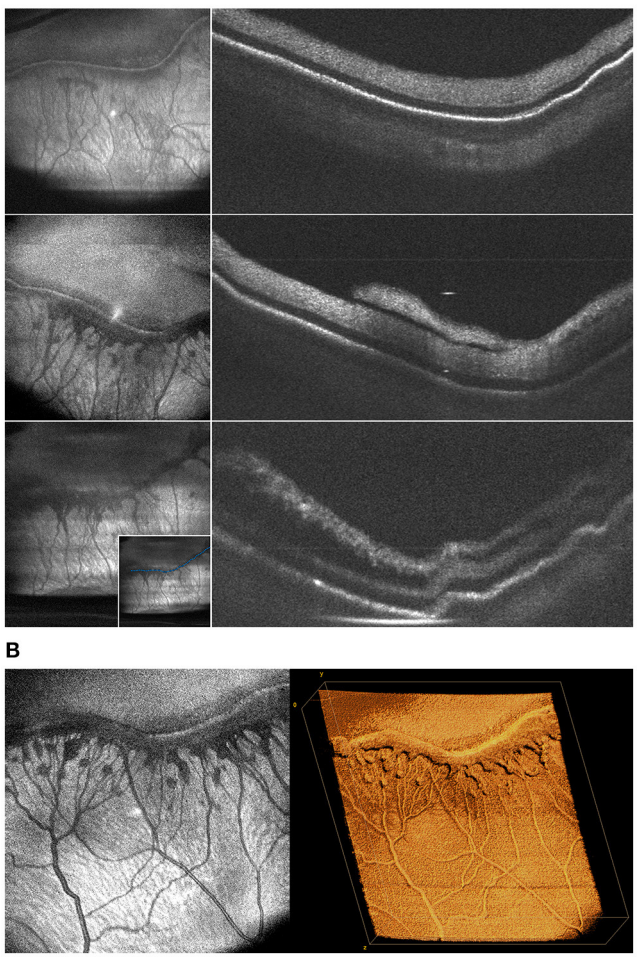

FIGURE 5 | (A) Changes in the morphology of fibrovascular proliferation demonstrated by cross-sectional B-scans taken along the length of the ridgeline every 2 weeks. These images were obtained from a baby born 25 weeks gestation and seen at 36, 39, and 41 weeks postmenstrual age. Left column shows *en face* projection of peripheral pathology. Right column shows progression of neovascularization and retinal traction on B-scan. The inset in the bottom-left image shows sample manual tracing of the ridgeline B-scan used to generate these cross-sections. **(B)** Volumetric rendering of ridgeline in stage 3 ROP. This is the same patient as **(A)** seen at 39 weeks. The image on the left shows an *en face* view of peripheral fibrovascular proliferation in stage 3 ROP. The image on the right shows three-dimensional rendering of the same volume.

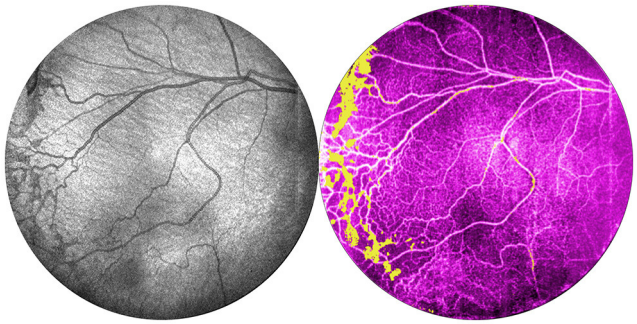

FIGURE 6 | Comparison of OCT and OCTA images of retinal vasculature. This is the same patient as **Figure 1** (24 weeks gestation, 770 g) seen at 35 weeks gestation. From left: OCT *en face* image, and corresponding OCTA *en face* image with flow signal in the vitreous shown in yellow.

CONCLUSION

In this paper, we have attempted to argue for the advantages of widefield OCT in the diagnosis and management of ROP. The main limitation of this work is that there are currently no commercially available devices that allow clinicians to incorporate these findings in clinical care, or develop further evidence for the role of OCT in the management of ROP. As this technology continues to improve, and costs come down, we believe that it is a matter of time before faster, higher resolution, and low-artifact OCTA may produce even more useful biomarkers for *in vivo* assessment of disease. We hope that this work may stimulate others to innovate further and for the added value of this technology to be clearly seen such that commercially available devices may be made available to improve the care of infants at risk for ROP around the world.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Oregon Health and Science University Institutional Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JC, MC, DH, YaJ, and YiJ designed the study and obtained the funding. SO developed and maintained the patient database and consented all patients. T-TN, SN, SK, and XW identified, processed, and contributed images to the final paper. All authors provided critical review and approved the final version of the manuscript.

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Computer-Aided Detection of Retinopathy of Prematurity Severity in Preterm Infants *via* Measurement of Temporal Vessel Width and Angle

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Retinopathy of prematurity (ROP) is a retinal disorder that occurs in preterm infants with low birth weight and is the leading cause of preventable blindness in children. Early identification of high-risk patients and early diagnosis and timely treatment of ROP can substantially improve patients' visual outcomes. However, manual screening consumes both time and resources. Telescreening using retinal fundus images has the potential to reduce the burden engendered by the necessity of on-site screening. Recently, substantial progress has been made in using computer-aided diagnosis with retinal fundus images, and this approach has attracted considerable attention for the diagnosis of eye diseases. Abnormalities of and alterations in retinal blood vessels may relate to the occurrence and progression of ROP. In this study, we examined the hypothesis that ROP severity may be associated with the angle and width of arteries and veins. We computationally determined the artery–artery and vein–vein angles in the temporal quadrants—the temporal artery angle (TAA) and temporal vein angle (TVA)—under normal conditions and in different ROP stages. We also estimated retinal vessel width—temporal artery width (TAW) and temporal vein width (TVW)—by applying the Radon transform method to fundus images. Our results revealed significant decreases in TAA and TVA and increases in TAW and TVW with increasing ROP severity (all $P < 0.0001$). In addition, we observed positive TAA–TVA and TAW–TVW correlations (both $P < 0.0001$). The TAA was negatively correlated with the TAW ($r = -0.162$, $P = 0.0314$). These retinal vessel features may be useful in assisting ophthalmologists in the early detection of ROP and its progression.

Keywords: retinopathy of prematurity (ROP), vessel width, vessel angle, Radon transform, computer-aided diagnosis

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INTRODUCTION

Retinopathy of prematurity (ROP) is a vascular eye disease that occurs in preterm infants, especially those with low birth weight (<1,500 g) and young gestational age (<32 weeks). Detecting the disease in its early stage and conducting regular follow-ups are critical for preventing blindness. In the International Classification of Retinopathy of Prematurity (1, 2), ROP is categorized into five stages

(stages 1–5) according to the severity of the disease: stage 1, involving a demarcation line at the juncture of the vascular and avascular peripheral retina; stage 2, involving a ridge; stage 3, involving neovascularization; stage 4, involving partial retinal detachment; and stage 5, involving total retinal detachment (2).

Screening for ROP to detect cases requiring treatment is crucial if a patient with ROP is to have a favorable outcome. Traditionally, ROP screening has been performed at the bedside through indirect ophthalmoscopy (3). Because of the limited personnel available for onsite screening, the use of tele-screening, in which a fundus image is captured using a wide-angle fundus camera, has increased (4). In one study, ROP features on fundus images could be identified with high accuracy (4).

Because of the recent development of artificial intelligence, automatic ROP diagnosis through the identification of plus disease has been achieved using deep learning technology (5–9). A few reports are available on retinal vessel angles and their relationship with ROP, especially as ROP progressively worsens (10, 11). Additionally, some studies have determined the width of retinal blood vessels. For example, a study determined the vessels' width by extracting the centerline after the segmentation of the vessels and using the pixel edges (12). In the other study, a Gaussian-based modeling approach has been employed to detect vessel width on the basis of centerline vessel intensity, and image processing techniques have been employed to determine vessel width on the basis of fundus images by using Gabor filters (13). However, these studies have applied image processing methods such as binarization and skeletonization and have used a manually set threshold for each image. The vessel segmentation and centerline extraction must be determined precisely in the middle of the vessel for accurate measurement of width, which is unlikely when automated image processing techniques are employed. The aforementioned methodologies are applicable only when the retinal images are of high quality with vessel contrast and full vessel development. However, in the case of fundus images of preterm infants, the vessels may not be completely developed, and the images are likely to be of low quality, which can result in inaccurate estimations of vessel width. Finally, the relationship between vessel angles and widths at various stages of disease severity has yet to be investigated.

To address these limitations, the present study used a Radon transform (RT)-based algorithm to determine the width of vessels automatically from fundus images of babies without ROP and babies with stage 1–3 ROP. The RT-based algorithm is robust and can reliably detect linear features even in the presence of noise (14, 15). Moreover, the algorithm can track thin vessel structures, for which the signal quality is low. The RT computation is executed through the integration of local intensities; accordingly, centerline smoothness is achieved using Gaussian smoothing based on spatial correlations. According to our review of the literature, the association between vessel angle and width has yet to be reported. In this study, we quantified the angles of the temporal artery and temporal vein and determined their correlations with the vessels' width as well as the extent to which they varied among preterm infants. We discovered the relationships of vessel angles and widths with an increase in ROP severity. Our study findings could offer information regarding the objective judgment of ROP severity and possibly complement the understanding of and improve screening strategies for ROP as well as aid its diagnosis and management.

TABLE 1 | Details of data used in this study.

ROP stage	No. of patients	No. of images	OS	OD
No ROP	44	66	32	34
Stage 1	19	28	13	15
Stage 2	20	33	16	17
Stage 3	35	49	31	18

MATERIALS AND METHODS

Dataset Details

In this study, we used a dataset containing the fundus images of preterm infants who underwent eye screening for ROP at Chang Gung Memorial Hospital, Linkou, Taiwan. All images were captured by an ophthalmic technician using a RetCam imaging system (RetCam III, Natus, Pleasanton, CA, USA). The fundus exams were performed for infants with a body weight of $\leq$1,500 g or gestational age of $\leq$32 weeks and for selected infants with a body weight of 1,500–2,000 g or gestational age of 32 weeks with any unstable clinical condition; the ROP screening was performed in the fourth week after birth (16–18). Data from a total of 118 patients were used in this study. In brief, the data comprised 66 retinal images from 44 patients with no ROP, 28 images from 19 patients with stage 1 ROP, 33 images from 20 patients with stage 2 ROP, and 49 images from 35 patients with stage 3 ROP. All the data were captured between May 2013 and June 2019. Herein, the term "no ROP" refers to normal eye health without ROP. Details on the data are presented in **Table 1**.

Image Labeling

All fundus images were labeled by two senior expert ophthalmologists (EYK and WCW) in accordance with the guidelines of the International Classification of Retinopathy of Prematurity (1, 2). Furthermore, the vessels in the images were annotated as being an artery or vein at the main superior and inferior temporal branches in the retina.

Image Analysis

The resolution of all fundus images was set as 1,600 × 1,200. The angles between the superior and inferior temporal arteries and between the superior and inferior temporal veins were measured using MATLAB software. The temporal artery angle (TAA) was determined by tracing a line along the superior and inferior temporal arteries. The vessel angle was calculated automatically at the point of intersection of these two straight lines by the algorithm using the inverse cosine function. A similar procedure was followed to measure the temporal vein angle (TVA) in each image. We calculated the TAA and TVA in all images in the dataset.

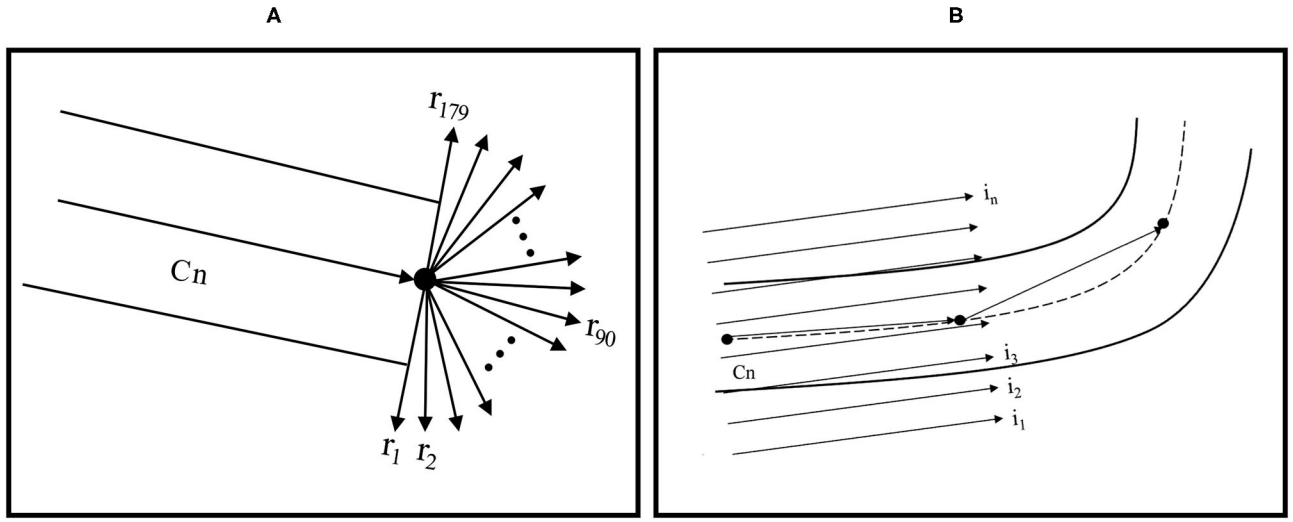

FIGURE 1 | (A) RT feature extraction and centerline tracking and **(B)** computing RT features for vessel edge extraction with linear integrals.

TABLE 2 | TAA and TVA in various stages of ROP.

		TAA (degrees)				TVA (degrees)			
ROP stage	**No. of images**	**Median**	**Min., Max.**	**Mean ± SD**	***P*-value**	**Median**	**Min., Max.**	**Mean ± SD**	***P*-value**
No ROP	66	122.44	98.53, 150.80	122.42 ± 10.02[bcd]	<0.0001[a]	123.75	88.62, 168.55	123.96 ± 16.55[d]	<0.0001[a]
Stage 1	28	117.12	87.48, 139.76	114.23 ± 14.95[be]		119.52	87.51, 157.29	120.79 ± 18.65[e]	
Stage 2	33	112.48	89.50, 135.30	111.87 ± 10.52[cf]		116.49	84.14, 147.49	115.26 ± 14.83	
Stage 3	49	92.15	57.66, 134.28	92.72 ± 13.93[def]		102.69	65.14, 160.09	102.86 ± 21.91[de]	

[a]*P-value was calculated using one-way ANOVA.*
bcdef: significant difference in the subgroup analysis between groups with the same letter.

Vessel Width Estimation

We used an RT-based algorithm to estimate the width of the vessels in all fundus images (15). The RT-based algorithm is robust and can detect linear features well even in the presence of noise. The intensity of an image generally fluctuates due to the presence of noise; however, when an RT-based algorithm is employed, these fluctuations are eliminated through an integration process. We used an RT-based linear feature detection algorithm to extract the centerline of vessels. The RT over a two-dimensional Euclidean space can be derived as follows:

$$R(\rho,\theta) = \int_{-\alpha}^{+\alpha}\int_{-\alpha}^{+\alpha} g\left(x,\ y\right)\delta(\rho - x\cos\theta - y\ \sin\theta)dx\,dy \quad (1)$$

where $g(x,y)$ is the image intensity at position (x,y), δ is the Dirac delta function, ρ is the distance of the origin from the straight line along the line perpendicular to the straight line and going through the origin, and θ is the angle between the normal and the x-axis.

The RT algorithm emphasizes the linear features in an image because the intensity is integrated along all possible lines in the image. The presence of the Dirac delta function forces the integration of $g(x,y)$ along a line with the normal representation $\rho = x\cos\theta + y\sin\theta$ (19). The parts of fundus images that show vessels can have more varied intensity than that in the background in the image and may contain areas of vessel curvature. Through the RT algorithm, vessel curvature and diameter could be estimated from previous values. Areas of curvature could be identified using a Gaussian process and by distinguishing positive from negative values by using means of zero. Initially, a center point on a vessel was selected manually and then defined as the centerline (Cn); the target direction point on the vessel was subsequently specified to predict the direction of Cn. The RT algorithm assigned a weight (ranging between 0 and 1) to each pixel on the basis of its distance from the selected Cn. The pixels nearer the selected Cn were assigned higher weights. A total of 179 vectors were formed near the selected Cn by computing the line integrals through cubic interpolation (**Figure 1A**). On the basis of the target direction and the similarity in intensity of the center pixels (compared with the vessel edge pixels), the corresponding Cn was calculated from the initial center point and moved a step forward. This process was continued until the target point was reached.

To determine vessel width, another RT with parallel line integrals was calculated in the vessel direction (**Figure 1B**).

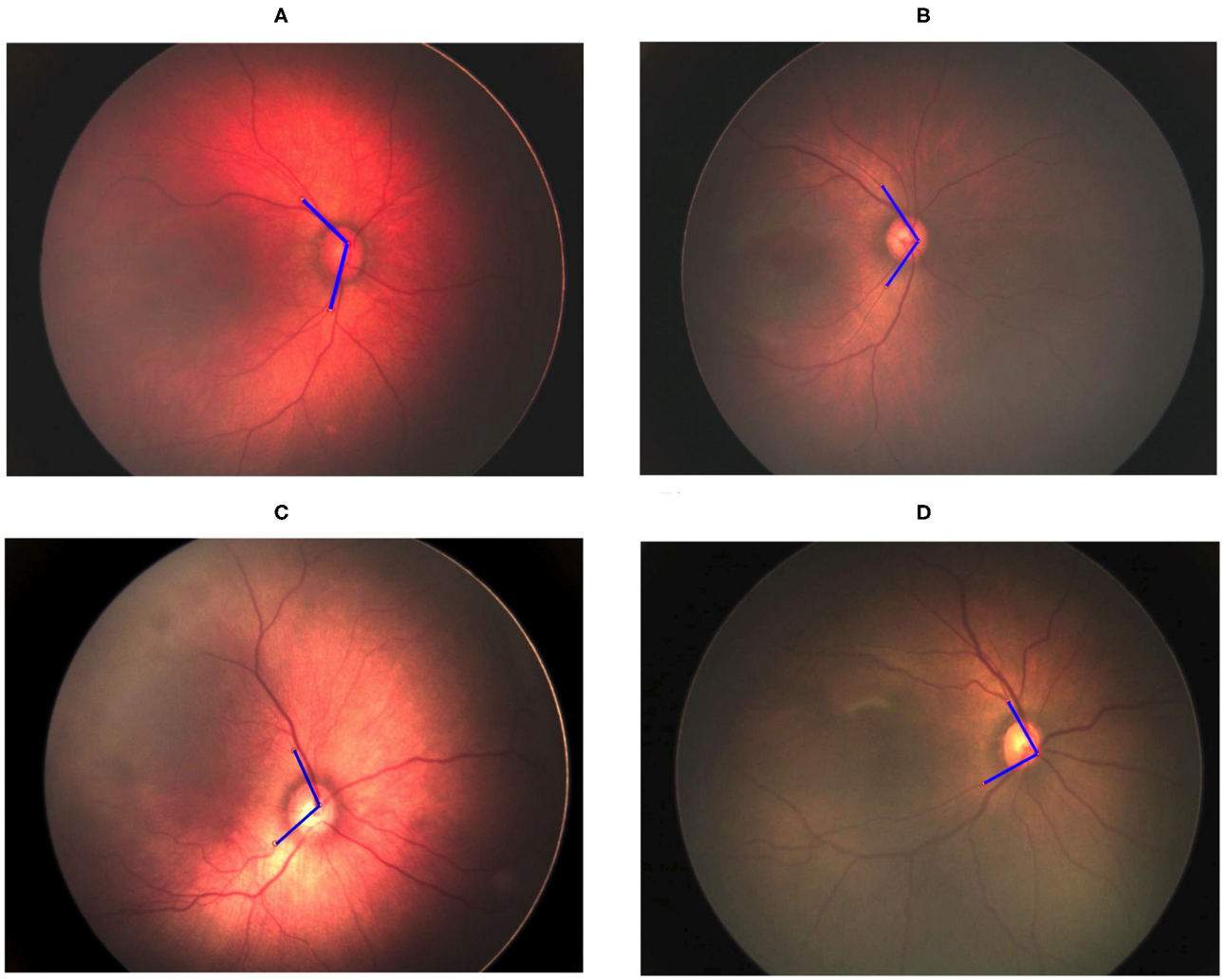

FIGURE 2 | Gradual decrement in TAA from no ROP to stage 3 ROP. **(A)** No-ROP, **(B)** stage 1 ROP, **(C)** stage 2 ROP, and **(D)** stage 3 ROP groups, with angles 128.60°, 112.63°, 107.84°, and 89.50°, respectively. The blue lines indicate the direction of temporal retinal vessels.

Because the boundaries of vessels are typically darker than the background of vessels, vessel edges could be determined. The diameter could be computed by calculating the Euclidean distance between the top-edge pixels and corresponding bottom-edge pixels. The average of these values was considered the vessel width.

We considered up to 100 pixels in length when determining vessel width because the TAA and TVA measurements were conducted near the optic disc. The superior and inferior artery and vein widths on the temporal side of the retina were quantified using the RT algorithm. We obtained the temporal artery width (TAW) and temporal vein width (TVW) by averaging the superior and inferior artery widths and vein widths, respectively. We obtained TAW and TVW values from all images, except for three images from patients with stage 2 ROP, from which we could not derive TAW values. Specifically, in these three images, we could accurately determine only the inferior artery width because an adjacent vein overlapped the artery in the images.

Statistical Analysis

The data in the datasets were confirmed to be normally distributed before they were analyzed. The data were subjected to one-way analysis of variance (ANOVA) to identify significant differences among the no-ROP, stage 1, stage 2, and stage 3 groups. Subsequently, Tukey's multiple-comparison test was performed to compare subgroups. To determine TAA–TVA and TAW–TVW correlations, we employed Pearson's correlation, calculating the correlation coefficient r. Statistical analysis was conducted using GraphPad Prism software 9.0 (GraphPad Software, San Diego, CA, USA). $P < 0.05$ was considered statistically significant.

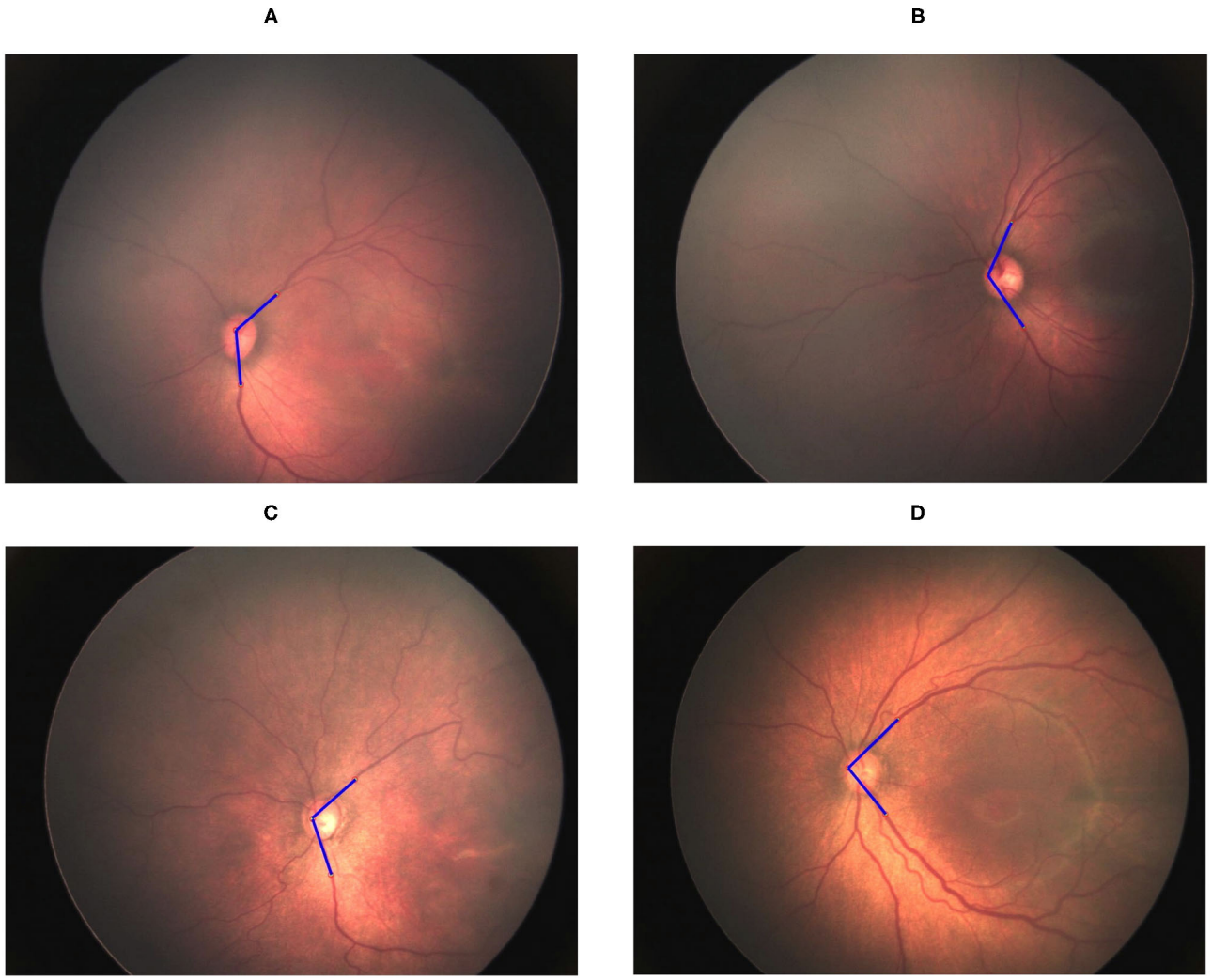

FIGURE 3 | Gradual decrement in TVA from no ROP to stage 3 ROP. **(A)** No-ROP, **(B)** stage 1 ROP, **(C)** stage 2 ROP, and **(D)** stage 3 ROP groups, with angles 131.50°, 127.12°, 114.4°, and 95.18°, respectively. The blue lines indicate the direction of temporal retinal vessels.

RESULTS

A total of 176 fundus images from 118 preterm infants were used in this study's analysis. All images were from different eyes; in addition, images from both eyes from 60 patients were included.

Determination of Retinal Vessel Angle

The vessel angle was determined through vessel tracing. The mean TAA values in the no-ROP, stage 1 ROP, and stage 2 ROP groups were 122.42° ± 10.02°, 114.23° ± 14.95°, and 111.87° ± 10.52°, respectively. The mean TAA in the stage 3 ROP group was 92.72° ± 13.93°. The TAA was thus smaller at higher degrees of severity (no ROP vs. stage 3 ROP, $P < 0.0001$; **Table 2**). Similar observations were made for the TVA. The mean TVA values in the no-ROP, stage 1 ROP, stage 2 ROP, and stage 3 ROP groups were 123.96° ± 16.55°, 120.79° ± 18.65°, 115.26° ± 14.83°, and 102.86° ± 21.91°, respectively ($P < 0.0001$). Representative TAAs and TVAs in various ROP stages are displayed in **Figures 2**, **3**, respectively.

Determination of Vessel Width

The TAW was obtained by averaging the widths of the superior and inferior arteries in all images, except for three images from a patient with stage 2 ROP. For those three images, we could only determine the inferior artery width because the superior artery was overlapped by an adjacent vein, which made it difficult to determine the width accurately. In these cases, we used only the inferior vessel width as the TAW in the analysis.

We observed significant differences among the ROP severity groups in terms of both the TAW and TVW ($P < 0.0001$ and $P = 0.0044$, respectively; **Table 3**). In the subgroup analysis, the TAW and TVW in the

TABLE 3 | TAW and TVW in various stages of ROP.

ROP stage	No. of images	TAW (pixels)				TVW (pixels)			
		Median	Min., Max.	Mean ± SD	*P*-value	Median	Min., Max.	Mean ± SD	*P*-value
No ROP	66	4.31	3.03, 5.20	4.21 ± 0.51^{b}	$<0.0001^{a}$	5.66	4.26, 7.03	5.63 ± 0.60^{b}	$= 0.0044^{a}$
Stage 1	28	4.29	3.36, 5.18	4.22 ± 0.49^{c}		5.75	4.78, 6.75	5.75 ± 0.52	
Stage 2	33	4.04	3.44, 5.07	4.10 ± 0.39^{d}		5.59	4.04, 6.97	5.61 ± 0.68^{d}	
Stage 3	49	4.59	3.46, 5.99	4.58 ± 0.59^{bcd}		6.29	4.43, 6.98	6.03 ± 0.65^{bd}	

[a]*P-value was calculated using one-way ANOVA.*
bcd: significant difference in the subgroup analysis between groups with the same letter.

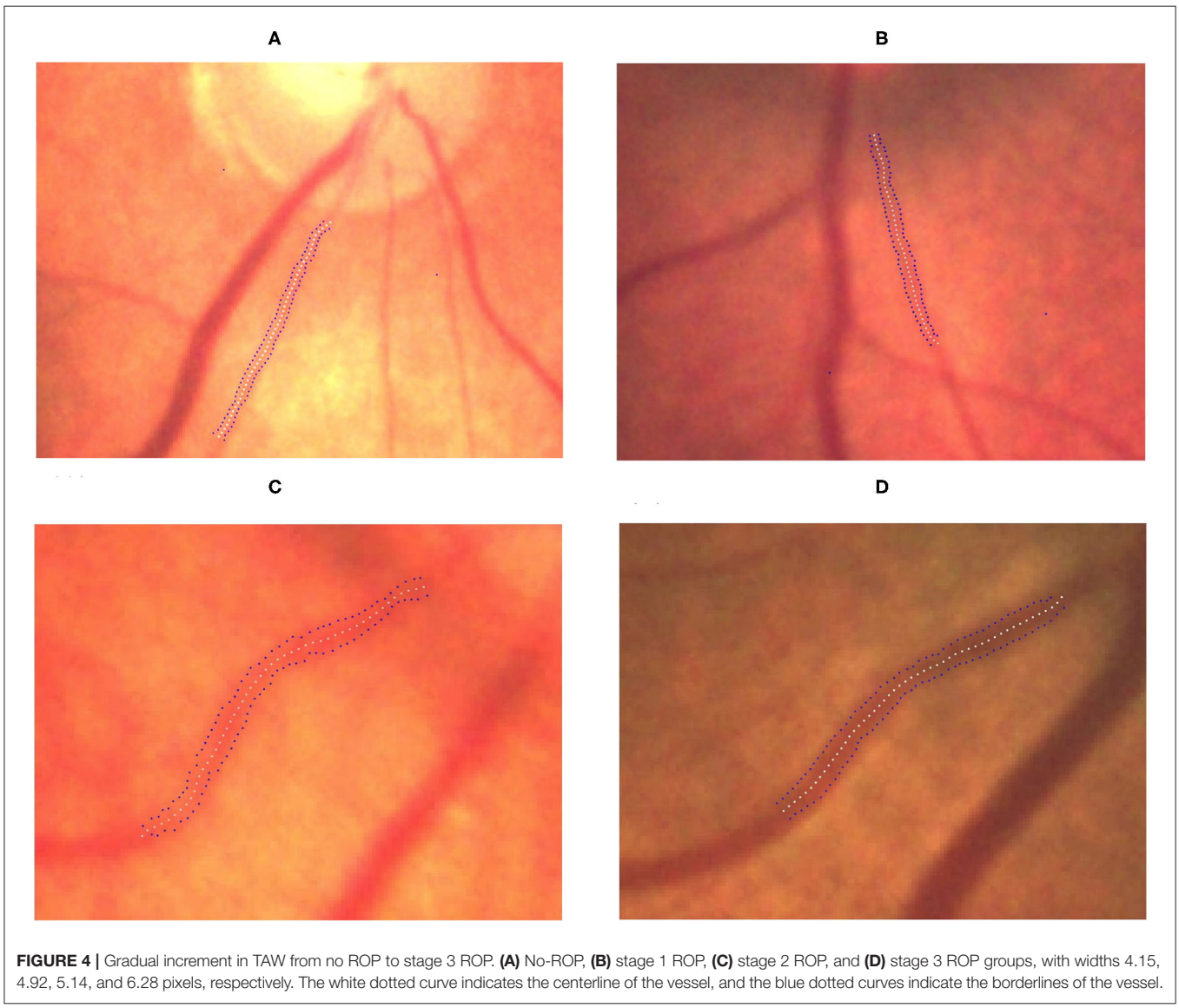

FIGURE 4 | Gradual increment in TAW from no ROP to stage 3 ROP. **(A)** No-ROP, **(B)** stage 1 ROP, **(C)** stage 2 ROP, and **(D)** stage 3 ROP groups, with widths 4.15, 4.92, 5.14, and 6.28 pixels, respectively. The white dotted curve indicates the centerline of the vessel, and the blue dotted curves indicate the borderlines of the vessel.

stage 3 ROP group were significantly greater than those in the no-ROP group (both $P < 0.05$). Representative figures of the TAW and TVW are presented in **Figures 4**, **5**, respectively.

Correlation of Vessel Angle With Vessel Width

The correlations between the vessel angles and vessel widths, for all stages of ROP, were plotted. Linear regression analysis

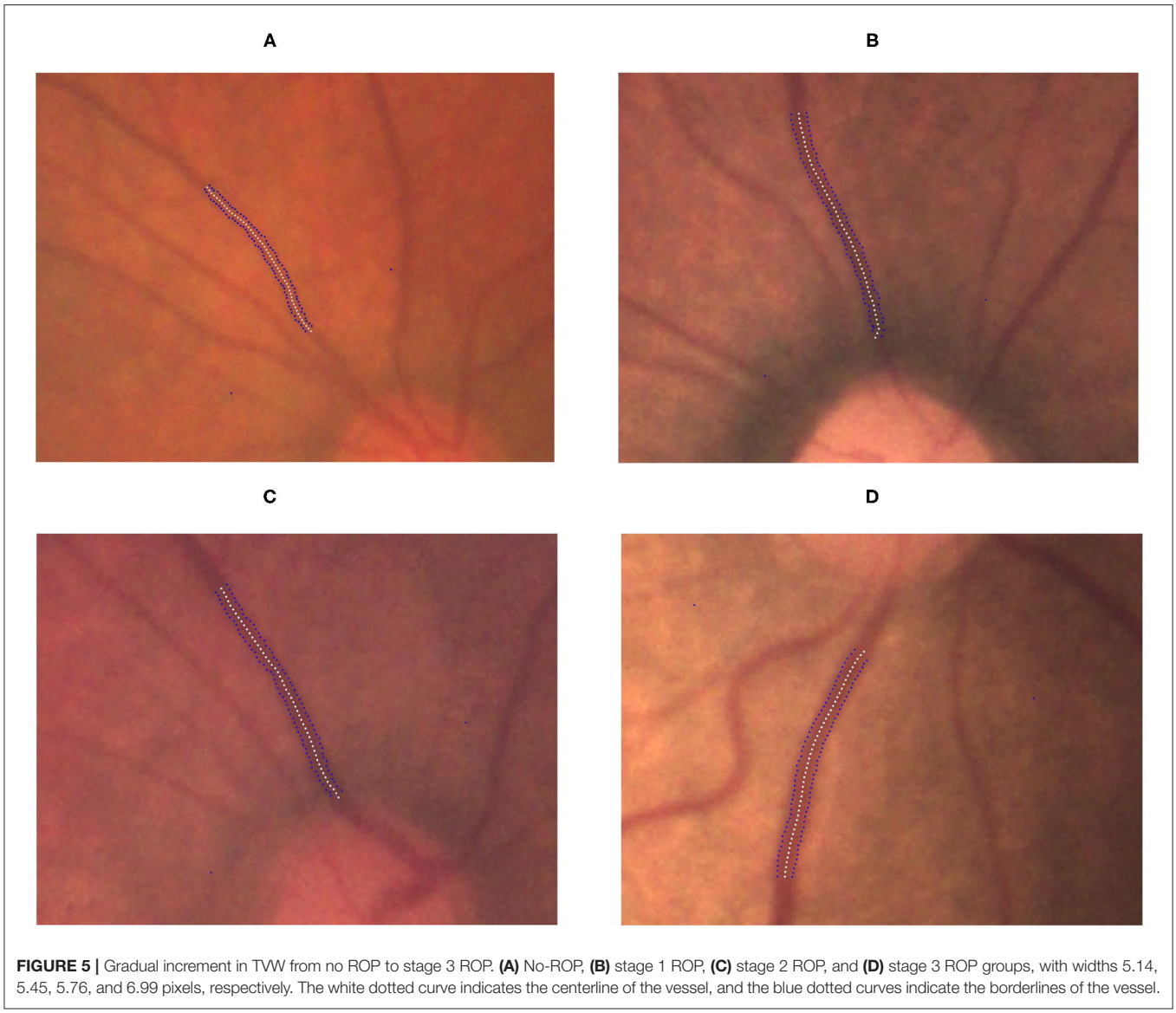

FIGURE 5 | Gradual increment in TVW from no ROP to stage 3 ROP. **(A)** No-ROP, **(B)** stage 1 ROP, **(C)** stage 2 ROP, and **(D)** stage 3 ROP groups, with widths 5.14, 5.45, 5.76, and 6.99 pixels, respectively. The white dotted curve indicates the centerline of the vessel, and the blue dotted curves indicate the borderlines of the vessel.

of each correlation was conducted to determine the correlation coefficient r for the TAA–TVA, TAW–TVW, TAA–TAW, TVA–TVW, TAA–TVW, and TVA–TAW correlations irrespective of the stage (**Figures 6**, **7**).

DISCUSSION

The present study obtained some notable findings. We discovered a significant decrease in the TAA and TVA and an increase in the TAW and TVW with increasing ROP severity (all $P < 0.0001$). In addition, we observed positive correlations between the TAA and TVA and between the TAW and TVW ($r = 0.411$, $P < 0.0001$; $r = 0.362$, $P < 0.0001$, respectively); we also noted negative correlations between the TAA and TAW ($r = -0.162$, $P = 0.0314$), the TAA and TVW ($r = -0.282$, $P = 0.0002$), and the TVA and TAW ($r = -0.082$, $P = 0.2787$). According to our review of the literature, this is the first study to investigate the relationship between temporal vessel angles and widths for various stages of ROP. Subtle retinal vessel changes are crucial because they can assist clinicians in the early detection of ROP and its progression. Serial information on vessel angle and width can indicate whether ROP is progressing or regressing. The identification of ROP progression to a higher stage in an eye gives surgeons time to react so that treatment can be performed without delay once stage treatment-requiring ROP is reached. In the future, the identified features could be incorporated into an algorithm for automatic ROP diagnosis in the era of telemedicine and artificial intelligence.

Previous studies have attempted to investigate how vessel angles vary in preterm infants with and without ROP (10, 11). In one of these studies, the TVA was manually measured by drawing an axis perpendicular to the fovea and optic disc center by using points on the vessels that vertically divided the fovea (10). The study focused on measuring retinal vein angles only.

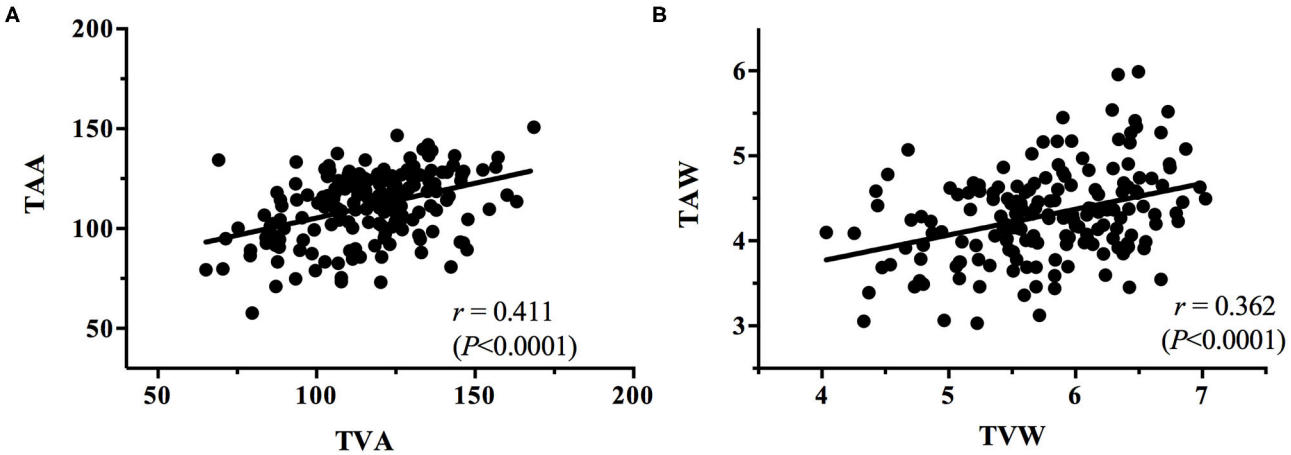

FIGURE 6 | Plots of the correlations between **(A)** TAA and TVA and **(B)** TAW and TVW.

In another study, the optic disc center was used to measure the artery and vein angles semiautomatically (11); the results revealed no significant differences between the no-ROP and mild-ROP (stages 1 and 2) groups, but they indicated a significant difference in vessel angle between the no-ROP and severe-ROP (stage 3) groups. In the present study, we initially applied the strategy employed in that study to our dataset, using the optic disc center to find the vessel angles. However, we observed that the strategy did not always correctly reflect the vascular angle in images because not all the vessel intersection points were located at the optic nerve center. Hence, in this study, we modified the methodology for measuring the angles. The superior and inferior vessels were traced back toward the optic disc to their point of intersection. The angle at this intersection point was considered the vessel angle. We noted that the current method is more reliable and precise in accurately determining the vessel angle.

The present study revealed an inverse relationship between ROP stage and the temporal vascular angle. The mean TAA and TVA decreased gradually from no ROP to stage 1, stage 2, and stage 3 ROP. These results indicate the progressive stretching of retinal vessels through fibrovascular proliferation as ROP progressed. Wilson et al. (10) reported that the mean differences in TVA between no-ROP and stage 3 ROP groups were 6.1° and 0.9° in the right and left eyes, respectively. Wong et al. (11) indicated that the differences in median TAA and TVA between no-ROP and stage 3 ROP groups were 16° and 13°, respectively. In the present study, the differences in median TAA and TVA between the no-ROP and stage 3 ROP groups were 30.29° and 21.06°, respectively (**Table 2**), considerably greater than the previously reported differences (10, 11). Wong et al. (11) hypothesized that after premature birth, the arteriole angle is more strongly affected than the venule angle. In our study, the retinal artery angle and retinal vein angle were equally significantly affected by ROP disease progression, and these angles were correlated with the vessel width.

In addition to a decrease in vessel angle, we observed variations in vessel width for the various stages of ROP. Retinal vessel dilatation, which is part of the parameters of plus disease, may be related to an increased vascular endothelial growth factor level in ROP eyes (20, 21). We estimated the vessel widths in all stages of ROP by using an RT-based algorithm that can detect linear features precisely even in the presence of noise (14, 15). Our results reveal significantly larger TAW and TVW values in the stage 3 ROP group than those in the no-ROP group (**Table 3**). However, the difference between the no-ROP and stage 1 ROP groups and that between the no-ROP and stage 2 ROP groups were not significant. Our results suggest that in the early stages (stages 1 and 2) of ROP, vessel width may not be significantly affected by vessel angle alterations but that when the disease has reached stage 3, the width of the vessels becomes significantly altered.

The angles and widths of the arteries and veins were correlated. The vessel angle decrease (TAA vs. TAW; TVA vs. TVW) was associated with an increase in vessel width from the stage of no ROP to stage 3 ROP. Positive TAA–TVA and TAW–TVW correlations were identified (**Figure 6**), whereas negative TAA–TAW (**Figure 7A**), TAA–TVW (**Figure 7C**), and TVA–TAW (**Figure 7D**) correlations were observed. These data show that only one of these measurements must be used to obtain a meaningful outcome in future studies.

The key findings of this study are as follows. First, we confirmed the hypothesis that ROP severity is associated with the angle and width of arteries and veins. The relationship between the temporal vessel angles and widths is a novel finding and, to our knowledge, has not been reported by previous studies. Second, other studies have measured the retinal angle centered in the optic disc, which is inaccurate because not all vessels intersect at the disc center. We measured the vessel angle as the vessels exited the disc margin and extended the line until intersection; this method can better reflect the actual angles of the vessels. Third, the measurement of the temporal vessel width was performed using RT, a new approach that provided reliable outcomes. The subtle retinal vascular changes that were discovered as ROP progresses can

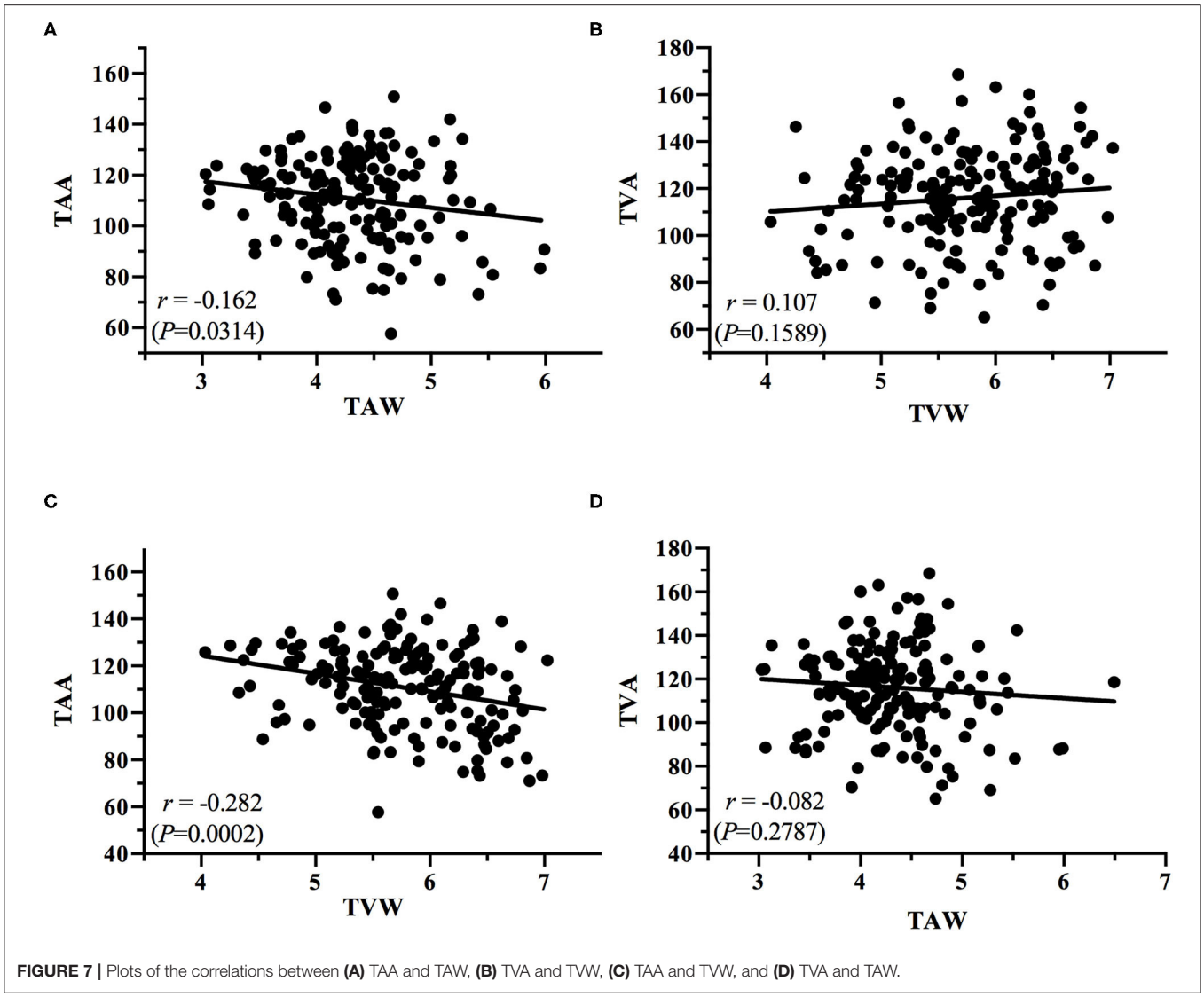

FIGURE 7 | Plots of the correlations between **(A)** TAA and TAW, **(B)** TVA and TVW, **(C)** TAA and TVW, and **(D)** TVA and TAW.

give clinicians objective feedback and aid clinical decision-making.

This study has some limitations. First, the dataset used contained fewer images from patients with stage 1 and 2 ROP compared with the number for no ROP and stage 3 ROP, which may have caused the lack of a difference in retinal vessel features between the no-ROP, stage 1 ROP, and stage 2 ROP groups. Second, artery and vein annotations had to be performed manually because of the large variation in the branching pattern of the retinal vessels, and this manual annotation is a time-consuming process. Third, because we did not sedate the infants while taking photographs, the infant may have moved during image capture, leading to the quality of the images not always being high quality and to difficulty in accurately determine vessel width.

In conclusion, this study demonstrated that the severity of ROP is related to retinal vessel angles and widths. We discovered an inverse relationship between ROP severity and retinal vessel angle, but we found a positive correlation between ROP severity and retinal vessel width. These data are valuable and could serve as indicators of disease progression or regression. Further study in this area is required. With the further development of artificial intelligence technology, the subtle changes discovered in the present study could be integrated with scientific computer-aided approaches to give clinicians an objective judgment of the progression or regression of ROP.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Chang Gung Memorial Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

Y-PH, SV, E-YK, and W-CW: conceptualization, investigation, and writing—review and editing. Y-PH and SV: methodology, formal analysis, and writing—original draft preparation. SV: software. Y-PH, E-YK, and W-CW: validation and supervision. Y-PH and W-CW: resources, project administration, and funding acquisition. E-YK and W-CW: data curation and visualization. All authors have read and agreed to the published version of the manuscript.

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Severe Retinopathy of Prematurity Associated With Neurodevelopmental Disorder in Children

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Objective: This study aimed to investigate whether severe retinopathy of prematurity (ROP) could be an association factor for neurodevelopmental disorders in premature infants without other risk factors—such as congenital anomalies, birth injuries, and neurological diseases—that may cause developmental delay.

Methods: We used health claims data recorded between 2007 and 2018 in the Korean National Health Insurance Service (KNHIS) database. We recruited a total of 18,256 premature infant born between 2007 and 2008 without congenital anomaly or birth injury (with ROP 6,995, without ROP 11,261) and divided them into four groups as follows: Group A, 209 extremely premature infants [gestational age (GA) < 28] with mild ROP; Group B, 75 extremely premature infants (GA < 28) with severe ROP; Group C, 6,510 other premature infants ($28 \leq$ GA < 37)with mild ROP; and Group D, 201 other premature infants ($28 \leq$ GA < 37) with severe ROP. Using regression analysis, we analyzed whether there was a correlation between ROP prevalence, severity, and developmental delay in premature infants without other risk factors.

Results: The prevalence of developmental delay, according to GA and ROP severity, was higher in patients with severe ROP than in the other patients. The prevalence gradually decreased after birth. Among extremely premature infants with ROP, those with severe ROP had a 3.082-fold higher association with neurodevelopmental complications than those with mild ROP ($p < 0.001$). Compared with other premature infants with ROP, those with severe ROP had a 3.269-fold higher association with neurodevelopmental complications than those with mild ROP.

Conclusion: The severity of ROP may be associated with neurodevelopmental disorders in premature infants.

Keywords: premature infants, retinopathy of prematurity, neurodevelopmental disorders, developmental delay, gestational age

INTRODUCTION

Recently, the birth rate of premature infants has been steadily increasing in South Korea; however, owing to the medical development of the neonatal intensive care unit (NICU), their survival has also increased (1–4). Since premature infants are more likely to have neurodevelopmental disorders than full-term infants and infants with a normal birth weight, the long-term neurodevelopmental prognosis of premature infants has gained attention (4–6). Early detection of neurodevelopmental delay in premature infants is important because early diagnosis and appropriate treatment can improve the patients' condition or alleviate their symptoms (4, 7). Therefore, the early identification of risk factors by conducting intensive developmental screening tests is imperative to classify high-risk groups for developmental delay (6, 8, 9).

Retinopathy of prematurity (ROP) is a disease wherein abnormal vascular proliferation occurs during retinal development in premature newborns (3, 10–12). As the incidence of premature births and low birth weight in newborns increases, the overall risk of ROP also increases (13, 14). Severe ROP is a major cause of childhood blindness, myopia, high myopia, disparity, amblyopia, and astigmatism strabismus. Additionally, continuous progression of ROP can lead to complications, such as secondary glaucoma and blindness, caused by retinal detachment secondary to fibrous tissue retinal traction. Nonetheless, most ROP cases undergo spontaneous regression during follow-up, without any special treatment (15). Recent studies have focused on the correlation between extraocular and neurodevelopmental complications, while previous studies have investigated the developmental and maturity status of the brain through imaging screening at a point in time (13, 16–18).

The age at diagnosis is different for each area of developmental delay in children; motor dysfunction is often detected early, while learning disabilities are only detected at an average age of 5–6 years (19). Thus, neurodevelopmental disorders should be assessed through continuous, long-term follow-up (7, 9), and are difficult to study using hospital-based data.

In this study, we aimed to investigate the association between ROP severity and neurodevelopmental disorders in children using the Korean National Health Insurance Service (KNHIS) database.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board (IRB no. 2018-04-001) of Hanyang University Guri Hospital, Gyeonggi-do, South Korea. The requirement for written informed consent was waived due to the retrospective study design. The research was conducted according to the tenets of the Declaration of Helsinki.

We used health claims data recorded between 2007 and 2018 in the KNHIS database. In South Korea, the health security system provides healthcare coverage to all citizens. The KNHIS database covers all citizens in South Korea and includes data regarding diagnoses, procedures, prescription records, medical treatment records, sociodemographic characteristics, and direct medical costs for claims made (11).

Participant Recruitment

We analyzed the health claims data recorded between 2007 and 2018 in the KNHIS database. In 2007, the National Health Screening Program for Infant and Children was initiated in Korea. Therefore, most children born after 2007 were regularly evaluated for development through health screening program (20). Consequently, we recruited premature infants born between 2007 and 2008 and followed them up for 10 years. Cases were identified according to the International Classification of Diseases, 10th edition (ICD-10). The KNHIS database manages claims using the Korean Classification of Disease, 6th edition, a modified version of the ICD-10 adapted for the Korean healthcare system (21).

A lower gestational age (GA) is associated with a higher probability of complications (22). Numerous other factors can cause neurological complications, such as birth injury and asphyxia. To account and adjust for possible errors, premature infants were divided into two groups: extremely premature infants (GA $<$ 28 weeks, diagnostic code P07.2), with a high possibility of neurodevelopmental complications, and "other premature infants" (GA, 28–37 weeks, diagnostic code P07.3), with a lower possibility of developmental complications. A comparative analysis was then performed within groups with similar possibility of neurodevelopmental complications.

In this study, we try to analyze the hazard ratio (HR) of having neurodevelopmental problems according to the severity of ROP among patients who less likely to have neurological disorders.

Therefore, we excluded other conditions that can cause neurological complications. The following diagnostic codes were excluded:

- Q000–Q002: anencephaly
- Q010, Q011, Q012, Q018: encephalocele
- Q02: microcephaly
- Q03, Q031, Q038, Q039: hydrocephalus
- Q040–Q049: malformations of the brain
- P910–P919: cerebral ischemia, periventricular leukomalacia (PVL), coma, acquired hydrocephalus
- P941, P942, P948, P949: hypertonia, hypotonia, floppy baby, muscle tone disorder
- P100–P159: birth injury
- P520–P529: intraventricular hemorrhage (IVH), subependymal hemorrhage
- P200–P219: asphyxia.

ROP

Retinopathy of prematurity was defined based on the diagnostic code (H35.1) within 180 days of the diagnosis of premature infants.

Severity of ROP

To classify ROP severity, patients were divided into two groups: mild and severe ROP. We defined patients who were diagnosed with ROP, but spontaneously healed without ophthalmic treatment, as the "mild ROP group." By contrast,

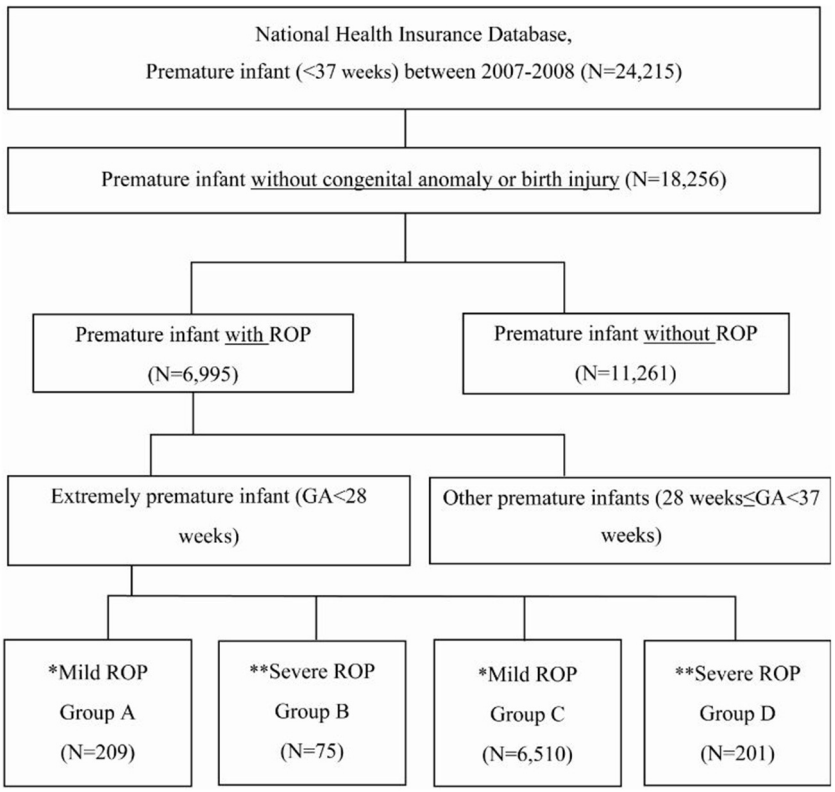


FIGURE 1 | Enrollment and grouping of study patients according to gestational age and retinopathy of prematurity severity. GA, gestational age. *Mild ROP: spontaneously healed without special treatment. **Severe ROP: underwent treatment for ROP.

patients who underwent ROP treatment after diagnosis were defined as the "severe ROP group."

Patients who underwent treatment were identified using procedure codes for pars plana vitrectomy (S5121-2), retinal detachment surgery (S5130), retinal photocoagulation (S5160), and cryopexy (S5140). We only included cases with the aforementioned procedure codes diagnosed within a year from ROP diagnosis to exclude treatment for other diseases. We assumed that the indications for treatment had been based on the treatment guidelines reported by the Early Treatment for Retinopathy of Prematurity Cooperative Group (ETROP) in 2003 (23): Indications for ROP treatment are type 1 ROPs (zone 1, any stage ROP with plus disease; zone 1, stage 3 ROP without plus disease; zone 2, stage 2 or 3 ROP with plus disease), and the treatment modalities include laser photocoagulation, cryotherapy, vitrectomy, or scleral bucking. Although there has been widespread use of intravitreal anti-vascular endothelial growth factor (VEGF) injections worldwide since the 2000–2010s (24, 25), the use of anti-VEGF in clinics began to be reported from the late 2000s in South Korea (26–29). And it was off-label use in South Korea, therefore, so it was not covered by the NHI service during the study period. Therefore, the treatment for ROP in the current study included the conventional treatment (laser photocoagulation, cryotherapy, vitrectomy, or scleral bucking).

We divided the infants into four groups (**Figure 1**): Group A, extremely premature infants with mild ROP; Group B, extremely premature infants with severe ROP; Group C, other premature infants with mild ROP; and Group D, other premature infants with severe ROP.

Neurodevelopmental Disorders

Neurodevelopmental disorders include three subcategories: neurocognitive function, speech and language, and motor function developmental disorders. Developmental disorders of neurocognitive function included delayed normal physiological development (R62.0), intellectual disability (F70.0–73.0, 78.0, 79.0), pervasive developmental disorder (F84.8, 84.9), and psychological developmental disorder (F89). Moreover, developmental disorders of speech and language included developmental disorders of speech and language (F80.0, 80.1, 80.8, 80.9), developmental disorders of scholastic skills (F81.9), and attention deficit (F90.0). Finally, motor developmental disorders included lack of coordination (R27.0, 27.8) and developmental disorders of motor function (F82, 83).

Statistical Analyses

We collected data of patients diagnosed with ROP among premature infants born between 2007 and 2008 and then followed-up their health insurance data for 10 years to confirm the diagnosis of neurodevelopmental disorders. The annual period prevalence of neurodevelopmental disorders over 10 years was calculated. We investigated whether there was a difference in

TABLE 1 | Annual prevalent number of cases and prevalence of overall neurodevelopmental complications among patients born between 2007 and 2008 with retinopathy of prematurity and treated, based on the KNHIS database throughout the 10-year follow-up period.

	GA < 28 weeks				28 weeks ≤ GA < 37 weeks			
	Mild ROP Group A (*N* = 209)		Severe ROP Group B (*N* = 75)		Mild ROP Group C (*N* = 6,510)		Severe ROP Group D (*N* = 201)	
Age	Prevalent case (*n*)	Period prevalence (%)	Prevalent case	Period prevalence (%)	Prevalent case	Period prevalence (%)	Prevalent case	Period prevalence (%)
0–1	70	24.65	29	38.67	623	9.28	41	20.40
1–2	59	20.77	31	41.33	324	4.83	12	20.90
2–3	32	11.27	17	22.67	235	3.50	25	12.44
3–4	25	8.80	16	21.33	227	3.38	16	7.96
4–5	24	8.45	14	18.67	179	2.67	15	7.46
5–6	17	5.99	11	14.67	176	2.62	16	7.96
6–7	21	7.39	9	12.00	193	2.88	24	11.94
7–8	13	4.58	7	9.33	191	2.85	18	8.96
8–9	14	4.93	7	9.33	184	2.74	17	8.46
9–10	12	4.23	6	8.00	194	2.89	17	8.46

GA, gestational age; KNHIS, Korean National Health Insurance Service; ROP, retinopathy of prematurity.

the prevalence between the severe ROP and mild ROP groups. Using regression analysis, we analyzed if there was an association between ROP prevalence and severity and developmental delay in premature infants without other risk factors. The annual period prevalence at each age was calculated by dividing the number of prevalent cases by population. A Cox proportional hazards regression model was used to calculate the HRs and 95% confidence intervals (CIs); HRs with CIs were estimated using logistic regression analysis adjusted for sex (male vs. female), year of diagnosis (2007 vs. 2008), income level (grouped based on income quintiles), and area of residence (metropolitan cities vs. others). The model included sex (male vs. female), income level of the patient's household (insurance payment classes: low vs. middle, high), area of residence (metropolitan cities vs. others), and year of premature diagnosis (2007 vs. 2008). Statistical significance was set at $p < 0.05$, and all analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC, USA).

RESULTS

Neurodevelopmental Disorders

Annual Prevalence of Total Neurodevelopmental Disorders After Birth Throughout the 10-Year Follow-Up Period

Comparing the prevalence of neurodevelopmental disorders according to ROP severity revealed that the prevalence of neurodevelopmental disorders was higher in patients with severe ROP (Groups B and D; **Table 1**). The prevalence of neurodevelopmental disorders in the first year of life was 24.65, 38.67, 9.28, and 20.40% in Groups A, B, C, and D, respectively. The prevalence gradually decreased after birth, from 24.65% in the first year to 4.23% after 10 years in Group A, 38.67–8.00% in Group B, 9.28–2.89% in Group C, and 20.4–8.46% in Group D (**Figure 2**). In both the extremely premature infant group and the other premature infant group, the prevalence was higher in the severe ROP group within the first year of life, even after 10 years.

Association With Neurodevelopmental Disorders According to ROP Severity

Among extremely premature infants with ROP, those with severe ROP had a higher association with neurodevelopmental disorders than those with mild ROP (hazards ratio: 3.082; $p < 0.001$).

Among other premature infants with ROP, those with severe ROP had a higher association with neurodevelopmental disorders than those with mild ROP (hazards ratio: 3.269; $p < 0.001$) (**Table 2**).

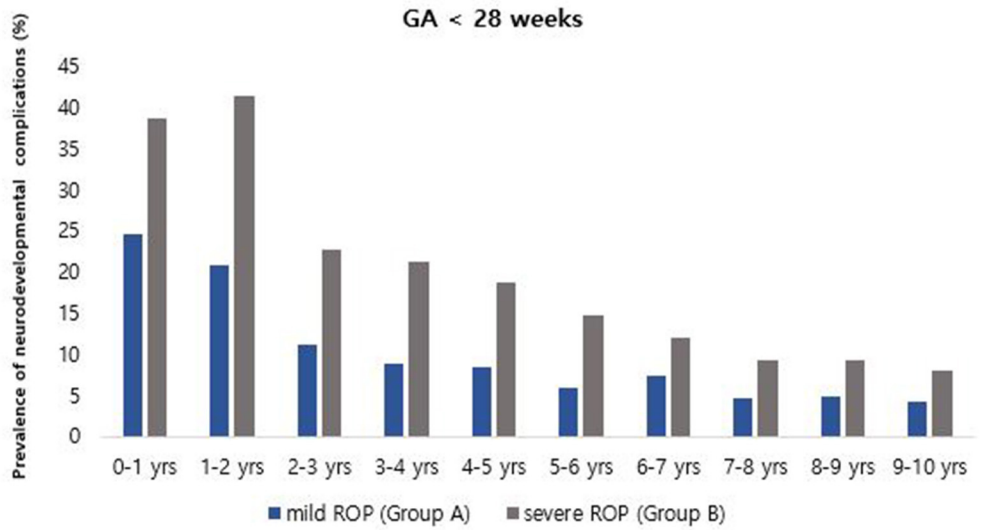
Detailed Neurodevelopmental Disorders in Premature Infants With ROP

We classified premature infants with ROP according to detailed neurodevelopmental disorders, including neurodevelopmental delay, neurocognitive functional, speech and language, and motor developmental disorders. Severe ROP had a higher association with each of the detailed neurodevelopmental disorders than those with mild ROP (neurodevelopmental delay, HR: 4.831; developmental disorders of speech and language, HR: 2.701; $p < 0.001$).

However, we couldn't obtain meaningful results for motor developmental delay and cognitive developmental delay due to the small number of patients.

DISCUSSION

In the present study, we found that the prevalence of neurodevelopmental disorders was higher in premature infants with severe ROP than in those with mild ROP, both in the first year of life and after 10 years. We tried to evaluate whether the prevalence of neurodevelopmental disorders differed based on



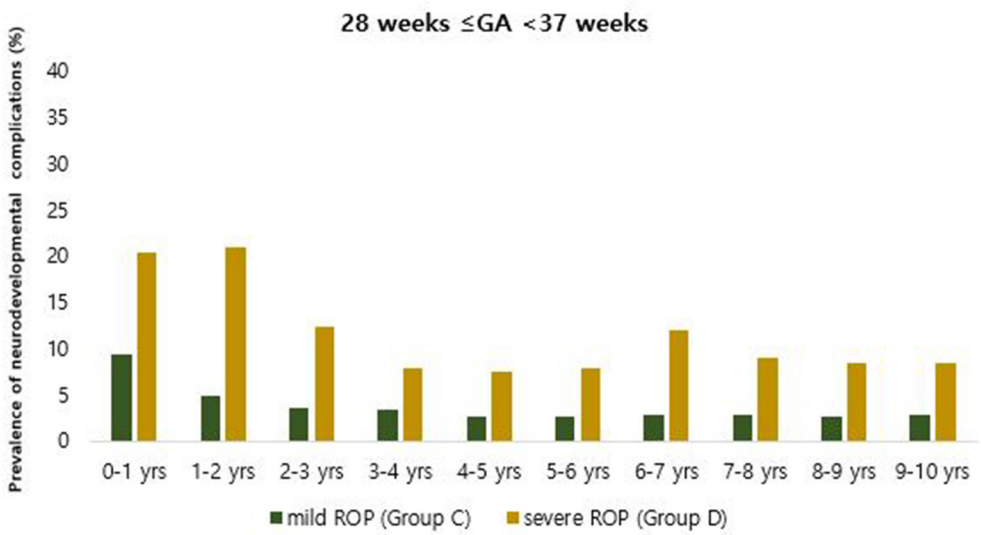


FIGURE 2 | Annual prevalence of overall neurodevelopmental complications among patients born between 2007 and 2008 with retinopathy of prematurity and treated, based on the Korean National Health Insurance Service database throughout the 10-year follow-up period.

the severity of ROP among the patients who were less likely to have neurological disorders, namely, those that were assumed to have the same possibility of suffering neurological developmental disorders. Moreover, this was the first to investigate long-term neurodevelopmental outcome of the ROP infants using nationwide population-based database.

We compared infants with a similar GA in the current study. Children with severe ROP generally have a lower GA, which is a risk factor for developing neurodevelopmental complications; therefore, this study selected patients within the same GA range with a similar probability of developing neurodevelopmental complications, classifying them based on ROP severity. We evaluated the association between developmental disorders and ROP severity in each group with similar risk of neurodevelopmental complications.

Intraventricular hemorrhage, PVL, and birth asphyxia, etc., are important risk of neurodevelopmental complications. Their severity is based on the levels and grades. To analyze the health insurance database, we used diagnostic codes to identify patients who have disorders/diseases, and the severity of IVH,

TABLE 2 | Crude and adjusted hazard ratios of neurodevelopmental complications according to retinopathy of prematurity severity, sex, and income level during the 10-year follow-up of premature infants.

	GA < 28 weeks							28 weeks ≤ GA < 37 weeks						
	Crude			Adjusted				Crude			Adjusted			
	HR	95% CI		HR	95% CI		*P*-value	HR	95% CI		HR	95% CI		*P*-value
ROP severity	2.844	1.974	4.099	**3.082**	**2.128**	**4.465**	**<0.001**	3.16	2.561	3.912	**3.269**	**2.644**	**4.043**	**<0.001**
Sex	0.718	0.499	1.034	0.695	0.479	1.009	0.056	0.744	0.663	0.835	0.738	0.658	0.828	0.001
Income level	0.943	0.582	1.53	0.925	0.565	1.515	0.756	0.946	0.8	1.119	0.936	0.792	1.108	0.4433
Region	0.771	0.539	1.104	0.68	0.47	0.984	0.113	1.039	0.928	1.162	1.067	0.952	1.195	0.2647
Year of diagnosis	0.94	0.657	1.345	0.905	0.625	1.31	0.5966	1.074	0.96	11.203	1.099	0.982	1.231	0.1005

The bold letters used to emphasize that the severity of ROP significantly increased the HR of neurodevelopmental complications in both GA <28 and GA 28–37 groups. GA, gestational age; HR, hazard ratio.

PVL, and birth asphyxia cannot be evaluated based on the diagnostic codes. Thus, we had to exclude patients who were diagnosed with other neurologic disorders, such as IVH and PVL, the severity of which would have affected the occurrence of neurodevelopmental complications.

Additionally, because there are differences in the frequency of neurodevelopmental evaluation and implementation of neurodevelopmental interventions according to the area of residence (metropolitan cities vs. others) and income level of patient's household (insurance payment classes: low vs. middle and high), these factors were adjusted. Even after adjusting for income level and area of residence, we found that a higher ROP severity was associated with a higher prevalence of neurodevelopmental disorders; therefore, severe ROP is likely to be associated with developmental and neurological disorders 10 years later in premature infants.

In our study, the prevalence of neurodevelopmental disorders was the highest during the first year of life and gradually decreased. Those with additional risk factors for early death—such as congenital anomalies and birth injuries—were excluded at the time of enrollment. So our study is based on the assumption that the missing data caused by death would have had little effect on the outcome. Therefore, the decreasing prevalence observed with increasing age was not attributed to early death. Since developmental delay requires continuous observation of the child's condition and recognition of associated abnormalities, diagnosis takes a considerably long time. Additionally, some developmental disorders can only be diagnosed after a certain period of time; therefore, some disorders may not have been diagnosed during the follow-up period of 10 years (study duration). As a result, the number of diagnosed patients may be lower than the actual prevalence. Further, we have used diagnosis codes to evaluate the prevalence each year. The neurodevelopment complications included all the severity stages from the lowest to the highest and developmental delay in the early assessment may naturally improve in cases with mild developmental delay while growing up. And another possible reason is that although many patients are diagnosed with neurodevelopmental disorders at an early age, their developmental status may have improved through early diagnosis, intervention, and developmental therapy. This demonstrates the importance of early detection and intervention in neurodevelopmental disorders.

Neurodevelopmental disorders are common, with a high prevalence of about 5–10%, in children (30, 31). With the recent increase in the survival rate of high-risk infants, the prevalence of developmental disorders has also increased. As of 2016, the prevalence of developmental disabilities in premature infants was 23% (7). In the mild ROP group in our study, the prevalence of developmental delay was approximately 10%, similar to the prevalence in the general population (5–10%) and slightly lower than in the general premature infant population (23%), due to the exclusion criteria. Meanwhile, the prevalence of developmental delay in the severe ROP group in our study was approximately 25%, which is higher than in both the general (5–10%) and general premature infant (23%) populations. These findings suggest that the severity of ROP may be associated with developmental delay.

Retinopathy of prematurity is known to cause severe ophthalmic complications, such as blindness, myopia, anisometropia, amblyopia, astigmatism strabismus, and secondary glaucoma (32–35). Several recent studies have reported a correlation between severe ROP and extraocular complications, particularly neurodevelopmental complications (16, 17). Drost et al. reported that severe ROP (stage 3–4) was associated with lower cerebellar and brainstem volumes and poorer neurodevelopmental outcomes (36). Moreover, ROP requiring treatment was associated with lower fractional anisotropy in the posterior white matter and decreased maturation measures in the optic radiation, internal capsule, and external capsule (16, 18). This suggests that brain abnormalities are frequent among children with ROP (18); furthermore, ROP requiring treatment increased the risk of motor impairment, cognitive impairment, or hearing loss (16, 17). While previous studies investigated the developmental and maturity status of the brain through imaging screening at a point in time, this study additionally investigated the annual change in prevalence for 10 years using the KNHIS database, which is another strength of this study. Children grow and develop as a result of interactions between innate attributes—such as physical

conditions, disposition, and cognitive abilities—and external factors, such as nutrition and environment (19, 31, 37). The molecular etiology of the relationship between the development of ROP and oxygen therapy thus demonstrates the role of VEGF in the development of retinal blood vessels, proliferation of endothelial cells, and formation and movement of blood vessels (10, 13, 38). Angiogenesis normally occurs in the physiological hypoxic environment of the uterus; however, during the administration of high oxygen pressure for therapeutic purposes after birth, transcription decreases, inhibiting angiopoiesis (14, 34, 38). By contrast, excessive transcription is induced when the oxygen pressure is low, and angiogenesis occurs in the avascular region (10, 15, 34). Whether these changes in the mechanisms of angiogenesis affect the brain or the change in visual stimuli caused by ROP affects developmental delay remain unidentified; thus, further studies with larger cohorts are required.

This was a large-scale data analysis with a sample size of 6,995 patients using data from the KNHIS database. To the best of our knowledge, this is the first study to demonstrate a relationship between ROP and neurodevelopmental disorders using a nationwide population-based database. The KNHIS database, organized by the National Health Insurance of Korea, includes all citizens of South Korea and includes data regarding their diagnoses, procedures, prescription records, medical treatment records, sociodemographic characteristics, and direct medical costs (21). It is noteworthy that all premature infants born in Korea and diagnosed with ROP between 2007 and 2008 were included in the study. Additionally, our study was designed to identify cases in which neurodevelopmental disorder was diagnosed later among patients diagnosed with ROP; therefore, we also demonstrated that ROP could be a risk factor for neurodevelopmental disorders. To prove this, future studies should confirm more precise causality. If severe ROP is determined as a risk factor for developmental delay, it is imperative to include severe ROP in the criteria of neurodevelopmental screening tests for premature infants. Classification of patients with severe ROP as a high-risk group for neurodevelopmental disorders will therefore facilitate early diagnosis and screening tests for appropriate intervention and treatment. Pediatricians currently pay great attention to use of oxygen therapy in NICU to prevent ROP (38). Additional efforts will be required to prevent possible long-term neurodevelopmental disorders.

The present study had several limitations; first, this was not a prospective cohort study. We used data from the KNHIS database, identified by diagnostic codes and registered by clinicians; the accuracy of the data may therefore differ depending on the accuracy of the diagnostic code determined by the physician and whether the code was deleted or added according to the condition evaluated yearly. Additionally, since patients with diagnostic codes indicating trauma or birth injury were excluded only in the early stage of birth, the possibility of neurodevelopmental complications due to other diseases or trauma at a later time cannot be excluded. Moreover, there could be a detection bias in the young age group during follow-up. Some neurodevelopmental complications are more likely to be diagnosed when a child can undergo a developmental test or around school-going age; therefore, prevalence—especially in younger children—should be interpreted in the context of detection bias. And it is difficult to know if a decrease in the cases with diagnosis codes indicates the actual improvement over time or faults in the early assessment. Finally, neurodevelopment complications may be related to the adverse events during the NICU stay (i.e., mechanical ventilation, NEC, PVL, IVH, etc.), which affect the general well-being of the infant. Although we set exclusion criteria to exclude infants diagnosed with other neurologic disorders which could confound the results of the present study, such adverse events could not be excluded, as it will lead to much loss of the enrolled patients. It should be considered as one of the limitations of a big data-based study based on the diagnostic codes.

Despite these limitations, we enrolled patients with the same probability of developing neurodevelopmental complications as possible. When comparing the prevalence of neurodevelopmental complications according to the severity of ROP in the group considered to have the same risk of neurodevelopmental complication, it can be regarded as reliable that the prevalence of neurodevelopmental complications was higher in the severe ROP group than in the mild ROP group.

CONCLUSION

In conclusion, the present study reported on developmental delay in premature infants with ROP in South Korea using the KNHIS database, over a 10-year follow-up period. There was a significantly higher association with developmental delay in patients with severe ROP than in those with mild ROP, suggesting that severe ROP is associated with developmental and neurological disorders in premature infants. If severe ROP is determined as a risk factor for developmental delay through further research, it is imperative to include severe ROP in the criteria of developmental screening tests for premature infants.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board (IRB no. 2018-04-001) of Hanyang University Guri Hospital, Gyeonggi-do, South Korea. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Y-JC and EH conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. YS, GB, and IK designed the data collection instruments, collected

data, carried out the initial analyses, and reviewed and revised the manuscript. IK and HC conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Aggressive Posterior Retinopathy of Prematurity: Long-Term Outcomes Following Intravitreal Bevacizumab

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Purpose: The purpose of this study is to review the neonatal and early childhood course of children who were treated with intravitreal bevacizumab for APROP and identify any long term limitations these children face years after treatment.

Methods: This retrospective consecutive case series reviewed both ophthalmologic and pediatric medical records to determine ocular and neurologic function following treatment with a single injection of intravitreal bevacizumab (IVB) for APROP. Patient records were reviewed to identify the gestational age, average birth weight, gender, post-menstrual age (PMA) at the time of injection, regression status, rescue therapy events, final visual acuity, final refraction, ophthalmologic diagnoses and complications, neurologic diagnoses, and duration of follow up.

Results: The study included 43 eyes from 13 male and 9 female children. The average gestational age was 24 weeks and average birth weight was 625.2 grams. The average follow-up was 4.08 years (range: 1.85–7.36 years). The average PMA at time of bevacizumab injection was 35.59 weeks. Thirty-five eyes eventually received laser photocoagulation at an average PMA of 53.17 weeks. All eyes in this study demonstrated regression without progression to retinal detachment. At last follow up, 67% (29/43) of eyes were able to discern letters or shapes, with an average visual acuity of 20/37. 16 (72%) children were diagnosed with perinatal neurological disorders. 59% ($n = 13$) developed chronic neurological impairment, 77% ($n = 10$) of whom developed neurodevelopmental delay. Several infants were diagnosed with endocrine disease or genetic syndromes.

Conclusions: Extreme prematurity is associated with significant morbidity. Nearly all infants (92%) who developed chronic neurologic disease were diagnosed with neurologic disease during the perinatal period. Intravitreal bevacizumab, often with adjuvant photocoagulation, led to regression without detachment in 100% of eyes, with most verbal children retaining functional vision.

Keywords: aggressive posterior retinopathy of prematurity, APROP, bevicizumab, intravitreal injection, laser, premature (babies), neurodevelopmental outcomes, ophthalmic outcomes

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INTRODUCTION

Retinopathy of prematurity (ROP) is one of the most common causes of blindness in children. It is a vasoproliferative disorder that occurs in two stages. First, preterm birth exposes infants to a relative hyperoxic environment. Hyperoxia decreases production of growth factors including vascular endothelial growth factor (VEGF) in the retina, leading to delayed vascular maturation. Second, as the retina matures, the increased metabolic activity overwhelms the oxygenation supply from the existing vascular supply resulting in retinal ischemia. This in turn results in increased production of VEGF leading to abnormal neovascular proliferation (1, 2).

Aggressive Posterior Retinopathy of Prematurity (APROP) is a rapidly progressing form of ROP characterized by its posterior location, presence of plus disease, and ill-defined features (3, 4). These eyes tend to have a poorer prognosis with a retinal detachment rate as high as 45% (5).

Laser photocoagulation was initially established as the standard of care by the Early Treatment for ROP (ETROP) Study (6). However, intravitreal bevacizumab (IVB), an anti-vascular endothelial growth factor (anti-VEGF) agent, was later shown to be effective in treating ROP through the Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT-ROP) trial (7). Today, although both laser and intravitreal bevacizumab (IVB) continue to be used in initial management of type 1 ROP, bevacizumab has become a critical component of the management of APROP (8). Bevacizumab is preferred to laser photocoagulation because it is a less invasive, shorter procedure, and has a decreased recurrence rate of zone 1 ROP (7). Moreover, laser photocoagulation in APROP can present technical challenges due to the presence of a persistent tunica vasculosa lentis, hazy vitreous, and difficulty in distinguishing the border between vascularized and non-vascularized retina (9, 10).

However, robust randomized controlled trials regarding the long term ophthalmic and systemic outcomes of intravitreal bevacizumab are lacking. There is longstanding concern that anti-VEGF medications have adverse systemic effects on these premature infants, particularly their neurodevelopmental outcomes. The purpose of this study is to review the neonatal and early childhood course of children who were treated with intravitreal bevacizumab for APROP and identify any chronic functional limitations these children face years after treatment.

METHODS

This retrospective consecutive case series reviewed both ophthalmologic and pediatric medical records to determine ocular and neurologic function following treatment with intravitreal bevacizumab for APROP. The protocol was exempted for review by the VSRF Salus Institutional Review Board and was compliant with the Health Insurance Portability and Accountability Act. The study adhered to the tenets of the Declaration of Helsinki.

A total of 43 eyes of 22 premature infants born over a 2-year period met inclusion criteria. The study included 13 males and 9 females. All infants were diagnosed with APROP and treated with a single intravitreal injection of bevacizumab. Patient records were reviewed to identify the gestational age, average birth weight, gender, post-menstrual age (PMA) at the time of injection, regression status, rescue therapy events, final visual acuity, final refraction, ophthalmologic diagnoses and complications, neurologic diagnoses, and duration of follow up. All neuro-developmental testing performed on this cohort was assessed by Bayley Scales of Infant and Toddler Development, third edition.

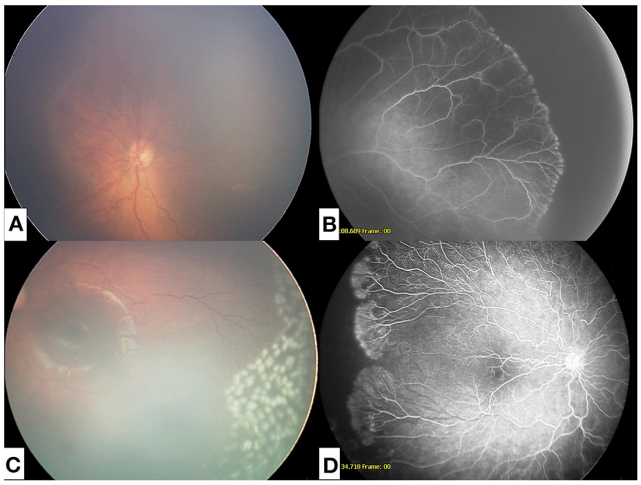

FIGURE 1 | (A) Fundus photograph at time of diagnosis of APROP. **(B)** Fluorescein angiogram of APROP demonstrating peripheral non-perfusion. **(C)** Fundus photograph of regressed APROP following intravitreal injection with bevacizumab and modified peripheral photocoagulation. **(D)** Fluorescein angiogram of reactivated APROP following intravitreal bevacizumab.

Treatment

Laser photocoagulation was used as adjunctive therapy for patients in this cohort. The typical treatment practice pattern observed by the senior author of this study include initial treatment with IVB at an average age of 35 weeks. Adjuvant treatment with laser photocoagulation was also used. Infants treated with intravitreal bevacizumab received injections in the neonatal intensive care unit. The eyes were prepped in the typical manner for intravitreal injections. Tetracaine drops were given for anesthesia, ocular adnexa were sterilized with betadine swabs, betadine was placed on the ocular surface, 0.0625 mg of intravitreal bevacizumab was injected 1 mm from the limbus using a short 32 g needle.

For patients who received laser, treatment was performed in the operating room under general anesthesia. Laser photocoagulation was performed using indirect ophthalmoscopy in an intentionally less confluent pattern to the peripheral avascular zone, as previously described in Mammo et al. (11) **Figure 1** illustrates a sample patient at time of APROP diagnosis and after treatment with both IVB and laser.

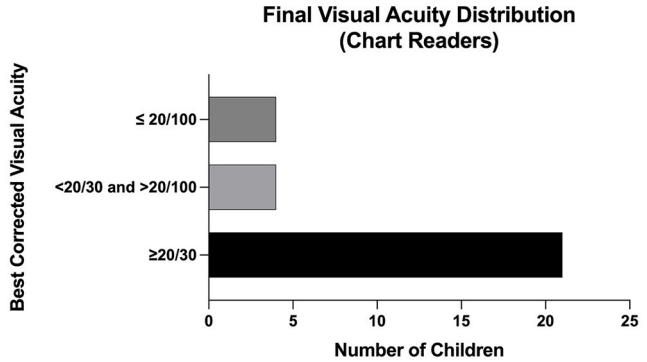

FIGURE 2 | Final Visual Acuity Distribution (Chart Readers) among patients with APROP treated with IVB.

TABLE 1 | Perinatal neurological diagnoses in study cohort.

Perinatal neurologic diagnosis	Number of children
Intraventricular/intracranial hemorrhage (Grade IV)	11
Brachycephaly/plagiocephaly	2
Neonatal cerebral leukomalacia	2
Cleidocranial syndrome	1
Substance withdrawal	1
Velocardiofacial syndrome	1
Other findings	3

TABLE 2 | Chronic neurological diagnoses in study cohort.

Chronic neurologic diagnoses	Number of children
Developmental delay	10
Di-/quadriplegia	1
Cerebral palsy	1
ADHD	3
Autism	3

RESULTS

The study included 43 eyes from 13 male and 9 female children. The average gestational age was 24 weeks (range: 23–27 weeks) and average birth weight was 625.2 grams. The average follow-up was 4.08 years (range: 1.85–7.36 years). The average post-menstrual age (PMA) at time of bevacizumab injection was 35.6 weeks (range: 26–41 weeks). 35 (81%) eyes eventually received laser photocoagulation at an average PMA of 53.2 weeks (39.3–60.9 weeks). One eye received a second laser treatment. All eyes ultimately demonstrated regression, without progression to retinal detachment.

At last follow up, 67% (29/43) of eyes were able to discern letters or shapes, with an average visual acuity of approximately 20/40 (logMAR 0.27). Those unable were largely young or non-verbal. 72% ($n = 21$) of eyes had a visual acuity of 20/30 or better, 14% ($n = 4$) of eyes had a visual acuity between 20/30 and 20/100, and 14% ($n = 4$) of eyes had a visual acuity of 20/100 or worse (**Figure 2**). Nineteen eyes developed subsequent ocular pathology, which included strabismus (58%, $n = 11$), amblyopia (58%, $n = 11$), nystagmus (21%, $n = 4$), and cataracts (16%, n=3).

Sixteen (72%) infants of the twenty-two infants in this cohort were diagnosed with perinatal neurologic disorders. This was most commonly intraventricular/intracranial hemorrhage (Grade IV) ($n = 11$ infants). One infant developed a thalamic tumor at 2 years old. Perinatal neurological diagnoses acquired by these infants is summarized in **Table 1**. Thirteen infants (59%) in this cohort ultimately demonstrated chronic neurologic impairment. Of the thirteen, twelve infants (92%) had previously been diagnosed with a neurological disorder in the perinatal period. The most common chronic neurological impairment seen in this cohort was neurodevelopmental delay, seen in 45% ($n = 10$) of infants. Neurodevelopmental delay was tested using Bayley Scales of Infant and Toddler Development, third edition. Chronic neurological impairments sustained by this cohort are summarized in **Table 2**.

Several infants were diagnosed with endocrine disease or genetic syndromes including congenital hypothyroidism ($n = 1$), rickets ($n = 1$), type 1 diabetes mellitus ($n = 1$), and Severe Combined Immunodeficiency (SCID) ($n = 1$). 27% ($n = 6$) infants were diagnosed with bronchopulmonary dysplasia/chronic lung disease.

DISCUSSION

The purpose of this study was to evaluate both long term ophthalmic and neurologic outcomes in infants with APROP who received intravitreal bevacizumab. Our study shows that extreme prematurity is associated with significant neurologic morbidity. Nearly all infants (92%) who developed chronic neurologic disease were diagnosed with neurologic disease during the perinatal period. 73% ($n = 16$) of infants diagnosed with APROP in this study sustained frank perinatal neurologic insult.

The functional and structural outcomes of this case series are promising. Intravitreal bevacizumab, often with adjuvant photocoagulation, led to regression without detachment in 100% of eyes, significantly improved from the 45% retinal detachment rate that has been reported in infants with APROP (5). The combination of IVB with laser treatment is supported by a recent study that found the combination of zone 1 sparing laser photocoagulation and IVB compared to conventional laser photocoagulation alone achieved ROP regression twice as fast (12). With regards to visual acuity, 67% of eyes in our study were able to distinguish letters or shapes and achieved an average acuity of close to 20/40 at an average follow up of 4 years that ranged up to 7 years. As indicated in **Figure 2**, 72% had a visual acuity better than 20/30 on final follow up. This is comparable to the visual acuity outcomes of infants with APROP treated with laser photocoagulation which reported 81% achieved 20/40 vision or better at an average follow up of 7 years (13).

Management of APROP has shifted toward primary use of intravitreal bevacizumab (8, 14). One reason for this shift is the improved anatomical outcomes with IVB. Similar to the 0% detachment rate in this study, Shah et al. recently reported only a 1% detachment rate in the intravitreal injection cohort compared to 10% in the laser-treated cohort (15). In addition to the reasons alluded to earlier, IVB is a more cost-effective, efficient, and readily available treatment. IVB also allows the retinal vasculature to develop more anteriorly without the permanent peripheral vision loss caused by laser (16). The success rate (defined as complete disease regression) of laser photocoagulation alone in the APROP population have been less promising. The success rate in the literature ranges from 70 to 85% while laser monotherapy in type 1 ROP was above 90% (17). Given the accelerated disease course of APROP, timely treatment is often required. Even when adequate treatment with laser photocoagulation is performed in a timely manner, it often requires 2–3 weeks before the full impact is observed. Treatment with intravitreal bevacizumab, however, has a more rapid onset, typically within 24 h (17). Moreover, 50% of cases treated with adequate laser continue to progress and have poor visual outcomes (2).

Finally, while intravitreal injections are typically performed using only topical anesthesia, laser treatment usually requires general anesthesia. The risks of general anesthesia cannot be understated. In December 2016, the U.S. Food and Drug Administration released a warning that lengthy general anesthesia on children <3 years old may result in neurodevelopmental delay (18, 19). Together, these findings support the primary treatment of APROP with intravitreal bevacizumab.

Our practice pattern often is to follow IVB treatment with adjunctive laser photocoagulation prior to discharge due to our large catchment area and often high risk of poor surgical follow-up. Even the anti-VEGF cohort from Shah et al. mentioned above did require additional laser treatment in 21.4% of infants for disease recurrence. While IVB can begin to provide resolution of APROP within 24 h, adjuvant laser treatment can more permanently treat the anterior avascular retina. In our study, IVB was commonly given at a PMA of 35 weeks, followed by laser at an average PMA 53 of weeks.

Other ophthalmic complications identified in this cohort included cataract formation, nystagmus, amblyopia, and strabismus. The specific incidence of several of these ophthalmic complications among patients with APROP has not been reported in the literature before. For example, 16% of patients in our cohort ($n = 3$) developed cataracts during the follow up period. In comparison, Davitt et al. reported a 1.9% incidence of cataract development by 6 month's corrected age in the ETROP study group (20). 21% of patients in this cohort developed nystagmus. In a large population-based Danish cohort study, the overall incidence of infantile nystagmus in the extremely preterm (<28 weeks GA) was 0.973%, 70% of which were attributable to retinopathy of prematurity (21).

Fifty-eight percentage of our cohort developed amblyopia. The incidence of amblyopia in patients with has previously been reported to be as high as 27.8% in type 1 ROP (22). Finally, 58% of our cohort also developed strabismus. In comparison, a previous study found the rate of strabismus in patients with APROP treated with laser was 40% and those treated with injections was 8% (23).

We suspect that the higher incidence of these ophthalmic complications in our study group compared to what has been previously reported in the literature is due to the longer follow up period in our study. A diagnosis of APROP may also portend more severe ocular comorbidities.

The use of IVB in premature infants remains controversial due to concerns for its possible association with neurodevelopmental delay. Many have also raised concerns regarding the use of IVB because VEGF has an important role in organogenesis of other organs including the lungs and kidneys. This is of particular concern in infants with APROP, a population subset that tends to be younger (gestational age <30 weeks), weigh less (birth weight <1,000 g), and have more medical comorbidities (17, 24). Previous studies have shown that 0.625 mg intravitreal injection of bevacizumab can last in the systemic circulation of premature infants for at least 8 weeks (25). There is some concern that use of IVB after laser treatment could potentiate further systemic spread.

Two major studies have suggested that intravitreal bevacizumab injections are associated with neurodevelopmental delay. Morin et al. showed that infants who received intravitreal bevacizumab were 3 times more likely to develop severe neurodevelopmental disabilities when compared to those who only received laser (26). Natarajan et al. reported higher mortality and worse cognitive outcomes in infants receiving IVB (27). However, in both studies, IVB was primarily given to sicker infants (19, 28, 29). Infants in the IVB group in the Morin et al. had more severe ROP at baseline. Infants in the IVB group in Natarajan et al. were born at a younger gestational age, had a lower median birth weight, required a longer length of ventilator support.

A growing body of evidence has shown no significant difference in neurodevelopmental outcomes between infants treated with IVB and those treated with laser (15, 28–31). A recent meta-analysis of eight studies published by Tsai et al. revealed that patients receiving IVB for ROP were not at an increased risk of severe neurodevelopmental impairment (32).

In the authors' view, the current evidence suggests a low risk of neurodevelopmental delay from IVB in infants. One confounding factor in these studies is that many infants who develop ROP are at risk for neurodevelopmental delay due to other independent risk factors (28, 33). ROP zone itself has been shown to be a risk factor for neurodevelopmental delay (33). On the other hand, the severity of ROP has not been shown to be associated with neurodevelopmental delay (22).

While these data are reassuring, a cautious approach to treatment with IVB is prudent. This is even more important the more vulnerable APROP population. One way to mitigate possible systemic effects of IVB is to reduce bevacizumab dosage to the lowest dose necessary. Clinical trials aimed at assessing the lowest effective dose of bevacizumab with the goal of mitigating impact on organogenesis systemically are ongoing (34).

Given that most infants who had chronic neurological impairment in our study had a prior neurological insult in the neonatal period, we would argue that optimizing these infants' visual potential is not only helpful from an ophthalmic perspective but from a neurologic perspective as well. The role of adequate vision in neurodevelopment cannot be understated.

Finally, our study also revealed several infants who were diagnosed with endocrine or genetic syndromes such as congenital hypothyroidism or SCID. While it is unlikely that these are related to the administration of IVB and more likely related to their extremely premature status, additional studies are required to further elucidate this association.

Limitations of this case series include its retrospective nature and limited sample size. This study is also limited by the lack of a control group to compare long term ophthalmic and neurologic outcomes.

In summary, the results herein indicates that infants with APROP had poor long term neurological outcomes. However, treatment with IVB and adjuvant photocoagulation, resulted in good structural and functional ophthalmic outcomes.

MEETING PRESENTATION

This work was previously as a poster at ARVO 2019 Annual Meeting.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because data is proprietary to the institutions from which they were collected. Requests to access the datasets should be directed to Ameay Naravane, ameay.naravane@gmail.com.

AUTHOR CONTRIBUTIONS

AN: manuscript drafting and revisions. PB and PQ: manuscript review. SR: data collection. All authors contributed to the article and approved the submitted version.

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Prevalence, Years Lived With Disability, and Time Trends for 16 Causes of Blindness and Vision Impairment: Findings Highlight Retinopathy of Prematurity

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Background: Cause-specific prevalence data of vision loss and blindness is fundamental for making public health policies and is essential for prioritizing scientific advances and industry research.

Methods: Cause-specific vision loss data from the Global Health Data Exchange was used. The burden of vision loss was measured by prevalence and years lived with disability (YLDs).

Findings: In 2019, uncorrected refractory error and cataract were the most common causes for vision loss and blindness globally. Women have higher rates of cataract, age-related macular degeneration (AMD), and diabetic retinopathy (DR) than men. In the past 30 years, the prevalence of moderate/severe vision loss and blindness due to neonatal disorders has increased by 13.73 and 33.53%, respectively. Retinopathy of prematurity (ROP) is the major cause of neonatal disorders related vision loss. In 2019, ROP caused 101.6 thousand [95% uncertainty intervals (UI) 77.5–128.2] cases of vision impairment, including 49.1 thousand (95% UI 28.1–75.1) moderate vision loss, 27.5 thousand (95% UI 19.3–36.60) severe vision loss and, 25.0 thousand (95% UI 14.6–35.8) blindness. The prevalence of new-onset ROP in Africa and East Asia was significantly higher than other regions. Variation of preterm birth prevalence can explain 49.8% geometry variation of ROP-related vision loss burden among 204 countries and territories. After adjusting for preterm prevalence, government health spending per total health spending (%), rather than total health spending per person, was associated with a reduced burden of ROP-related vision loss in 2019 (−0.19 YLDs for 10% increment). By 2050, prevalence of moderate, severe vision loss and blindness due to ROP is expected to reach 43.6 (95% UI 35.1–52.0), 23.2 (95% UI 19.4–27.1), 31.9 (95% UI 29.7–34.1) per 100,000 population.

Conclusion: The global burden of vision loss and blindness highlights the prevalent of ROP, a major and avoidable cause for childhood vision loss. Advanced screening techniques and treatments have shown to be effective in preventing ROP-related vision loss and are urgently needed in regions with high ROP-related blindness rates, including Africa and East Asia.

Keywords: prevalence, years lived with disability, blindness, visual impairment, retinopathy of prematurity

INTRODUCTION

Vision loss is a major cause of functional impairment globally, greatly decreasing life quality and increasing social burden. Recently, two comprehensive reports on the burden of vision loss were published by GBD and The Vision Loss Expert Group (1, 2). It is estimated that 43.3 million [95% uncertainty intervals (UI) 37.6–48.4] people were blind globally, and 295 million (95% UI: 267–325) people had moderate and severe vision loss in 2020 (1). The leading causes globally for vision loss are uncorrected refractive error and cataract (2, 3). Other vision-threatening conditions include age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy (DR). Communicable diseases, such as trachoma and onchocerciasis, are still major communicable causes for vision loss in underdeveloped countries and areas (4, 5). Besides, because of the rapid advance of neonatal care, retinopathy of prematurity (ROP) and other neonatal disorders are now the most common causes of vision loss in children (6, 7). Despite national programs of vitamin A supplementation has implemented in 82 countries, vitamin A deficiency remains prevalent in south Asia and sub-Saharan Africa (8, 9).

Cause-specific prevalence data of distance vision loss and blindness is fundamental for making public health policies and is essential for prioritizing scientific advances and industry research. Previous studies have focused on primary blinding eye disease, including glaucoma, cataract, AMD, DR, and refractive error. Less attention has been paid to minor causes, such as neonatal disorders and nutritional deficiencies. These causes are the major contributions to the vision loss burden among children and adolescents (7).

The present study aimed to quantify the vision loss estimates due to 16 kinds of diseases from 1990 to 2019 using the Global Burden of Diseases 2019 (GBD 2019). Based on the current epidemiological situation, we mainly explore the current disease burden, associated factors, and future ROP-related vision loss burden.

METHOD

Data Source

The GBD 2019 Study provided Cause-specific vision loss data in the Global Health Data Exchange (http://ghdx.healthdata.org/gbd-results-tool, accessed on December 15, 2020). We included distance vision loss and blindness data from GBD dataset. Details of the study's methodology have been described previously (6). In brief, The Vision Loss Expert Group has systematically reviewed the scientific literature published between 1980 and 2018 by commissioning the York Health Economics Consortium, UK, to search Embase, SciELO, MEDLINE, WHOLIS, and Open Gray, and additional gray literature sources (2). Bayesian meta-regression tool synthesized all available data, adjusting for different case definitions or sampling strategies. Distance vision loss was divided into three categories: moderate vision impairment (defined as visual acuity of $\geq$6/60 and $<$6/18), severe vision impairment (visual acuity of $\geq$3/60 and $<$6/60), and blindness (visual acuity of $<$3/60 or $<10^{\circ}$ visual field around central fixation). Then, location, year, age, and sex-specific estimates of vision loss and blindness were calculated using a wide range of standardized analytical procedures, including data screening, data adjustment, DisMod-MR 2.1 modeling.

Outcomes and Related Factors

The primary outcomes of the present study were the total number of cases in the population (Number), total cases per 100,000 population (Rate), age-standardized cases per 100,000 population (age-standardized rate), and years lived with disability (YLDs) due to various causes. YLDs were calculated by multiplying the prevalence of the eye disease and its associated disability weight in each age-sex-country-year population. The disability weight represents the magnitude of health loss associated with the outcome. It was measured on a scale from 0 to 1, where 0 implied a state equivalent to full health, and 1 was equivalent to death (10). Age-standardization was computed using a standard population age structure updated in each GBD round. Currently, the standard population was taken as the average of age-specific distributions (non-weighted) from GBD 2019 population estimates for countries with at least 5 million people in the year 2019 (11).

A total of 16 causes of vision loss were included in the analysis: communicable diseases (meningitis, encephalitis, onchocerciasis, trachoma, malaria), neonatal disorders (retinopathy of prematurity, neonatal sepsis and other neonatal infections, hemolytic disease, and other neonatal jaundice, neonatal encephalopathy due to birth asphyxia and trauma), nutritional deficiency (vitamin A deficiency), glaucoma, cataract, AMD, DR, refractive error, and a residual category of other vision loss (**Supplementary Table 1**).

We analyzed the relationship between temporal trends of vision impairment burden and socio-demographic index (SDI). SDI is a summary measurement constructed based on the geometric mean of income per capita, average years of schooling among people aged 15 years or older, and the total fertility rate. It quantitates a country or territory's level of socio-demographic

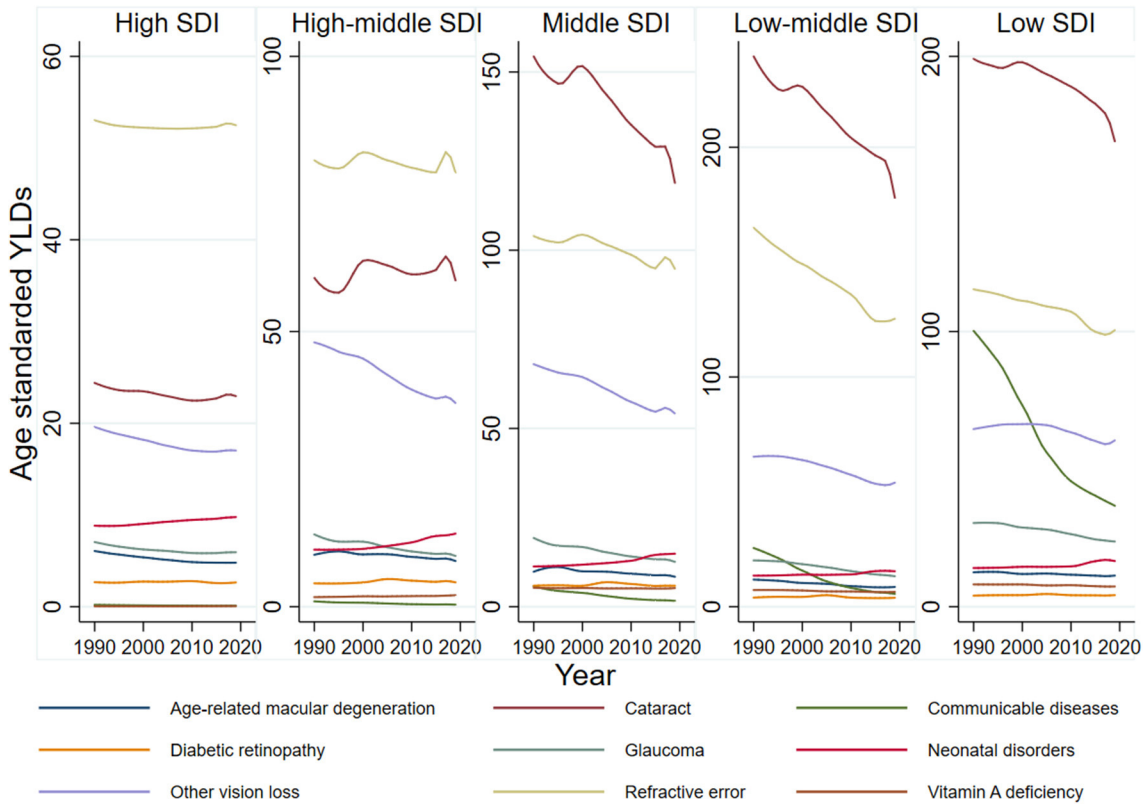

FIGURE 1 | Age-standardized, cause-specific YLD rate of blindness and distance vision impairment by Socio-Demographic Index groups, 1990–2019.

development (12). Then SDIs were transformed into quintiles for analysis (low-SDI, low-middle-SDI, middle-SDI, high-middle-SDI, or high-SDI). For health spending estimates, four financing sources were included in the analysis: government, out-of-pocket, and prepaid private health spending, which collectively makes up domestic health spending; and development assistance for health, which includes international disbursements for health low-income and middle-income countries (13).

Forecasting ROP-Related Vision Loss Burden to 2050

Auto-Regressive Integrated Moving Average (ARIMA) model predict future ROP-related vision loss burden. In ARIMA (p, d, q) model, p represents the number of lag observations; d represents the number of times input raw data are different to make the model stationary; q represents the size of moving average window applied to lagged observations. It was performed on Stats package (version 4.1.1) to forecast the health burden caused by ROP in terms of age-standardized prevalence rates from 2020 to 2050.

Statistics Analysis

Linear regression was used to estimate associated factors of ROP disease burden. All analysis was performed in Stata version 15.0 (StataCorp LLC, College Station, TX, USA) and R Statistical Software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The Burden for Vision Loss and Blindness in 2019

Regional differences were found in the burden of vision impairment in 2019. We estimated that Southeast Asia, South Asia, North Africa, Middle East, Ease and West Sub-Saharan Africa, Tropical and Andean Latin America remained the primary area with high age-standardized YLDs for all-cause distance vision loss and blindness. To explore regional differences, the predominant causes for vision loss in 204 countries and territories were plotted (**Supplementary Tables 2–4**; **Supplementary Figures 1–18**). Cataract and uncorrected refractive error have become the most common causes for vision impairment in most countries and territories.

The burden of distance vision loss and blindness was also different between age and sex. As exhibited in **Supplementary Figure 19**, we observed a strong association between age and vision impairment. To further elaborate on the sex differences in all 16 causes of vision impairment, we generated cause-YLD ratios by female YLD rates divided by male YLD rates (**Supplementary Figure 20**). Among sex groups, glaucoma [11 cases (95% UI 7–16) per 100,000 males vs. 10 (7–15) per 100,000 females] has a higher YLD rates in men, while cataract [77 (95% UI 54–108) per 100,000 males vs. 113

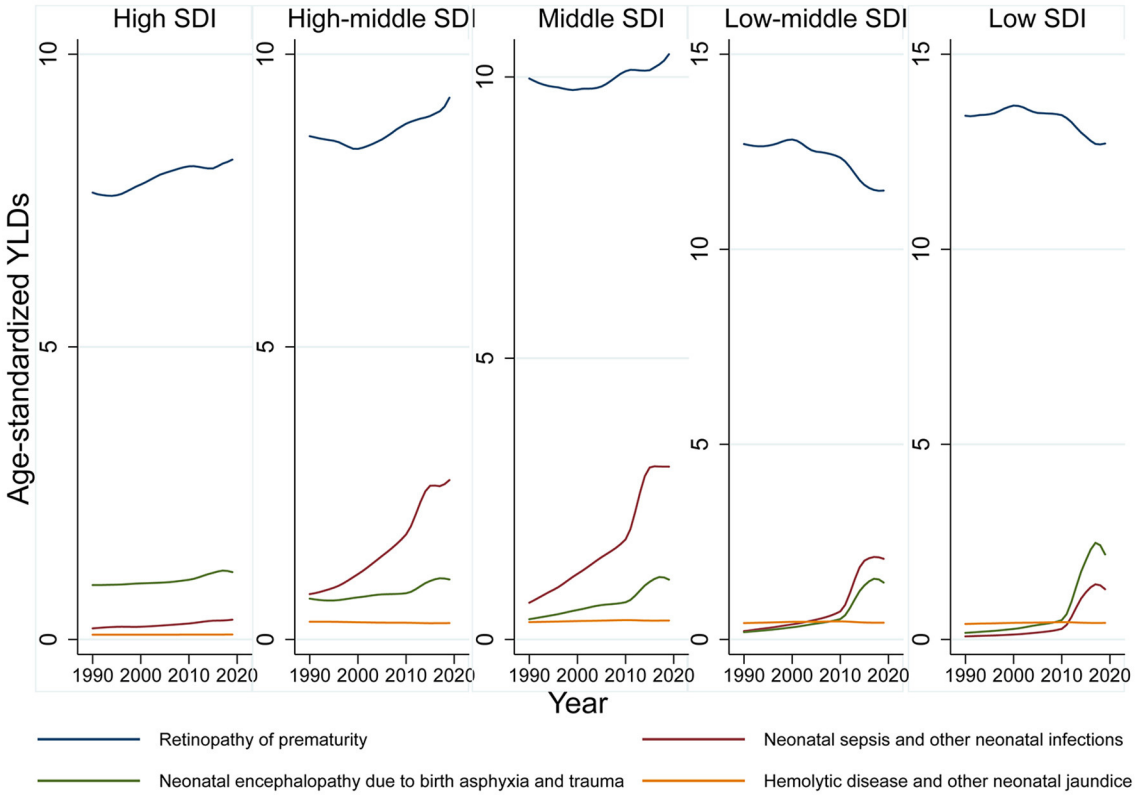

FIGURE 2 | Age-standardized, cause-specific YLD rate due to neonatal disorders.

(79–157) per 100,000 females], AMD [6.4 (95% UI 4.3–9.2) per 100,000 males vs. 9.8 (6.6–13.9) per 100,000 females], and DR [4.1 (95% UI 2.6–5.8) per 100,000 males vs. 5.3 (3.5–7.6) per 100,000 females] have higher YLD rates in women. We did not find a gender difference in neonatal disorders (including ROP) or vitamin A deficiency in children.

Change of Burden for Vision Loss in 1990–2019 Highlights Neonatal Disorders

Globally, age-standardized blindness prevalence decreased by −27.14% from 1990 to 2019. Although total cases of moderate, severe vision loss and blindness increased, age-standardized prevalence decreased or remained stable, which indicated population growth and aging contributed to increased total cases (**Supplementary Table 5**). YLDs trend across SDI quintiles revealed refractive error was the major vision-threatening condition in high and high-middle SDI countries. Cataract was the major cause in middle, middle-low, and low SDI countries, and it continued to decline alongside refractive error during this period. Vision loss due to communicable diseases, the third leading cause for vision impairment in low SDI countries, has rapidly declined in last 30 years (**Supplementary Figure 21**). In contrast there has been an increasing diseases burden of neonatal disorders related vision loss during the past 30 years (**Figure 1**). From 1990 to 2019, prevalence of moderate/severe vision impairment and blindness due to neonatal disorders has increased by 13.73 and 33.53%, respectively. ROP is the major cause of neonatal disorders related vision loss. By 2019, the prevalence of moderate, severe vision loss and blindness due to ROP reached 35 (95% UI 20–53), 20 (95% UI 14–26), and 32 (95% UI 24–40) (**Figure 2**).

The Global Burden and Trend of ROP-Related Vision Loss Burden

For all age groups combined, it is estimated that 15.2 million (95% UI 15.1–15.3) preterm babies, with 9.4% (95% UI 7.7–11.4) complicated with any stage of ROP that causes moderate/severe vision loss or blindness. The prevalence of ROP-related blinding varies among 21 GBD regions, with the highest of 44 (95% UI 32–56) in Southern Sub-Saharan Africa and the lowest of 17 (95% UI 11–24) cases per 100,000 population in East Asia (**Figure 3**). The prevalence of ROP among all infants<1-year-old reflects the annual incidence of ROP. In 2019, new-onset ROP caused 101.6 thousand (95% UI 77.5–128.2) cases of vision impairment, including 49.1 thousand (95% UI 28.1–75.1) moderate vision loss, 27.5 thousand (95% UI 19.3–36.60) severe vision loss, and 25.0 thousand (95% UI 14.6–35.8) blindness. Especially, the incidence of new-onset ROP-related blindness was still higher in Sub-Saharan Africa and Asia than other regions.

Variation of preterm birth prevalence can explain 49.8% geometry variation of ROP-related vision loss burden among 204 countries and territories (**Figure 4A**). Health expenditure

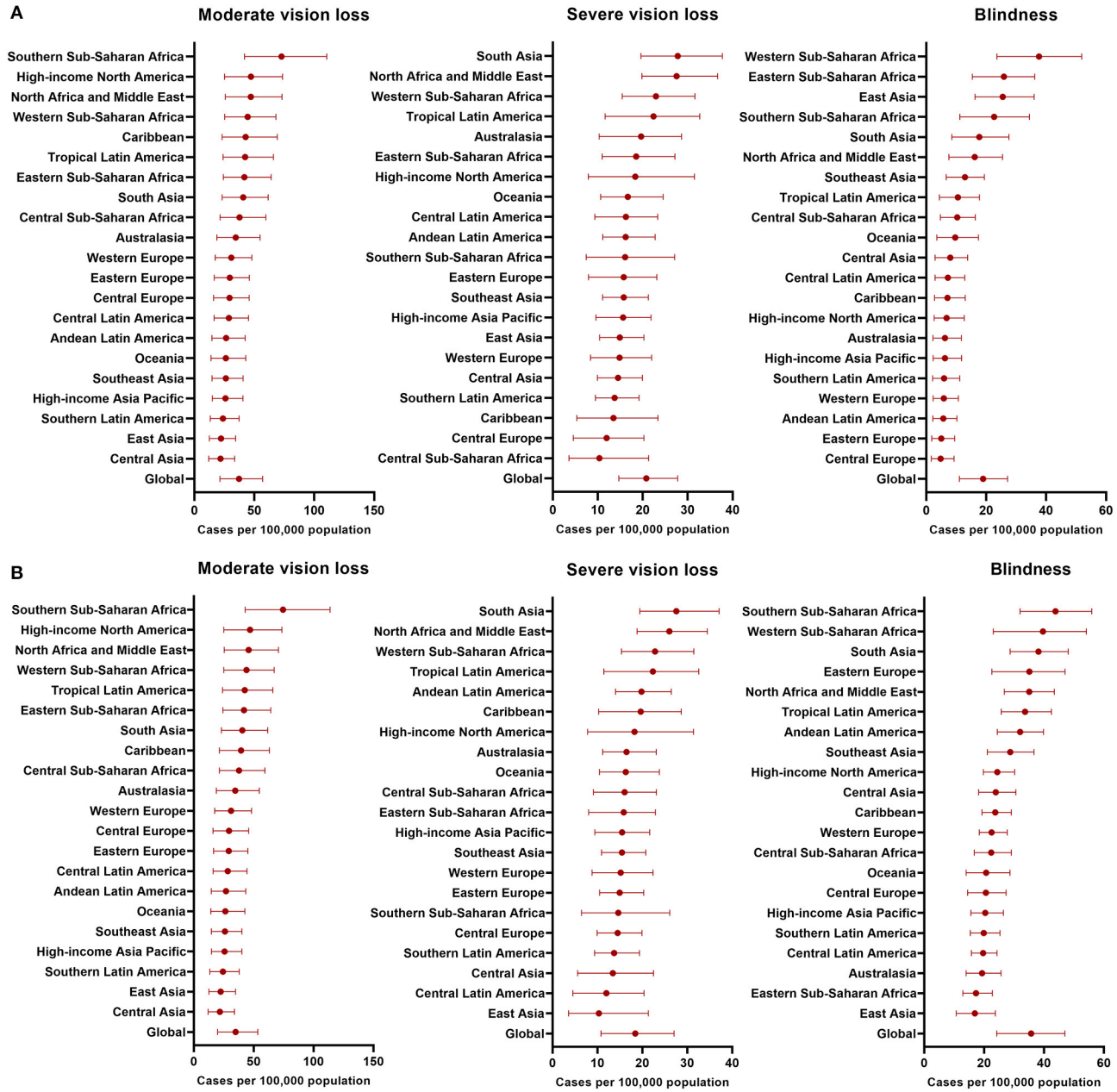

FIGURE 3 | Incidence and Prevalence of ROP-related blinding varies among 21 GBD regions. **(A)** Incidence of ROP in 2019; **(B)** Prevalence of ROP in 2019.

and social development were expected to be closely related to preterm birth prevalence. Cross-sectional analysis revealed that total healthy spending per person (−39.83 cases/100,000 population for 1,000 USD increment) and socio-demographic index (−28.75 cases/100,000 population for 0.1 increment) was significantly associated with preterm birth prevalence (**Table 1**). As for financing sources of total health spending, government health spending out-of-pocket health spending per person were negatively associated with the preterm birth prevalence. Development assistance for health per person was positively associated with the preterm birth prevalence, reflecting deficient total health spending. After adjusting for preterm prevalence, only government health spending per total health spending was associated with a reduced burden of ROP-related vision loss in 2019 (−0.19 YLDs for 10% increment, **Table 1** and **Figure 4B**). This association remained significant after adjusting for both preterm prevalence and total health spending per person [−0.22 YLDs for 10% increment, 95% confidence interval (CI) −0.38 to −0.06, $P = 0.006$].

During the past 30 years, the ROP-related vision loss burden has increased in high, high-middle, middle SDI countries, and decreased in low-middle, low SDI countries. By 2050, global

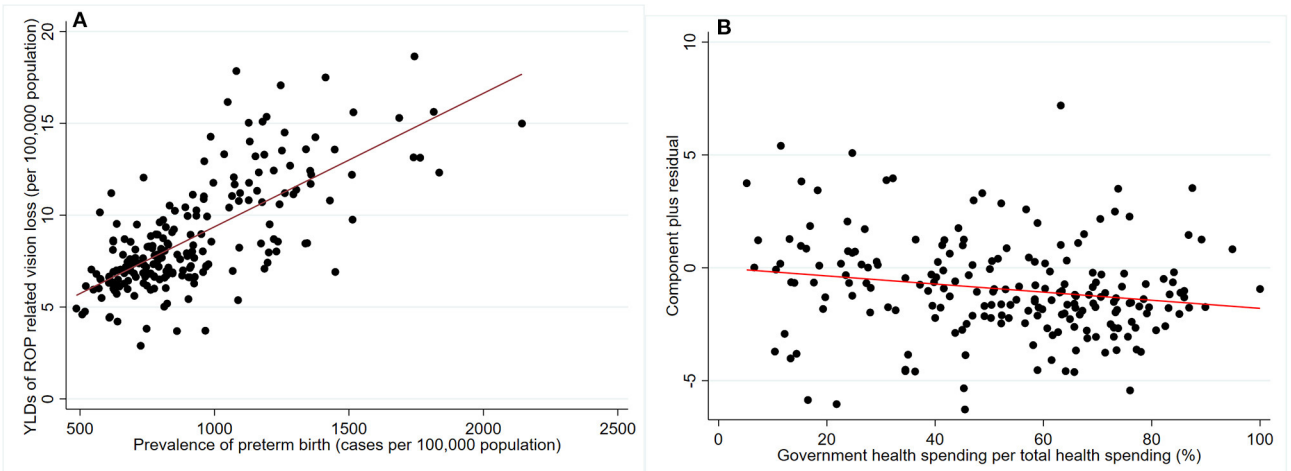

FIGURE 4 | Scatter plot and linear prediction of YLDs related to retinopathy of prematurity. **(A)** association between preterm birth prevalence and ROP-related vision loss burden among 204 countries and territories; **(B)** association between government health spending per total health spending (%) and ROP-related vision loss burden among 204 countries and territories, adjusted for preterm birth prevalence.

TABLE 1 | Association between Health spending with burden of ROP-related vision loss and preterm prevalence among 204 countries and territories in 2019.

	ROP-related vision loss (YLDs)†		Preterm birth prevalence	
	Coefficient	**95% Confidence interval**	**Coefficient**	**95% Confidence interval**
Socio-demographic index (per 0.1 increment)	−0.01	[−0.28, 0.10]	**−78.09**	**[−98.84, −57.35]**
Total health spending per person (per 1,000 USD increment)	−0.06	[−0.23, 0.10]	**−39.84**	**[−61.01, −18.67]**
Total health spending per person (per 1,000 PPP increment)	−0.01	[−0.18, 0.16]	**−47.39**	**[−68.28, −26.50]**
Government health spending per person (per 1,000 USD increment)	−0.07	[−0.31, 0.17]	**−63.11**	**[−93.23, −33.00]**
Government health spending per person (per 1,000 PPP increment)	−0.02	[−0.25, 0.22]	**−69.34**	**[−97.98, −40.69]**
Prepaid private health spending per person (per 1,000 USD increment)	−0.20	[−0.74, 0.34]	−13.09	[−87.31, 61.13]
Prepaid private health spending per person (per 1,000 PPP increment)	−0.10	[−0.72, 0.51]	−7.35	[−91.67, 76.97]
Out-of-pocket health spending per person (per 1,000 USD increment)	−0.24	[−1.23, 0.75]	**−283.34**	**[−406.59, −160.09]**
Out-of-pocket health spending per person (per 1,000 PPP increment)	0.28	[−0.65, 1.21]	**−318.02**	**[−427.18, −208.85]**
DAH per person (per 1,000 USD increment)	−11.36	[−26.05, 1.33]	863.01	[−1015.49, 2741.67]
DAH per person (per 1,000 PPP increment)	−4.81	[−15.16, 5.55]	**2124.18**	**[769.89, 3478.47]**
Government health spending per total health spending (per 10% increment)	**−0.19**	**[−0.33, −0.04]**	**−51.27**	**[−68.29, −34.26]**
Total health spending per GDP	−0.03	[−0.13, 0.07]	**−14.62**	**[−27.56, −1.68]**
Government health spending per GDP	−0.10	[−0.22, 0.02]	**−38.71**	**[−53.59, −23.83]**

PPP, Purchasing power parities; DAH, Development assistance for health. Preterm birth prevalence was measured as cases per 100,000 population.
†*Adjusted for Preterm birth prevalence in 2019. Bold value indicates P < 0.05.*

prevalence of moderate, severe vision loss and blindness due to ROP is expected to reach 43.6 (95% UI 35.1–52.0), 23.2 (95% UI 19.4–27.1), 31.9 (95% UI 29.7–34.1) per 100,000 population (**Figure 5**).

DISCUSSION

This study found that cataract and uncorrected refractive error remains the most common causes for distance vision loss and blindness. Moreover, the gender difference was found in the disease burden of vision loss. Women have higher rates of cataract, AMD, and DR than men. In the past 30 years, there has been an increasing diseases burden of neonatal disorders related vision loss. ROP is the primary cause of neonatal disorders related vision loss. Without more effective screening and interventions strategy, the burden of ROP-related vision loss was expected to increase in the future.

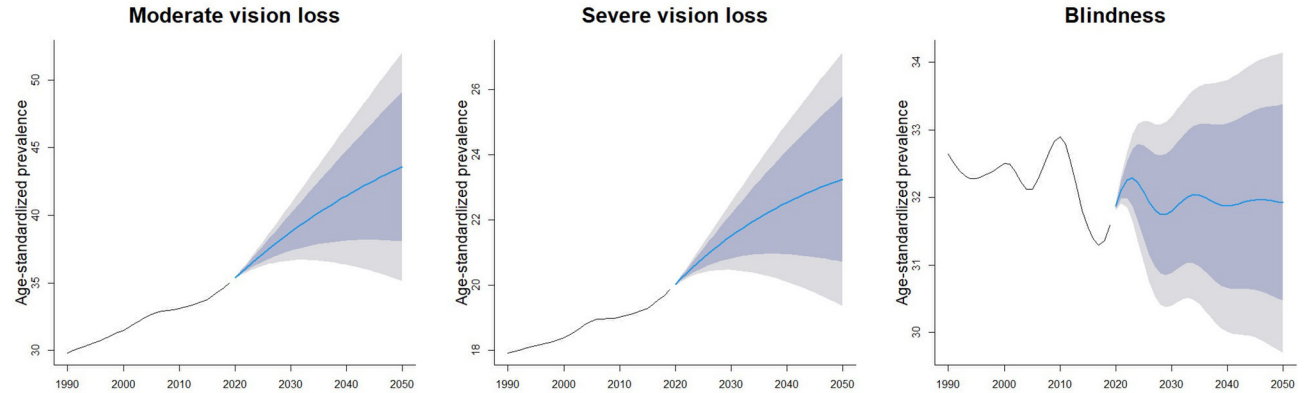

FIGURE 5 | Forecast of age-standardized prevalence per 100,000 population due to retinopathy of prematurity.

Avoidable visual impairments constitute major burden of vision loss globally. We found that age-standardized YLDs for cataract have declined rapidly in middle SDI, low-middle SDI, and low SDI counties, indicating the improved efficiency of ophthalmic screening and the quality of treatment delivered in these areas. However, the residual YLDs indicated that it had not been fully addressed in most world regions, including high-incomes and high-SDI regions. Further efforts need to promote the accessibility of high-quality cataract surgery, especially in developing countries and remote areas. Further initiatives, programs, or mass campaigns are needed to develop infrastructure, personnel, and economic strategies to provide sustainable, high-quality training, counseling, and facility (14). Uncorrected refractive error, including myopia, hyperopia, and astigmatism, is another major cause of vision impairment (15). It is prevalent in Latin America, North Africa, the Middle East, and South Asia and that is leading cause of vision impairment in high and high-middle SDI countries. With decreased outdoor time, increased near-work activities, and excessive use of near electronic devices and other factors, myopia and high myopia have been anticipated to significantly increase (16, 17). It is estimated that 5.2% of the global population will have high myopia in 2020 and will significantly increase to 9.8% of the global population in 2050 (18). Myopia brings further vision challenges because high myopia increases the risk of pathologic ocular changes such as glaucoma, retinal detachment, and myopic maculopathy, all of which can cause irreversible vision loss (19). Because effective interventions for myopic maculopathy are still limited, future researches need to focus on preventing or delaying myopia onset and retarding myopia progression through lifestyle modifications and medical interventions.

In 2019, ROP caused 49.1 thousand, 27.5 thousand, and 25.0 thousand moderate, severe vision loss and blindness cases, respectively. The increasing diseases burden of ROP-related vision loss may be caused by the rapid advance of neonatal care that improves preterm infants' survival (20, 21). As advance of ROP screening and treatments in the past 30 years (22), the blindness rate due to ROP sightly decreased by 3.23%. However, we observed a significant disparity between prevalence and new-onset ROP-related blindness incidence. The developed regions, such as Europe and North America, exhibited the "high prevalence and low incidence," whereas the developing regions, such as Africa and East Asia, exhibited the "high prevalence and high incidence" of ROP-related blindness incidence. These results highlight that advanced screening techniques and treatments effectively prevent ROP-related blindness but are unevenly distributed. Early diagnosis and timely treatments are urgently needed in these regions.

Compared to cataract and most uncorrected refractive error, progression of glaucoma, AMD, DR, and myopic maculopathy can lead to irreversible vision loss. The characteristics of these diseases and limited options for curing these diseases highlight the screening and effective management once diagnosed. Unfortunately, we still lack precise diagnostic measures for glaucoma in the screening setting, and a large proportion of patients with glaucoma remain undiagnosed in developed, developing, and underdeveloped regions of the world (23). Furthermore, the number of adults with diabetes was expected to surpass 700 million globally (24), and it is estimated that about one-third of people with diabetes will develop DR (25). Moreover, with global population growth and aging, AMD increasingly becomes an important vision-threatening condition in the elderly (26). Artificial intelligence-based screening and referring could tackle these challenges. Nowadays, artificial intelligence is applied for detecting DR, AMD, glaucoma, myopic maculopathy, and papilledema by using multimodality imaging, including fundus photographs, optical coherence tomography (OCT), and fundus fluorescence angiography (FFA) images (27, 28). Novel algorism systems have been developed that are able to identify multiple ocular diseases and lesions (29, 30). It can be anticipated that artificial intelligence would provide automated, immediate feedback in screening settings.

Vitamin A deficiency and communicable diseases used to be two leading causes of vision impairment in underdeveloped counties. Despite the established national vitamin A supplementation programs in 82 countries,

vitamin A deficiency remains prevalent in south Asia and Africa (**Supplementary Figure 18**). With COVID-19 interrupting global nutrition programs, it is entirely possible vision loss due to vitamin A deficiency may become newly resurgent in many countries (31). Among communicable diseases, onchocerciasis is still the most common cause of vision impairment in Central Africa. Although the prevalence of these diseases declines rapidly, national programs are needed to fully eliminate these diseases (32).

This study has several limitations. First, the number of studies and quality of the available data are still limited. We found that "other causes" contributed to 124 (95% UI 105–144) blindness in every 100,000 age-standardized population worldwide. Thus, a major part of the causes of blindness and vision impairment has remained uncovered, such as corneal occupation and eye injury. Second, the burden of vision loss may be underestimated due to lacking precise diagnostic measures and universal diagnosis criteria for glaucoma. Furthermore, Furthermore, SDI was used to measure socio-economic position, but this index could not fully represent level of health care. The application of SDI also ignored the social heterogeneity within countries.

CONCLUSIONS

This study demonstrates the prevalence and time trend of 16 disease-related vision loss from 1990 to 2019, stratified by age, gender, and regions. The efforts to eliminate avoidable vision loss and improve unavoidable vision loss have been suboptimal over the last 30 years, especially in ROP. Advanced screening techniques and treatments are effective in preventing ROP-related blindness and are urgently needed in regions with high ROP-related blindness rates, including Africa and East Asia.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: http://ghdx.healthdata.org/gbd-results-tool.

AUTHOR CONTRIBUTIONS

R-HZ, Y-ML, LD, and W-BW: conception, design, provision of study materials or patients, and collection and assembly of data. W-BW: administrative support. R-HZ, LD, Y-ML, H-YL, Y-FL, W-DZ, and H-TW: data analysis and interpretation. All authors manuscript writing and final approval of manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.735335/full#supplementary-material

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REVIEW
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Health Equity and Disparities in ROP Care: A Need for Systematic Evaluation

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Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder that can have devastating visual sequelae if not managed appropriately. From an ophthalmology standpoint, ROP care is complex, since it spans multiple care settings and providers, including those in the neonatal intensive care unit (NICU), step down nurseries, and the outpatient clinic setting. This requires coordination and communication between providers, ancillary staff, and most importantly, effective communication with the patient's family members and caregivers. Often, factors related to the social determinants of health play a significant role in effective communication and care coordination with the family, and it is important for ophthalmologists to recognize these risk factors. The aim of this article is to (1) review the literature related to disparities in preterm birth outcomes and infants at risk for ROP; (2) identify barriers to ROP care and appropriate follow up, and (3) describe patient-oriented solutions and future directions for improving ROP care through a health equity lens.

Keywords: retinopathy of prematurity (ROP), health equity, disparities, social determinants of health, premature infants

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INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder that can have devastating visual sequelae if not managed appropriately. Retinal examinations at regular intervals performed by a trained ophthalmologist are imperative to diagnose vision-threatening disease, and current treatment options can have excellent outcomes if disease is recognized and treated in a timely fashion. An estimated 400–600 infants in the United States become legally blind from ROP (1), and though there has been an overall increase in ROP screening from 2008 to 2018, ∼10% of infants were not screened (2). From an ophthalmology standpoint, ROP care is complex, since it spans multiple care settings and providers, including those in the neonatal intensive care unit (NICU), step down nurseries, and the outpatient clinic setting. This requires coordination and communication between providers, ancillary staff, and most importantly, effective communication with the patient's family members.

There is significant medicolegal liability associated with ROP care, often related to system-wide challenges that result in failure to engage the family, ineffective communication between ancillary staff and family members, failure of care coordination between the inpatient and outpatient setting, and physician factors related to knowledge and skills related to diagnosis and treatment (3). Major

risk factors for the development of ROP such as birth weight, gestational age, oxygen use, and maternal and infant factors have been well described (4). However, barriers to ROP follow up and adherence to care have not been systematically evaluated and there is limited literature related to disparities in ROP care and outcomes.

It is often factors related to the social determinants of health that can play a significant role in effective communication and care coordination with the family, and it is important for ophthalmologists to recognize these risk factors. The aim of this article is to (1) review the literature related to disparities in preterm birth outcomes and infants at risk for ROP; (2) identify barriers to ROP care and appropriate follow up, and; (3) describe patient-oriented solutions and future directions for improving ROP care through a health equity lens.

METHODS

A literature search was performed between July and October 2021, including literature published in English between 1992 and 2021. We only excluded articles that were not related to ROP care in the United States. Electronic databases used included PubMed, Scopus, Google Scholar, and Dimensions. PubMed search terms and variants included health services accessibility, health services needs and demands, healthcare disparities, premature birth, quality of healthcare, retinopathy of prematurity, social determinants of health, socioeconomic factors, treatment outcome, and poverty areas. Scopus search criteria included retinopathy of prematurity, low birth weight, socioeconomic and related factors, inequities, disparities, insecurities, economic, income, racism, retina. Other search terms include access to care, financial insecurity, social support networks, social services, community health workers, race, gender, parents, health literacy, language barriers, limited English proficiency, outpatient follow up, transitions of care, and insurance. Variations of these terms were used to ensure exhaustive search results. Our search strategy was supplemented by manual reference searching of relevant article bibliographies and other review articles.

Disparities in Preterm Births and Retinopathy of Prematurity

Health disparities have been defined by the Centers for Disease Control as preventable differences in the burden of disease, or opportunities to achieve optimal health, that are experienced by populations (5). Understanding and identifying trends in preterm births is essential to identify the characteristics of populations at risk for worse outcomes in ROP that are related to systemic health disparities. From 1971 to 2018, preterm births (PTB) constituted 11% of all births in the United States (6). Determinants of PTB include race, socioeconomic status, history of maternal substance abuse, and maternal health factors (7). There are profound racial disparities in PTB in the United States. In 2019, the rate of preterm birth among Black women (14%) was about 50 percent higher than the rate of preterm birth among White or Hispanic women (9.3 and 10%, respectively) (7, 8). In a study analyzing 2016 U.S. birth certificate data, results found that nearly 38% of the preterm birth disparities were noted between black and white infants (9). Another study found that these differences still existed even among college-educated women with private insurance (10). Even when controlling for socioeconomic risk factors, racial disparities in neonatal outcomes have been shown to exist (11). Although these disparities remain largely unexplained, they are thought to be due to multifaceted risk exposures from generations of socioeconomic disadvantage. It has also been hypothesized that neighborhood deprivation (12–16) and a family history of preterm birth (17) may also play a significant role.

In the United States, there have been noted racial and ethnic variations in ROP. This was explored in the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) Cooperative group, noting that ROP occurred with similar frequency in all racial subgroups, though severe ROP was less common in Black infants (18). Additionally, it was found that there was an increased risk of reaching threshold ROP associated with lower birth weights, younger gestational age, white race, multiple births, and being born outside a study center nursery (19). Port et al. also noted that black race was found to be a protective factor for treatment-requiring ROP (20).

There are variable trends in ROP outcomes in different geographic areas. Trends in increased neonatal mortality amongst Alaskan Natives, another darkly pigmented population, demonstrated increased susceptibility to ROP and more severe ROP amongst Native populations compared to non-natives (21–23). Townsel et al. performed a retrospective analysis of over 4,000 infants admitted to a NICU in Connecticut and found that Hispanic neonates experienced 70% more ROP and mixed-race neonates experienced 55% less ROP. Though Black and mixed neonates were more likely to have Medicaid in this study, the primary and secondary outcomes of the study remained unchanged after controlling for Medicaid status (24). Many studies have suggested that black infants have a lower risk for severe ROP (18, 20, 25), and are also more likely to be born premature (7–9). Future studies are needed to understand if this finding is due to increased black infant mortality prior to ROP screening, or if there are other variables affecting ROP severity in infants of color.

Socioeconomic status, geography, and race/ethnicity play crucial roles in health care access and utilization. Black and Hispanic families are known to be more affected by housing instability, longstanding residential segregation, systemic racism, and food insecurity which adversely affect child health (26, 27). Additionally, studies have demonstrated racial and ethnic differences in rates of necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), and sepsis which are sequelae of prematurity (28–31). The transition from the inpatient setting to the outpatient clinic setting for ROP screening and follow up is a vulnerable period during which loss to follow up can lead to devastating visual outcomes. Identifying barriers to follow up in the outpatient setting is crucial as part of discharge and care planning, and requires the neonatology and ophthalmology teams to coordinate strategies to address these challenges prior to discharge.

In the sections below, we will discuss barriers to outpatient ROP follow up including access to care, high healthcare utilization, high readmission rates, patient health literacy, language barriers, social support and parental mental health.

Access to Care

Insurance coverage has been shown to correlate with improved vision and eye health outcomes and lower rates of vision impairment (32). However, simply having health insurance does not equalize health care utilization or health outcomes across different racial/ethnic groups (33).

Wang et al. conducted a series of focus groups and interviews of parents and found that respondents' ability to manage their children's health care was limited by parental understanding of ROP, feeling overwhelmed by the infant's care, and unmet needs for resources to address social stressors. Other challenges include access to ophthalmologists with expertise in ROP care, coordinating and attending multiple outpatient appointments across different medical specialties, and lack of transportation (34). Even at sites with a tracking database and ROP coordinator, it was noted to be time and resource-intensive to ensure that exams and treatments were being performed according to protocol. Similar findings were noted in another study surveying 131 parents with preterm infants where it was found that the most common access barriers to attending ROP appointments reported by parents included few available ophthalmologists with expertise in ROP care (23%) and social situations (i.e., housing, transportation, or childcare) (22%) (35).

High Healthcare Utilization

Multiple Clinic Visits

Healthcare utilization for families of preterm infants in the first 2 years of life is extremely high with increased clinic visits, hospitalizations, and medication usage (36–39). Most readmissions and use of healthcare services occur in the first weeks and months after initial NICU discharge (40–44). In addition to ocular sequelae, these infants are at risk for many other preterm comorbidities. These include BPD, NEC, IVH, patent ductus arteriosus, among others. These infants are also at risk for longer term sequelae of prematurity including neurologic abnormalities, developmental delays, and functional delays (45–47). Many of these diagnoses require multiple outpatient subspecialist follow up visits, which is a burden on the families who may also struggle with financial and employment insecurity due to missed work and loss of income (48).

The American Academy of Pediatrics recommends a minimum of seven well child care (WCC) visits in the first year of an infant's life (49). One study found that preterm infants average 20 or more visits to the doctor (WCC or specialty follow up), and preterm infants with multiple comorbidities averaged >30 visits per year (37). Twenty-five percent of these visits were for respiratory symptoms, growth, development, infections, or ROP follow-up.

In a study surveying parents of premature infants, 17% reported that having a large number of different appointments related to their infants' care was a barrier to ROP appointment follow up (35). The enormous amount of medical care for preterm infants after NICU discharge is an important barrier to follow up that should be addressed. Disparities in outpatient follow up rates have been noted, with lower attendance in post-discharge subspecialty care which occurs more often among Black families compared to White families (50, 51). Black infants were also more likely to miss their ROP follow up appointments than White infants (51).

High Readmission Rates

Preterm infants are a high risk population for readmission following discharge from the NICU (52–54). Morris et al. examined rehospitalizations of 1,591 extremely low birth weight infants from 14 centers of the National Institute of Child Health and Human Development Neonatal Research Network and found that 49% of these infants were readmitted before 18 months corrected age with respiratory, surgery, and infection listed as the top three causes (53). A larger study of 263,000 infants born between 1992 and 2000 in California found that readmission rates were much lower at 15%, but found similarly that the top causes of readmission were respiratory complications and infection (54).

Other studies have found racial, ethnic, and maternal age-related disparities in readmission rates (38, 42). In one study, compared to white infants, Hispanic and Black preterm infants were more likely to be readmitted in the first year of life (38). Additionally, infants born to mothers 19 years or younger had significantly increased odds of medical rehospitalizations and emergency department visits during the first 3 months after initial discharge compared with preterm infants born to young adult mothers (20–29 years of age) (42). This data suggests that identifying patients with these risk factors for high readmission rates should be considered by all members of the patients' care team and appropriate resources for support provided in order to ensure the best health outcomes for the child.

Patient Health Literacy

Healthy People 2010 defines health literacy as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions" (55). Baker et al. found that even when socioeconomic status and baseline health status are accounted for, poor health literacy is associated with increased mortality (56). As described by the definition above there are many important components to patient health literacy such as provider communication, language barriers, and the patient and family's internalization of their disease process. Adverse outcomes associated with ineffective communication among any of these components can include misunderstandings of a patient's concerns, misdiagnosis, unnecessary testing, poor adherence, and inappropriate follow-up.

The American Medical Association and National Institutes of Health recommend that written resources be written at 3rd to 7th grade level. John et al. analyzed articles for common pediatric ophthalmology conditions available online *via* search engine, including those available on professional society websites, and found that the majority of articles were written above recommended guidelines (57). In a prospective observational

study of medication adherence in pediatric glaucoma, Freedman et al. utilized the Rapid Assessment of Adult Literacy in Medicine, a word recognition test that involves words commonly used in the health care setting, and found that decreased adherence was associated with lower health literacy (58).

It is also important to consider the role of recognizing parents' health literacy at the time of diagnosis, and to utilize health communication techniques when counseling parents. Eneriz-Wiemer et al. noted in a study of four California NICUs that only half of parents with preterm infants in the NICU reported receiving information about their infants' ROP status at discharge (35). This finding raises the question of whether providers failed to discuss the diagnosis or if the diagnosis was not understood by families, and emphasizes the importance of using effective health communication techniques.

Language Barriers

Limited English proficiency (LEP) describes individuals who do not speak English as their primary language and who have a limited ability to read, speak, write, or understand English (59). In the United States, 30% of people are considered LEP (60), and patients with LEP have been shown to report poor communication with their provider, receive lower quality of care, have higher rates of misdiagnoses, and have significantly more emergency department visits and rehospitalizations (61–68). Parents are essential partners for ensuring timely outpatient follow up for ROP care. Studies have shown that LEP parents are more likely to report poor communication with health care providers compared to English proficient parents (65–67). Eneriz-Wiemer et al. found that among parents with premature infants, regardless of parent literacy level, parents with LEP had significantly lower odds of knowing that ROP is an eye disease of premature infants compared to literate, English-proficient parents (35).

Health care quality and outcomes improve for LEP patients and families when professional interpreters are used or language-concordant providers are available (69, 70). Unfortunately, it has been shown that LEP patients and families do not receive appropriate language services. A retrospective cohort analysis in an academic hospital showed that 66% of patients with LEP never had documentation of interpreter use during their hospital stay (71). Palau et al. conducted a structured interview of 132 English-speaking vs. Spanish-speaking parents in a Colorado NICU and found that NICU providers provided updates to Spanish-speaking parents in their native language only 39% of the time. In this same study, Spanish-speaking parents were four times more likely to incorrectly identify their child's diagnosis than English-speaking parents (72). These findings show that there are language-related health disparities that may be addressed to improve ROP care for patients with LEP.

Social Support and Parental Mental Health

For parents with multiple children, childcare is essential to ensure that parents can attend outpatient ROP follow up, particularly in the COVID-19 era where multiple family members are often not allowed in the waiting rooms to reduce crowding. In a survey done among 71 parents who had an infant who required outpatient ROP care in California, 22% reported that childcare was amongst the barriers to attending ROP appointments (35). In another study by Miguel-Verges et al. interviewing 45 Latinx families, 28% reported that they had no primary support person in the US to help with childcare (73).

Parental mental health is an important component to ensuring appropriate ROP follow up. Parenting premature infants is a difficult and demanding task for parents (74–76). Parents report feelings of guilt and grief with the perceived loss of their "normal" child (77). This grief can lead to depression for one or both parents. Postpartum depression (PPD) has also been shown to occur more frequently in women of lower socioeconomic status (78). Yonkers et al. found that half of postpartum major depressive episodes begin prior to delivery (79) indicating that PPD may impact parental functioning prior to parents arriving to the NICU with their infant. Given that depressive symptoms include fatigue, loss of energy, loss of interest, hypersomnia, and feelings of guilt, PPD may be another barrier to health literacy and comprehension of physician counseling during outpatient follow up visits for ROP. In a focus group with 47 parents of very low birth weight infants, psychosocial stressors such as feeling overwhelmed by the infant's care, and unmet needs for resources to get to or pay for appointments were noted as factors in preventing these parents from taking their infants to outpatient ROP appointments (34).

Patient-Oriented Solutions and Future Directions

Solutions to address the barriers to outpatient ROP follow up must consider the child in the setting of his or her environment and utilize a multidisciplinary approach that includes not only the ophthalmologist, but also ROP care coordinators, neonatologists, pediatricians, social workers, health communications workers and other healthcare providers. As outlined above, identifying risk factors such as access to care, health literacy, family and parental stressors, and health communication challenges, while recognizing the challenges specifically faced by minority populations in which disparities have been identified. Support for these interventions must be prioritized in policy setting at the local and national level. In the sections below, we proposed a series of patient-oriented solutions and future directions. **Table 1** summarizes the potential barriers to outpatient ROP follow up. **Table 2** highlights specific interventions that address the potential barriers of care described above.

Standardizing Personnel and Roles

ROP Coordinators

In high income countries, ROP coordinators are considered to be standard practice in the ROP care continuum to improve care coordination and follow-up. While the role of this coordinator is well-recognized, there are few standardized protocols, outcome and performance metrics, and training for this role to measure care outcomes and the effectiveness of the role. Wang et al. conducted an interview with 28 ROP providers (ophthalmologists, nurses, coordinators) who stressed the importance of the ROP coordinator role (34). The coordinator was able to build rapport with the families which was thought to encourage attendance at follow up ROP

TABLE 1 | Potential barriers to outpatient ROP follow up.

Potential barrier to follow up	Significant findings	References
Access to care	1. Insurance 2. Lack of Transportation 3. Few ROP Specialists within distance	(34, 35)
High healthcare utilization *a. High number of follow up clinic visits* *b. High readmission rates*	1. Multiple outpatient subspecialist follow up visits 2. There are racial and ethnic disparities in clinic follow up rates for ROP 3. Readmission rates for premature infants are high and may affect ROP follow up rates 4. There are racial, ethnic, and age related disparities for outpatient clinic follow up rates	(35, 37, 38, 42, 51, 54)
Patient health literacy	1. Majority of online pediatric ophthalmology resources for the public are written above recommended reading level guidelines 2. Decreased adherence for pediatric glaucoma patients was associated with lower parental health literacy 3. Only half of parents with preterm infants in the NICU reported receiving information about their infants' ROP status at discharge.	(35, 57, 58)
Language barriers	1. Regardless of parent literacy level, parents with limited English proficiency had significantly lower odds of knowing that ROP is an eye disease of premature infants 2. NICU providers provided updates to Spanish-speaking parents in their native language only 39% of the time 3. There are language related disparities that may be addressed to improve ROP care	(35, 71, 72)
Social support and parental mental health	1. Lack of childcare 2. Psychosocial stressors such as feeling overwhelmed by the infant's care, and unmet needs for resources to get to or pay for appointments 3. Postpartum depression (PPD) occurs frequently in women of lower socioeconomic status. PPD may be another barrier to health literacy and comprehension of physician counseling during outpatient follow up visits for ROP	(35, 73, 78, 79)

TABLE 2 | Patient-oriented solutions to improve outpatient ROP follow up.

Barrier to care	Patient-focused intervention
High healthcare utilization (multiple follow-up visits, high readmission rates)	1. Utilizing ROP care coordinators to schedule follow-up visits on the same day as other visits 2. Creating tracking systems to monitor post-discharge care 3. Coordinating with inpatient providers to schedule ROP screening visits inpatient during readmission
Health literacy and limited English proficiency	1. Providing patients with ROP informational resources at recommended reading levels 2. Utilizing health communication techniques to confirm family's comprehension of physician counseling 3. Standardized counseling by ROP coordinators during outpatient clinic visits 4. Utilization of interpreter services at all visits in the inpatient and outpatient setting
Access to care	1. Utilization of social work to coordinate transportation and childcare to enable parents to attend follow up visits 2. Coordination with financial services to determine which providers are in-network and at minimal cost to patient
Social support and parental mental health	1. Engaging primary care physicians and mental health providers to proactively screen for postpartum depression and parental mental health

appointments, though the role of these subjective characteristics are more difficult to elucidate.

The Ophthalmic Mutual Insurance Company (OMIC) provides a toolkit for ROP care that outlines recommended protocols for screening, diagnosis, management, and care coordination (80). The OMIC Safety Net tool describes the role of both a hospital ROP coordinator (H-ROPC) and an outpatient ROP coordinator (O-ROPC). At the time of initial diagnosis, the role of the H-ROPC is to maintain the screening list, track infants, and work with the O-ROPC at discharge planning. The role of the O-ROPC includes scheduling the initial outpatient visit, coordinating transitions between outpatient ophthalmologists including the retina specialists and pediatric ophthalmologists, provide ongoing education, and manage a reminder system to ensure follow up.

Social Workers

Recognizing that families of patients with ROP are navigating multiple follow up appointments in addition to social and financial barriers, creating a team of healthcare providers to support the family may improve adherence. A social worker with expertise in pediatric care would be able to provide education and resources that take into consideration a family's individual social, behavioral, and cultural factors. Patients should be screened with a formal assessment for any barriers to care (cost, insurance, transportation, distance, housing insecurity, food insecurity, childcare) in the NICU before discharge and at their first ROP appointment so they can be provided with the appropriate resources. The success of social work intervention in pediatric screening programs has been demonstrated. In a study involving social workers in an inner-city vision outreach program, after the inclusion of a social worker, the follow-up rates for positive screenings increased from $< 5\%$ to 59% (of 96 participants who required follow-up) (81). Silverstein et al. assessed the follow-up patterns of children referred for eye examination following a school based vision screening program, and offered social worker services and financial support to enable referred children to complete the eye examination (82).

Lack of transportation has been recognized as a barrier to ROP follow up as noted in multiple studies (26, 27). In a study cohort of very low birth weight infants, Catlett et al. were able to substantially increase developmental clinic attendance by providing transportation which was utilized in 31% of

families (83). Providing transportation or reimbursement is a potential strategy to mitigate the barrier of transportation especially for families who travel significant distances. Although not specifically designed for children with ROP, addressing transportation challenges was identified as an area for further development in the Wills Eye Vision Screening Program for Children to improve follow up, Silverstein et al. described methods used to incentivize referral visits for eye exams, such as the provision of transportation tokens (82). This is one example of a specific area where social workers can provide ancillary support.

Monitoring Post-discharge Care

Building on the previous discussion of the role of ROP coordinators, the second intervention is scheduling and monitoring post-discharge care, as well as ensuring that parents have the tools to communicate with the healthcare team. A key point is ensuring ROP follow up appointments are scheduled prior to NICU discharge and coordinating this with the ophthalmologists' staff and ROP coordinator. The effect of scheduling an appointment before discharge has been shown in many prior studies. In a randomized trial of pediatric asthma patients seen in a large urban emergency department, patients were significantly more likely to follow up with their primary care physician (64% vs. 46%) when an appointment was made for them at the time of the emergency department visit (84). A prospective study of 111 patients discharged from a pediatric intensive care unit found that compliance with subspecialty follow-up was significantly higher when follow-up was scheduled for a family vs. recommended (92% vs. 67%) (85). Attar et al. found that preterm infants at risk for ROP were much more likely to complete ROP follow up when it was scheduled for them prior to discharge (86).

Health Communication Interventions

Use of Technology to Increase Follow Up

At the time of NICU discharge it is also important to assist families in enrolling in the electronic health record to utilize integrated communication platforms which enables parents to stay in contact with the healthcare team. Additionally, ensuring that telephone numbers as recorded in the patient chart are accurate so that telephone reminders can reach the appropriate family members. One study showed that 79% of parents surveyed reported telephone reminders were helpful at prompting attendance for their child's appointment (87). It is also important to consider the timing of telephone reminders when parents must juggle multiple commitments; while many reminders are provided 48 hrs in advance, phone calls placed more than 1 week in advance allowed families time to arrange for transportation, child care, and work coverage (88).

Due to the increase in smartphone use in our society, health systems are expanding their use of mobile Health (mHealth) to improve communication with patients, especially text messaging. The National Institutes of Health defines mHealth as "the use of mobile and wireless devices (cell phones, tablets, etc.) to improve health outcomes, health care services, and health research (89)". There has been some variability in the evidence supporting the use of mHealth and text messaging to increase patient adherence to follow up. Tofighi et al. used text messaging to send appointment reminders to patients in an outpatient buprenorphine treatment program with 95% of patients reporting that text messaging was effective and favored over receiving telephone call reminders (90). Another study eliciting 50 parents opinions on text messaging showed that 100% of parents were willing to receive text messages for immunization reminders for their children (91). In a study done in Urology, a mHealth reminder, education program, and procedure preparedness assessment was created for patients to schedule a transrectal prostate biopsy. They found that in the post intervention cohort there were significantly fewer canceled or rescheduled appointments (33.8 vs. 21.2%), fewer same-day cancellations (3.8 vs. 0.5%), and increased patient satisfaction (4.5/5) (92). On the other hand, in a randomized controlled trial of 543 caregiver/child dyads using voicemail reminders vs. text messaging in a dental pediatric clinic, text messages were not as effective as voice reminders in increasing outpatient follow up (93). Future studies are needed to understand if using text messaging reminders or mHealth technology would be useful for parents of ROP infants to increase follow up adherence.

Improving Health Literacy and Language Barriers

Given the role of health literacy in improving communication between providers and families, the provision of health literature at an appropriate level is important for families to understand ROP and follow up screening and treatment. OMIC published a template that providers may use to standardize their approach in the hospital and in clinic on how to discuss ROP with families diagnosed in the NICU and a contract explaining the benefits and risks of treatment (80).

For families with LEP, it is necessary to increase professional medical interpreter use. Providers often believe that they spend more time with LEP patients than English-speaking patients even though it has been shown that there are no differences in appointment durations when professional on-site interpreters are used (94, 95). In a semi-structured interview conducted with 39 healthcare professionals from five specialties, providers reported that interpreters' ability to redirect and guide patients in the communicative process is valuable for time management (96). Telephone interpreter services (TIS) are useful and more accessible for healthcare providers especially now during the COVID-19 era. In a study interviewing 13 LEP patients, participants reported that TIS allowed them access to physicians with whom they felt the most comfortable, regardless of language ability and provided patients reassurance of accurate communication about their medical care (97). More research is needed to assess the use of interpreters and the reasons why ophthalmologists may not use interpreters in ROP clinics to better understand what solutions are needed.

CONCLUSIONS

This review article highlights the complexity of ROP care, and the need for a team-based approach to identify and address barriers to care including access to care, health literacy, language barriers, high healthcare utilization, and frequent need for follow-up. Parents of infants with ROP often face a multitude of social,

emotional, and financial factors that can affect adherence to care, and it is important for not only ophthalmologists, but the entire care team, to recognize and align resources to provide the best care possible to prevent vision loss.

AUTHOR CONTRIBUTIONS

TN, EC, AS, and RC: conception and design. TN, EC, and MChe: data collection and literature review. TN, EC, and RC: analysis, interpretation, and drafting of manuscript. TN, EC, AS, MChi, JC, and RC: critical revision of manuscript and overall responsibility. RC: obtained funding. All authors contributed to the article and approved the submitted version.

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Characteristics of Eyes Developing Retinal Detachment After Anti-vascular Endothelial Growth Factor Therapy for Retinopathy of Prematurity

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Background: We investigated the incidence and clinical characteristics of eyes showing retinal detachment (RD) after anti-vascular endothelial growth factor (VEGF) for retinopathy of prematurity (ROP).

Methods: A retrospective chart review of 76 consecutive eyes of 45 patients (18 girls and 27 boys) with stage 3 ROP who received anti-VEGF therapy between January 2012 and August 2020 with a minimum follow-up of 6 months was conducted. Eyes were divided into two groups: the vitrectomy (V) group that required vitrectomy for RD after anti-VEGF therapy and the non-vitrectomy (non-V) group that did not require vitrectomy. Data were collected from patient charts, including sex, postmenstrual age (PMA) at birth, birth weight, PMA at anti-VEGF therapy, comorbidities, reactivation, examination interval, and subsequent vitrectomies.

Results: The median PMA at birth was 24.7 (range, 22.1–29.3) weeks. Twenty-seven eyes (35.1%) exhibited ROP reactivation at 6.4 ± 3.1 weeks after anti-VEGF therapy. The V group included six eyes of five patients, all of whom exhibited reactivation and developed RD 10.1 ± 6.5 weeks after anti-VEGF therapy. The types of RD were conventional (classic) in two eyes and circumferential (unique to RD after anti-VEGF) in four eyes. Three eyes required repeated vitrectomy. All eyes, except one eye in the V group, achieved retinal attachment at the last examination. The non-V group included 70 eyes of 40 patients, of which 21 exhibited reactivation and were treated successfully with laser (17 eyes) or second anti-VEGF (4 eyes). The proportion of eyes with plus disease was significantly higher in the V group (50.0%) than in the non-V group (10.0%) ($P = 0.035$). V group included 3 of 22 eyes (13.6%) in which the interval between the last examination and the diagnosis of reactivation was <1 week and 3 of 5 eyes (60.0%) in which the interval was more than 1 week ($P = 0.024$). The two groups showed no significant differences in the other factors.

Conclusion: Approximately 8% of eyes developed RD about 10 weeks after anti-VEGF therapy for ROP. Eyes with history of plus disease should be carefully monitored at appropriate intervals after anti-VEGF therapy for ROP.

Keywords: vascular endothelial growth factor, anti-vascular endothelial growth factor, retinopathy of prematurity, reactivation, retinal detachment, vitrectomy

INTRODUCTION

Retinopathy of prematurity (ROP), which is caused by abnormal development of the retinal vessels of preterm infants (1), is the leading cause of infant blindness in both developed and developing countries (2). Over the past few decades, the standard treatment for avascular immature retinas has been laser ablation in patients with treatment-requiring ROP (3). However, the use of intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents has recently gained prominence. Bevacizumab (Avastin; Genentech Inc., South San Francisco, CA) and ranibizumab (Lucentis; Genentech Inc.) are the commonly used anti-VEGF drugs for these cases, and intravitreal injections of bevacizumab (IVB) and ranibizumab (IVR) have demonstrated efficacy in the treatment of stage 3 ROP (4–7). However, ROP reactivation after anti-VEGF therapy is not uncommon. Previous studies assessing the clinical outcomes of IVB or IVR therapy in eyes with ROP have reported reactivation rates of 6–14% (4, 7–11) and 0–80% (5, 7, 8, 12–14), respectively. Thus, timely detection and management of reactivation are major considerations for anti-VEGF therapy in cases of ROP.

Eyes with reactivation often present with recurrent plus disease or recurrent stage 3 ROP and may require treatment with laser ablation or repeated anti-VEGF therapy. Some eyes may progress to stage 4 or higher ROP, which may include, in addition to the typical traction RD seen in ROP, posterior atypical RD caused by fibrovascular contraction (15–19). The previous studies describing reactivation after anti-VEGF therapy focused on the reactivation rate and the risk factors for reactivation (7, 9, 12, 13, 20). However, to date, information regarding the characteristics and treatment outcomes of more severe cases showing RD development and requiring vitrectomy after IVB or IVR has not been well-documented.

Thus, the purpose of this study was to report the incidence, clinical characteristics, and treatment outcomes of eyes with RD after anti-VEGF therapy for ROP. We also examined the factors associated with the eyes that required vitrectomy.

METHODS

The study was approved by the Institutional Review Board of Kindai University Hospital (#26-251) and adhered to the tenets of the Declaration of Helsinki.

Patients

The medical records of consecutive patients with stage 3 ROP who were treated with IVB or IVR at Kindai University Hospital, a tertiary referral pediatric retina center, between January 2012 and August 2020 were retrospectively reviewed. One patient who received IVB at a referring hospital and subsequently underwent vitrectomy at Kindai University Hospital was also included. Patients were excluded if they received anti-VEGF therapy as adjunctive therapy before planned vitrectomy or underwent follow-up assessments for <6 months. Patients were also excluded if they received anti-VEGF therapy between April 2018 and November 2019, because the procedures performed during that period were not approved by the institutional review board due to policy changes in the Clinical Trial Act in Japan.

Ocular Examinations

At the initial examination, fundus photographs, and fluorescein angiograms were taken with a RetCam 3 digital fundus camera (Natus, San Carlo, CA, USA). The ROP stage and zone were evaluated by two pediatric retinal specialists based on the International Classification of Retinopathy of Prematurity, Third Edition (21). Ophthalmic examinations were performed before and 1, 7, 14, and 28 days after IVB or IVR therapy at our hospital and biweekly or monthly thereafter at the referring hospitals, depending on the fundus findings and systemic conditions. The efficacy of anti-VEGF therapy was evaluated by assessing improvements in the tortuosity and dilation of the retinal vessels and the dilation of the tunica vasculosa lentis. Reactivation was defined by the reappearance of vascular dilation, tortuosity, or new/recurrent neovascularization that required further treatment.

Intravitreal Injections of Anti-vascular Endothelial Growth Factor

The choice of IVB or IVR was dependent on the treatment period. Patients treated between January 2012 and June 2015 received IVB (0.25 mg/0.01 mL), and those treated between July 2015 and March 2018 received IVR (0.25 mg/0.025 mL). Since ranibizumab 0.2 mg/0.02 mL was approved by the Japanese Pharmaceuticals and Medical Devices Agency for the treatment of ROP in November 2019, the dosage of ranibizumab was changed thereafter. The anti-VEGF agent was administered as monotherapy for treatment-naïve patients or as an additional therapy to treat reactivation or persistent disease after laser therapy (salvage therapy). All parents or guardians were well-informed about the efficacy and possible complications before IVB or IVR, and written informed consent was obtained from each patient's parents or guardians. Anti-VEGF drugs were injected intravitreally with a 30-gauge needle, 0.5–1.0 mm away from the limbus, in the neonatal intensive care unit under topical anesthesia.

Vitrectomy

Vitrectomy was performed in eyes with vascularly active, progressive stage 4A or worse ROP associated with ROP reactivation. RDs were categorized into three configurations as described by Yonekawa et al. (15): (1) conventional, peripherally elevated ridge- or volcano-shaped stage 5 detachment, (2) midperipheral detachment with tight circumferential vectors, and (3) very posterior detachment with prepapillary contraction. All surgeries were performed by a single surgeon (S.K.). All eyes underwent lens-sparing vitrectomy (LSV) during the initial surgery. The surgical techniques for LSV that were first described by Maguire and Trese (22) in infants were modified as described previously (23). In brief, after conjunctival peritomy, sclerotomies were performed 0.5–1 mm away from the limbus, followed by insertion of 25-gauge or 27-gauge cannulas. The direction of insertion was more posterior than toward the center of the eyeball to avoid lens damage (24). The wide-angle viewing system Resight® (Carl Zeiss Meditec AG, Jena, Germany) was used for the fundus view. Fibrous tissue traction was released to achieve retinal reattachment. Membrane dissection using 25- or 27-gauge horizontal and/or vertical scissors (DORC, Zuidland, Netherlands) was minimized to avoid intraoperative bleeding and/or the creation of an iatrogenic retinal break. For eyes that could not achieve retinal reattachment after the initial vitrectomy, repeated vitrectomies were performed. In patients showing severe fibrous tissue traction who could not be expected to show postoperative retinal reattachment with gas or silicone oil (SO) tamponade, short-term perfluoro-*n*-octane (PFO) tamponade (25) was used. Lensectomy was performed as part of the reoperation, if necessary.

Statistical Analysis

Statistical analyses were performed using JMP version 14.0, for Windows (SAS Institute, Cary, NC, USA). Data were presented as means and standard deviations, unless otherwise stated. Statistical analyses of continuous variables were performed using Mann-Whitney test. Categorical variables were compared using Fisher's exact test. Statistical significance was set at $P < 0.05$.

Risk Factors

The potential systemic risk factors obtained from medical records included sex, postmenstrual age (PMA) at birth, birth weight (BW), BW at first fundus examination, Apgar scores (1 and 5 min), history of oxygen inhalation (intubation or nasal inhalation), tracheal intubation, comorbidities (respiratory distress, bronchopulmonary dysplasia, gastrointestinal perforation, patent ductus arteriosus, meconium aspiration syndrome, chorioamnionitis, sepsis, disseminated intravascular coagulation, hydrocephalus, periventricular leukomalacia, and intraventricular hemorrhage), and treatment (erythropoietin administration, red blood cell transfusion, and total parenteral nutrition).

Additionally, the medical records of each eye were reviewed to obtain information regarding the zone of ROP, aggressive ROP (A-ROP) which is defined by the International Classification of Retinopathy of Prematurity, Third Edition as an "rapid development of pathologic neovascularization and severe plus disease without progression being observed through the typical stages of ROP (21), presence of plus disease, previous treatment, PMA at the time of first examination, PMA at the first treatment (laser ablation at the referring hospital or anti-VEGF therapy), PMA at anti-VEGF therapy, and types of anti-VEGF drugs (bevacizumab or ranibizumab).

Patients were divided into two groups: vitrectomy (V) and non-vitrectomy (non-V) groups. The V group included infants who required vitrectomy for RD after anti-VEGF therapy. The non-V group included infants who did not require vitrectomy after anti-VEGF therapy. The demographic and ocular characteristics of the V and non-V groups were compared. In the comparison of demographic characteristics, patients with one eye in the V group and the other in the non-V group were categorized in the V group. For eyes showing reactivation, the period between anti-VEGF therapy and reactivation, PMA at reactivation, and the period between the diagnosis of reactivation and the last examination before reactivation were also reviewed. For eyes in the V group, PMA at the diagnosis of RD, RD configuration, and the vitrectomy procedure were also reviewed.

RESULTS

A total of 76 eyes of 45 patients with stage 3 ROP who received anti-VEGF therapy were analyzed in this study. All the patients were Japanese. The patient demographics are listed in **Table 1**. The median follow-up period was 48.3 months (range, 9.4–104.5 months). The median PMA at birth was 24.7 weeks (range, 22.1–29.3 weeks), and the median BW was 591 g (range, 304–1,198 g). The V and non-V groups showed no significant differences in sex, BW, PMA at birth, BW at first examination, Apgar scores (1 and 5 min), or the rates of patients with comorbidities (respiratory distress, bronchopulmonary dysplasia, gastrointestinal perforation, patent ductus arteriosus, meconium aspiration syndrome, chorioamnionitis, sepsis, disseminated intravascular coagulation, hydrocephalus, periventricular leukomalacia, and intraventricular hemorrhage), a history of oxygen inhalation (intubation or nasal inhalation), tracheal intubation, or systemic treatment (erythropoietin administration, red blood cell transfusion, and total parenteral nutrition).

Thirty and 46 eyes received IVB and IVR, respectively. All eyes showed regression of tortuosity and dilation of the retinal vessels and tunica vasculosa lentis. The ocular characteristics of the patients are presented in **Table 2**. The two groups showed no significant differences in the ROP zone at the diagnosis of ROP or the ratio of A-ROP. However, the proportion of eyes with plus disease was significantly higher in the V group (50.0%) than in the non-V group (10.0%) ($P = 0.035$). The two groups showed no statistically significant differences in the mean PMA at the first examination, the first treatment, and at anti-VEGF therapy. No systemic or ocular complications related to intravitreal injection were noted, except for reactivation and subsequent RD.

The baseline data of the eyes showing reactivation are presented in **Table 3**. Reactivation occurred in 27 of 76 eyes (35.1%) 6.4 ± 3.1 weeks after anti-VEGF therapy, including all six eyes in the V group and 21 eyes in the non-V group. The mean

TABLE 1 | Demographic characteristics of the study groups.

	All patients ($n = 45$)	V group ($n = 5$)	Non-V group ($n = 40$)	*P*
Boy/Girl	27/18	2/3	25/15	0.339*
Birth weight (grams)	625.0 ± 190.0	604.6 ± 118.2	629.0 ± 208.2	0.914**
Postmenstrual age (weeks)	24.7 ± 1.5	24.1 ± 1.1	24.8 ± 1.7	0.575**
Body weight at first examination (grams)	1,015.1 ± 302.0	976.8 ± 248.5	1021.7 ± 318.8	0.903**
Oxygen inhalation (intubation/nasal inhalation)	34 (75.6%)	5 (100%)	29 (72.5%)	0.083*
Length of oxygen intake (days)	148.9 ± 117.8	122.8 ± 38.5	153.1 ± 125.9	0.945**
Tracheal intubation	13 (28.9%)	2 (40.0%)	11 (27.5%)	0.572*
Apgar score at 1 min	3.0 ± 1.9	3.0 ± 1.6	3.0 ± 2.0	0.759**
Apgar score at 5 min	5.2 ± 2.1	6.0 ± 2.0	5.1 ± 2.1	0.305**
RDS	38 (84.4%)	5 (100%)	33 (82.5%)	0.459*
BPD	35 (77.8%)	5 (100%)	30 (75.0%)	0.231*
Gastrointestinal perforation	7 (15.6%)	1 (20.0%)	6 (15.0%)	0.899*
PDA	28 (62.2%)	4 (80.0%)	24 (60.0%)	0.590*
Meconium aspiration syndrome	1 (2.2%)	0 (0%)	1 (2.5%)	0.600*
Chorioamnionitis	23 (51.1%)	2 (40.0%)	21 (52.5%)	0.652*
Sepsis	8 (17.8%)	2 (40.0%)	6 (15.0%)	0.210*
DIC	7 (15.6%)	2 (40.0%)	5 (12.5%)	0.154*
Hydrocephalus	4 (8.9%)	1 (20.0%)	3 (7.5%)	0.455*
PVL	4 (8.9%)	0 (0%)	4 (10.0%)	0.281*
IVH	17 (37.8%)	1 (20.0%)	16 (40.0%)	0.635*
Period of EPO administration (days)	46.8 ± 30.5	58.2 ± 38.1	45.1 ± 30.0	0.309**
RBC transfusion	34 (75.6%)	4 (80.0%)	30 (75.0%)	0.954*
The amount of RBC transfused (mL/kg)	48.2 ± 48.2	40.0 ± 40.0	49.3 ± 50.9	0.871**
The period of TPN (days)	32.2 ± 47.8	57.6 ± 94.4	28.2 ± 38.2	0.722**

BPD, bronchopulmonary dysplasia; DIC, disseminated intravascular coagulation; EPO, erythropoietin; IVH, intraventricular hemorrhage; non-V group, the non-vitrectomy group; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; RBC, red blood cell; RDS, respiratory distress syndrome; TPN, total parenteral nutrition; V group, the vitrectomy group.
**Fisher's exact test.*
***Mann–Whitney U test.*

TABLE 2 | Ocular characteristics of the study groups.

	All eyes ($n = 76$)	V group ($n = 6$)	Non-V group ($n = 70$)	*P*
A-ROP	10 (13.2%)	2 (33.3%)	8 (11.4%)	0.181*
Zone at the diagnosis of ROP				
Zone 1	35 (46.1%)	4 (66.7%)	31 (44.3%)	0.405*
Zone 2	41 (53.9%)	2 (33.3%)	39 (55.7%)	
Plus disease	10 (13.2%)	3 (50.0%)	7 (10.0%)	0.035*
PMA at the first examination (weeks)	30.5 ± 1.7	30.5 ± 1.7	30.5 ± 1.7	0.922**
PMA at the first treatment (weeks)	34.0±1.9	33.3 ± 2.1	34.1 ± 1.9	0.247**
PMA at anti-VEGF therapy (weeks)	36.3±3.1	34.3 ± 2.5	36.5 ± 3.1	0.096**
VH before anti-VEGF therapy ($n = 66$)	9 (13.6%)	1 (16.7%)	8 (13.3%)	0.821*
Treatment				
IVB	30 (39.5%)	3 (50.0%)	27 (38.6%)	0.587*
IVR	46 (60.5%)	3 (50.0%)	43 (61.4%)	
Previous Treatment				
Laser	43 (56.6%)	2 (33.3%)	41 (58.6%)	0.232*
None	33 (43.4%)	4 (66.7%)	29 (41.4%)	

A-ROP, aggressive retinopathy of prematurity; IVB, intravitreal injection of bevacizumab; IVR, intravitreal injection of ranibizumab; non-V group, the non-vitrectomy group; PMA, postmenstrual age; VEGF, vascular endothelial growth factor; V group, the vitrectomy group; VH, vitreous hemorrhage.
**Fisher's exact test. **Mann–Whitney U test.*

TABLE 3 | Ocular characteristics of eyes showing reactivation.

	All eyes ($n = 27$)	V group ($n = 6$)	Non-V group ($n = 21$)	*P*
A-ROP	6 (22.2%)	2 (33.3%)	4 (19.0%)	0.473*
Zone at the diagnosis of ROP				
Zone 1	17 (63.0%)	4 (66.7%)	13 (61.9%)	0.830*
Zone 2	10 (37.0%)	2 (33.3%)	8 (38.1%)	
Plus disease	7 (25.9%)	3 (50.0%)	4 (19.0%)	0.144*
PMA at the first examination (weeks)	30.2 ± 1.7	30.5 ± 1.7	30.2 ± 1.8	0.558**
PMA at the first treatment (weeks)	33.3 ± 1.7	33.3 ± 2.1	33.3 ± 1.7	0.682**
PMA at anti-VEGF therapy (weeks)	33.7 ± 1.9	34.3 ± 2.5	33.5 ± 1.8	0.726**
VH before anti-VEGF therapy ($n = 25$)	4 (16.0%)	1 (16.7%)	3 (15.8%)	0.959*
Treatment				
IVB	11 (40.7%)	3 (50.0%)	8 (38.1%)	0.603*
IVR	16 (59.3%)	3 (50.0%)	13 (61.9%)	
Previous treatment				
Laser	8 (29.6%)	2 (33.3%)	6 (28.6%)	0.823*
None	19 (70.4%)	4 (66.7%)	15 (71.4%)	
Period between anti-VEGF therapy and reactivation (weeks)	6.4 ± 3.1	5.7 ± 3.8	6.6 ± 3.1	0.381**
PMA at reactivation (weeks)	40.1± 3.7	40.0 ± 2.7	40.1 ± 4.1	0.953**
Examination interval longer than 1 week	5 (18.5%)	3 (50.0%)	2 (9.5%)	0.024*

A-ROP, aggressive retinopathy of prematurity; IVB, intravitreal injection of bevacizumab; IVR, intravitreal injection of ranibizumab; non-V group, the non-vitrectomy group; PMA, postmenstrual age; VEGF, vascular endothelial growth factor; V group, the vitrectomy group; VH, vitreous hemorrhage.
**Fisher's exact test. ** Mann–Whitney U test.*

period between anti-VEGF therapy and reactivation was 5.7 ± 3.8 and 6.6 ± 3.1 weeks in the V and non-V groups, respectively ($P = 0.381$). The mean PMA at reactivation was 40.0 ± 2.7 and 40.1 ± 4.1 weeks in the V and the non-V groups, respectively ($P = 0.953$). The V group included three of 22 eyes (13.6%) in which the interval between last examination and the diagnosis of reactivation was 1 week or less, and three of five eyes (60.0%) in which the interval was more than 1 week. ($P = 0.024$).

Among the 21 eyes showing reactivation in the non-V group, 17 received laser therapy and four received second anti-VEGF therapy, resulting in regression of the disease in all eyes. The detailed clinical characteristics of the six eyes in the V group are shown in **Table 4**. In the V group, after reactivation was identified, three eyes received additional laser therapy before the development of RD. RD was first diagnosed 10.1 ± 6.5 (range, 2.6–22.4) weeks after anti-VEGF therapy and subsequent vitrectomy for the treatment of RD was performed 10.9 ± 6.4 (range, 2.9–23.1) weeks after anti-VEGF therapy. The stages of RD in the six eyes in the V group were stage 4A in one eye, 4B in two eyes, 5A in one eye, and 5B in two eyes. The types of RD (15) were conventional (classic) in two eyes and circumferential (unique to RD after anti-VEGF therapy) in four eyes. The mean PMA at vitrectomy was 46.5 ± 7.6 weeks (range, 35.0–56.6 weeks). All six eyes underwent LSV during the first vitrectomy. Three eyes achieved retinal reattachment after the first vitrectomy. Two eyes underwent subsequent lensectomy and vitrectomy with short-term PFO tamponade (25) during the second vitrectomy. One patient showed retinal reattachment after PFO removal. The remaining eye required vitrectomy with SO tamponade for the treatment of RD after PFO removal and showed retinal reattachment after SO removal. One eye underwent PPV and lensectomy as the second surgery; however, it was judged to be inoperable during surgery (**Figure 1**). Overall, the numbers of vitrectomies were one for 3 eyes, two for 1 eye, three for 1 eye, and four for 1 eye. Finally, all except one eye in the V group showed retinal reattachment at the last examination.

DISCUSSION

The present study investigated the incidence, features, and treatment outcomes of RD requiring vitrectomy after anti-VEGF therapy in Japanese patients with ROP at a single tertiary referral hospital. The results demonstrated that, of all eyes that received anti-VEGF for ROP, 7.9% eventually developed RD. In addition, plus disease at first examination, as well as a long interval between the last examination prior to reactivation and the diagnosis of reactivation were identified as significant risk factors for the development of RD.

Reactivation of ROP after anti-VEGF therapy in some infants can occur because of a resurgence of VEGF when the anti-VEGF agent is cleared from the eye (27). Such infants may require more than one treatment session (27). To identify high-risk patients and monitor them diligently, several reports have investigated risk factors for reactivation after IVR or IVB. Lower BW, lower gestational age, longer duration of hospitalization, extensive retinal neovascularization, requirement for supplemental oxygen, pre-retinal hemorrhage before injection, younger PMA at treatment, and A-ROP were

TABLE 4 | Clinical characteristics of infants and eyes developing RD after anti-VEGF therapy.

No.	PMA at birth (weeks)	Birth Weight, (gram)	Eye	PMA at initial anti-VEGF (weeks)	Zone at the diagnosis of ROP	IVB or IVR	PMA at reactivation (weeks)	Interval between reactivation and the last examination before the reactivation (days)	Treatment for reactivation before vitrectomy [PMA (weeks)]	PMA at the diagnose of retinal detachment (weeks)	Stage and Retinal detachment configuration (26)	Procedure of vitrectomy [PMA (weeks)]	Final retinal reattachment
1	24	470	OS	34	1	IVB	38	4	laser [39]	56	S4A: Relatively peripheral with a circumferential configuration	LSV [57]	Yes
2	24	704	OD	35	2	IVB	38	7	None	38	S4B: peripheral ridges	LSV [38]	Yes
3	24	686	OS	37	2	IVR	42	10	None	44	S5B: Relatively peripheral with a circumferential configuration anterior and posterior	LSV [46] PPV+PPL+PFO [52] PFO removal [54]	Yes
4	23	682	OD	32	1	IVR	44	18	laser [39] IVR and laser [43]	44	S5A: Relatively peripheral with a circumferential configuration anterior and posterior	LSV [56] PPV+PPL+PFO [59] PPV+PFO removal+SO [61] SO removal [70]	Yes
5	23	682	OS	32	1	IVR	39	7	laser [39]	43	S5B: Volcano-shaped anterior and posterior	LSV [43] PPV + lensectomy [44]	No
6	22	481	OD	37	1	IVB	39	9	None	43	S4B: Relatively peripheral with a circumferential configuration	LSV [43]	Yes

IVB, intravitreal injection of bevacizumab; IVR, intravitreal injection of ranibizumab; LSV, lens-sparing vitrectomy; OD, right eye; OS, left eye; PMA, postmenstrual age; PFO, perfluoro-n-octane; PPL, pars plana lensectomy; PPV, pars plana vitrectomy; S4A, stage 4A; S4B, stage 4B; S5A, stage 5A; S5B, stage 5B; SO, silicone oil; VEGF, vascular endothelial growth factor.

FIGURE 1 | Fundus images of the left eye of one patient in the V group (case 5), who received intravitreal ranibizumab monotherapy (IVR) for zone 1 plus retinopathy of prematurity. After receiving laser therapy for reactivation 7 weeks after IVR, vitreous hemorrhage occurred, and the fundus continued to be invisible for 4 weeks until absorption of the vitreous hemorrhage. **(A)** The fundus image obtained immediately before IVR demonstrated a blurred retina due to a prominent tunica vasculosa lentis. **(B)** Fundus image obtained 2 days after IVR showing improved transparency of the fundus and dilation of the retinal vessels. **(C)** Fundus image obtained 11 weeks after IVR showing volcano-shaped stage 5B ROP with thick proliferative membrane. This eye underwent LSV at 43 weeks postmenstrual age (PMA), and PPV and lensectomy for persistent retinal detachment at 44 weeks PMA, however, it was judged to be inoperable during surgery.

reported to be possible risk factors for reactivation (7, 9, 12, 13, 20). These individual factors were important for reactivation; however, we found that they were not significant for development of RD after anti-VEGF therapy. On the other hand, plus disease was a possible risk factor for the development of RD after IVR or IVB for the treatment of stage 3 ROP.

Plus disease, which was first defined during the 1980s by an international consensus panel (28) as abnormal posterior pole retinal vessel dilation and tortuosity, is a major indicator for the treatment of severe ROP (21). Eyes with plus disease are likely to show rapid progression of ROP and the development of RD. Biochemical analysis of the vitreous of stage 4 ROP eyes showed significantly elevated VEGF and transforming growth factor-beta (TGF-β) concentrations (29). In addition, studies in adults have demonstrated that the levels of the profibrotic cytokine TGF-β may increase with anti-VEGF therapy (30). TGF-β is a profibrotic cytokine, and upregulation of TGF-β following anti-VEGF therapy might be the cause of tractional RDs in eyes with plus disease receiving anti-VEGF therapy.

Another risk factor for the development of RD after IVR or IVB was the period between the diagnosis of reactivation and the last examination before the reactivation, which was significantly longer in the V group than in the non-V group. This result highlights the importance of close monitoring after anti-VEGF therapy. Although screening criteria for ROP have been established (31), there is no consensus regarding the

follow-up of patients treated with anti-VEGF therapy. Martínez-Castellanos et al. (26) recommended that patients who receive IVB should undergo the first follow-up examination at 3–7 days, followed by examinations at 1–2-week intervals based on both the degree of improvement and the stage until complete retinal vascularization. However, frequent visits are often difficult once infants are discharged, especially for infants who may require treatment for other systemic comorbidities. Most previous reports have not described examination schedules or periods between visits after anti-VEGF therapy. On the basis of our findings, whether or not seeing these patients more frequently would have changed the need for vitrectomy. We believe that careful follow-up and early detection of reactivation are critical in reducing the development of RD after anti-VEGF therapy.

With regard to the proportion of cases showing RD after anti-VEGF therapy for ROP, 6 of 76 eyes (7.9%) developed RD in this study. The BEAT-ROP study reported that 2 of 75 eyes (2.7%) developed RD after IVB (4). Another case series found that the incidence of RD was 0–2.0% (10–13). The relatively higher incidence in this study may reflect differences in the timing of anti-VEGF therapy (monotherapy or salvage therapy), types of anti-VEGF drugs (IVB or IVR), variable follow-up schedules, presence or absence of routine additional laser therapy after anti-VEGF therapy, and the degree of immaturity in our patients.

Anti-VEGF crunch syndrome has been described in eyes with proliferative diabetic retinopathy and ROP following anti-VEGF therapy (15, 17, 32). The progression of preexisting tractional RDs after IVB as a surgical adjunct for tractional RDs secondary to proliferative diabetic retinopathy has been reported previously (33). The absence of previous laser photocoagulation and the presence of a ring-shaped fibrovascular membrane were relevant findings in eyes with these IVB-induced complications. RD configurations in this study were classified into three types according to a previous study by Yonekawa et al. (15). In this study, conventional RDs were noted in two eyes (33%), and circumferential RDs were noted in four eyes (67%). None of the eyes developed RDs with pre-papillary configuration, which was noted in 29% of the eyes with or without anti-VEGF therapy in the study by Yonekawa et al. (15). Xu et al. (16) also reported the details of nine eyes that showed RD after anti-VEGF therapy, including three eyes showing conventional RDs and six eyes with circumferential RDs. The proportion of conventional and circumferential RDs and the absence of a prepapillary configuration were similar to our results. RDs with pre-papillary and circumferential configurations have been reported to be difficult to repair, with anatomic success rates of 67 and 75%, respectively (15). In our study, all but one patient with conventional RD achieved retinal reattachment. This variability is likely due to differences in patient populations, small sample sizes, and variable postoperative follow-up periods.

One eye without retinal attachment in our study (Case 5, **Figure 1**) was diagnosed with stage 5B at 11 weeks after IVR. Before RD was confirmed, the fundus was invisible due to vitreous hemorrhage for 4 weeks. Development of vitreous hemorrhage was likely to be a symptom of increased activity of retinopathy, and earlier vitrectomy was probably desirable considering the risk of RD. The other two cases that required vitrectomy for stages 5B and 5A were cases in which reactivation was found 10 and 18 days after the last examination, respectively. In contrast, in the remaining three eyes, surgical interventions were possible at relatively earlier stages, that is, at stage 4A (one eye) and 4B (two eyes). These patients were followed up with relatively short examination intervals (4, 7, and 9 days). Retinal reattachment was achieved after initial vitrectomy in these eyes. Since the anatomical and functional results of vitrectomy for stage 4 ROP are generally better than those for stage 5 ROP (23), earlier detection of RD and vitrectomy are critical in achieving better surgical results.

This study had several limitations. First, the ROP-related conditions at the time of anti-VEGF therapy, such as the presence or absence of previous treatment before anti-VEGF therapy or follow-up schedules after anti-VEGF therapy, were not uniform, since most of the patients were referred to our hospital and were followed up at the referring hospitals after discharge from our hospital. This could have led to a lack of uniformity in the diagnosis of plus disease and A-ROP. However, our results are likely to reflect real-world clinical data during the period when laser ablation is still the gold standard for primary treatment for ROP. Second, due to the small number of cases with RD, adequate statistical analysis could not be performed. Third, the dosing of IVB (0.25 mg) used in our study was not generalizable, since it was different from the commonly used dosage of 0.625 mg. Lastly, there was a lack of consideration of maternal perinatal comorbidities. Despite these limitations, our study demonstrates that plus disease is a risk factor for the development of RD after anti-VEGF therapy and highlights the importance of close monitoring after anti-VEGF therapy, providing useful information regarding the clinical characteristics of eyes developing RD after anti-VEGF therapy.

In conclusion, nearly 8% of eyes developed RD approximately 10 weeks after anti-VEGF therapy for ROP. The presence of plus disease at the first examination and a long interval between the diagnosis of reactivation and the last examination before reactivation were associated with the development of RD. Careful follow-up with appropriate intervals is recommended after anti-VEGF therapy for ROP.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Kindai University Hospital (#26-251). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained

from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

CK, SU, YK, and NW acquired the data. CK, SU, CI, and RK analyzed the data and drafted the manuscript. KK and SK revised the manuscript. All authors contributed to conception, design of the research, interpretation of the results, and edited the manuscript.

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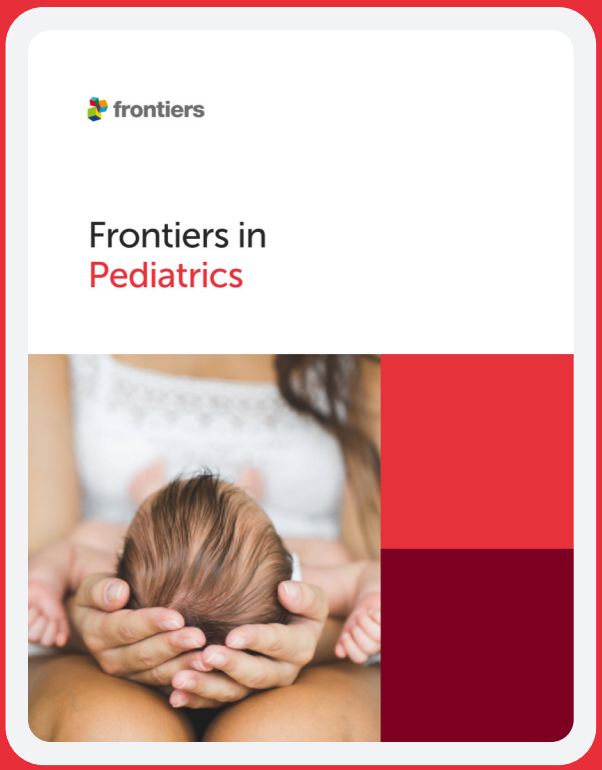

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