Association Between Retinopathy of Prematurity in Very-Low-Birth-Weight Infants and Neurodevelopmental Impairment

GYULE HAN[1], DONG HUI LIM[1], DANBEE KANG, JUHEE CHO, ELISEO GUALLAR, YUN SIL CHANG, TAE-YOUNG CHUNG, SANG JIN KIM, AND WON SOON PARK

• PURPOSE: To evaluate the impact of retinopathy of prematurity (ROP) severity and the treatment of very-low-birth-weight infants (VLBWIs) on neurodevelopmental impairment in early childhood.

• DESIGN: Prospective cohort study.

• METHOD: This was a prospective cohort study. The data were obtained from the Korean Neonatal Network (KNN), a nationwide registry for VLBWIs. Infants who were born from 2013 to 2015 and underwent ROP evaluation at birth and neurodevelopmental examinations at corrected ages of 18 to 24 months were included in the study. Infants with a history of meningitis or severe congenital anomalies were excluded. The VLBWI patients were grouped into no ROP, no treatment-requiring ROP (non−TR-ROP), and treatment-requiring ROP (TR-ROP) groups. Neurodevelopmental impairment was defined as participants who had at least 1 developmental problem according to the Bayley Scales of Infant and Toddler Development−2nd Edition (Bayley-II; <70), Bayley Scales of Infant and Toddler Development−3rd Edition (Bayley-III; <70), and Korean Developmental Screening Test (K-DST) tests (below −1 SD), and the Korean Ages and Stages Questionnaire (K-ASQ) (below the threshold) and Gross Motor Function Classification System (GMFCS; at level 2 or above). Multivariable logistic regression analysis was performed to evaluate the association between ROP and neurodevelopmental impairment.

• RESULT: Among 3132 infants, 1093 (34.9%) had ROP. Among the ROP infants, 644 were not treated for ROP (non-TR-ROP group) and 449 received ROP treatments (TR-ROP group). The patients in the TR-ROP group had an increased risk of developing neurodevelopmental problems compared to those in the no ROP group (odds ratio [OR] = 1.72, 95% CI = 1.33-2.21). The TR-ROP group had a higher risk of all 3 types of neurodevelopmental problems: mental (OR = 1.62, 95% CI = 1.25-2.09), social (OR = 1.62, 95% CI = 1.12-2.09), and motor (OR = 1.69, 95% CI = 1.31-2.18). The risk of neurodevelopmental problems in patients treated with laser therapy did not differ from that in patients treated with anti−vascular endothelial growth factor (anti-VEGF) therapy (OR = 1.17, 95% CI = 0.73-1.88).

• CONCLUSION: ROP was independently associated with neurodevelopmental impairment in early childhood. The type of ROP treatment (anti-VEGF or laser treatment) did not affect neurodevelopmental impairment in patients in the TR-ROP group. (Am J Ophthalmol 2022;244: 205–215. © 2022 Elsevier Inc. All rights reserved.)

Although the survival rate of very-low-birth-weight infants (VLBWIs; <1500 g of birth weight) has increased up to 80% to 90% in developed countries,[1] there has been no equivalent improvement in neurodevelopmental outcomes. According to a recent study, nearly half of the surviving extremely premature infants had significant neurodevelopmental disabilities on short- and long-term follow-up.[2] As neurodevelopmental disability−free adults born preterm are known to have a similar health-related quality of life compared to term-born peers, reducing the neurodevelopmental impact of prematurity is considered to be important in neonatal care.[3] Prematurity itself is not inevitably associated with adverse neurodevelopmental outcomes.[4] However, a variety of comorbidities affect the brain maturation of the actively maturing preterm brain. Bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and severe retinopathy of prematurity (ROP) are the known risk factors for neurodevelopmental impairment.[5] BPD has been considered to influence neurodevelopmental delay by chronic intermittent hypoxia, growth deficiencies, and altered environmental stimulation.[6] The pathogenesis of neurodevelopmental impairment following

Accepted for publication August 10, 2022.

From the Department of Ophthalmology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Sciences & Technology (SAIHST), Sungkyunkwan University, Seoul, Korea; Center for Clinical Epidemiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; Department of Epidemiology, Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; Department of Health Science and Technology, SAIHST, Sungkyunkwan University, Seoul, Korea

Inquiries to Won Soon Park and Sang Jin Kim, Sungkyunkwan University School of Medicine, Seoul, Korea; e-mail: sangjin.kim.md@gmail.com, wonspark@skku.edu

[1] Gyule Han and Dong Hui Lim contributed equally to the work as first authors

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2022.08.010

NEC is likely multifactorial, with both nutritional and nonnutritional factors (growth impairment, inflammation, and intestinal microbiota) at play.[7]

Previous studies have reported inconsistent results with regard to the association between ROP and neurodevelopment. Some studies have found that severe ROP was an independent predictive marker for neurodevelopmental impairment and functional disability.[8,9] Other studies have reported that neurodevelopmental disabilities were not related to severe ROP.[10,11] In a meta-analysis of prognostic factors for poor cognitive development in very preterm or VLBWI, ROP was not found to be an indicator of poor developmental outcomes.[12] The results varied depending upon the proportion of gestational ages (GA) in the observed individuals, factors accounted for as covariates, and quality of neonatal intensive care unit (NICU) care.

Thus, we conducted a prospective cohort study using a nationwide VLBWI registry to evaluate the effect of ROP and ROP treatment of VLBWIs on neurodevelopmental impairment in early childhood.

METHODS

• **STUDY POPULATION AND DESIGN:** This is a prospective cohort study. The Korean Neonatal Network (KNN) is a nationwide prospective registry to collect standardized data for evaluating modality, morbidity, and mortality of VLBWIs. The KNN was established in 2013, and 69 NICUs in Korea are participating in the registry.[13]

Because our objective was to evaluate the association between ROP and neurodevelopmental impairment, we included study infants who had examinations for ROP from January 1, 2013, to December 31, 2015, and a neurodevelopmental examination at the corrected ages of 18 to 24 months. Informed consent was obtained from the parents of each infant prior to participation in the KNN registry. Detailed information on the cohort is described elsewhere.[13] The Institutional Review Board of Samsung Medical Center approved this study (IRB no.: SMC 2020-01-008) and waived the requirement for informed consent because only de-identified data were used.

• **DATA COLLECTION:** The KNN includes maternal, delivery, neonatal, and follow-up data collected by trained staff using a standardized operating procedure.[14] The KNN coordinating center, which is located at the Clinical Research Institute of Samsung Medical Center in Seoul, Korea, is in charge of quality control and assurance of the data. Data acquisition for the registry covers 3 visits as follows: at discharge from the NICU, long-term outpatient follow-up at 18 to 24 months of corrected age, and at the age of 3 years.

The maternal and neonatal variables include approximately 120 items, including GA, birth weight, sex, Apgar score at 1 and 5 minutes, patent ductus arteriosus, moderate-to-severe BPD, sepsis, intraventricular hemorrhage, NEC, neonatal seizure, periventricular leukomalacia, respiratory distress syndrome, use of antenatal steroids, mechanical ventilator care, hearing problems at discharge, and about 70 items including ophthalmological disease, ophthalmological outcomes, hearing outcomes, and neurodevelopmental assessment at corrected ages of 18 to 24 months follow-up. Among the ophthalmologic outcomes, the diagnosis of blindness was made by certified ophthalmologist if the child was unable to both fix and follow. Hearing test was done by auditory brainstem response threshold (ABR-T) test and impedance audiometry (otoacoustic emission if possible). Threshold equal to or greater than 40 decibels from ABR-T was diagnosed as hearing impairment. The diagnosis of hearing loss was made by a certified otolaryngologist based on hearing test results.

• **RETINOPATHY OF PREMATURITY:** In the KNN registry, ophthalmic examinations and treatment were done by a certificated ophthalmologist at the participating centers. In this study, we classified the VLBWIs into 3 groups according to the presence and treatment of retinopathy of prematurity (ROP): the no ROP group; the ROP with no treatment (non−TR-ROP) group; and the ROP with treatment (TR-ROP) group. ROP treatment was performed based on the guidelines from the Early Treatment of Retinopathy of Prematurity study, which were any stage of ROP with plus disease (abnormal dilation and tortuosity of the blood vessels) or stage 3 ROP in zone I, stage 2 or 3 ROP in zone II with plus disease, and equal to or worse than stage 4.[15] The treatment for ROP included surgery (laser photocoagulation) and/or the intravitreal injection of anti−vascular endothelial growth factor (anti-VEGF) agent. Infants who had ROP treatment according to the guideline were classified as being in the TR-ROP group. Infants who had at least 1 eye treated were classified as being in the TR-ROP group. Whether the infant had the treatment in 1 eye or in both eyes was not recorded in the registry.

• **NEURODEVELOPMENTAL OUTCOMES:** To evaluate neurodevelopmental outcome, we used the results of the neurodevelopmental assessment conducted at corrected 18 to 24 months by pediatricians or physiatrists. Because different hospitals used different measures for neurodevelopment assessment, we developed a composite outcome (yes/no) of the following: Bayley Scales of Infant and Toddler Development−2nd Edition (Bayley-II) scores; Bayley Scales of Infant and Toddler Development−3rd Edition (Bayley-III) scores; Korean Developmental Screening Test (K-DST) scores; Korean Ages and Stages Questionnaire (K-ASQ) scores; or/and the Gross Motor Function Classification System (GMFCS) scores.

The Bayley-II[16] and Bayley-III[17] tests are standardized developmental assessment instruments that identify children with developmental delays and aid in interventional planning.

TABLE 1. Characteristics of the Very-Low-Birth-Weight Infant Participants

Characteristic	Retinopathy of Prematurity[a]				*P* Value[b]	*P* Value[c]
	Total (N = 3132)	No ROP (n = 2039)	Non−TR-ROP (n = 644)	TR-ROP (n = 449)		
Neurodevelopmental delay, n (%)	1179 (37.6%)	644 (31.5%)	277 (43.0%)	258 (57.5%)	<.01	<.01
Gestational age, wk, mean (SD)	28.5 (2.6)	29.5 (2.3)	27.0 (2.0)	25.7 (2.0)	<.01	<.01
Birth weight, g, mean (SD)	1094.3 (264.0)	1190.6 (216.7)	965.5 (242.7)	842.1 (243.1)	<.01	<.01
Sex, n (%)					.89	.87
Female	1537 (49.1)	1000 (49.0)	315 (48.9)	222 (49.4)		
Male	1595 (50.9)	1039 (51.0)	329 (51.1)	227 (50.6)		
Apgar Score, Median (IQR)						
1 min	5 (4-6)	5 (4-6)	4 (3-6)	3 (2-5)	<.01	<.01
5 min	7 (6-8)	7 (6-8)	7 (6-8)	6 (5-7)	<.01	<.01
Use of Antenatal Steroids, n (%)					.05	.46
No	616 (19.7)	414 (20.3)	119 (18.5)	83 (18.5)		
Yes	2471 (78.9)	1602 (78.6)	512 (79.5)	357 (79.5)		
Unknown	45 (1.4)	23 (1.1)	13 (2)	9 (2)		
Mechanical Ventilator Care, n (%)					<.01	<.01
No	1562 (49.9)	1328 (65.1)	184 (28.6)	50 (11.1)		
Noninvasive	921 (29.4)	550 (27.0)	244 (37.9)	127 (28.3)		
Invasive	649 (20.7)	161 (7.9)	216 (33.5)	272 (60.6)		

IQR = interquartile range; ROP = retinopathy of prematurity.

[a]Study participants were divided into 3 groups according to the presence and treatment of ROP: no ROP, ROP with no treatment required (non−TR-ROP), and ROP with treatment required (TR-ROP).

[b]Result of analysis of covariance among the no ROP, non−TR-ROP, and TR-ROP groups.

[c]Result of analysis of covariance between the TR-ROP groups vs no ROP, and non−TR-ROP.

The K-DST is a recent screening test developed to verify whether an infant in Korea has standard development.[18] Several validations of this tool have been executed and revealed its usefulness.[19-21]

The K-ASQ is a standardized and culturally modified Korean version of the ASQ and has been used as a screening tool to identify infants with developmental delays[22] in Korea.

The GMFCS is a multi-level categorization technique that helps to describe varying levels of severity in people with cerebral palsy (CP).[23]

In this study, neurodevelopmental impairment was defined as participants who had at least 1 developmental problem according to the Bayley-II (<70), Bayley-III (<70), K-DST (below −1 SD), K-ASQ (below the threshold), and GMFCS (level 2 or above). If the infants were recorded to have CP or disability indicating an unlikely probability of being able to sit alone or walk 10 steps independently, they were regarded as being at GMFCS level 2 or above. To evaluate the neurodevelopmental impairment by domain, we classified the domains in each assessment tool as mental, motor, and social domains (Supplemental Table 1).

• **CONFOUNDING VARIABLES:** Confounding variables that were included in the analysis were chosen *a priori*. GA, moderate-to-severe BPD, NEC, sepsis, grade 3 or 4 intraventricular hemorrhage, periventricular leukomalacia, and year of birth were selected as confounding factors.

• **SUBGROUP ANALYSIS:** We performed stratified analyses to determine whether the association between ROP and neurodevelopmental impairment differed in prespecified subgroups defined by GA (<26 vs ≥26 weeks) and birth weight for GA (small for GA [SGA] vs normal vs large for GA [LGA]).

In the TR-ROP group, the neurodevelopmental impairments of infants who received anti-VEGF treatment were compared to those of the infants who underwent laser treatment. Infants with both treatments were included in the anti-VEGF group. Infants who had unspecified treatment were excluded.

• **STATISTICAL ANALYSIS:** We used logistic regression to examine the association between ROP and the risk of having neurodevelopmental impairment at the corrected ages of 18 to 24 months adjusted for GA, moderate-to-severe BPD, NEC, sepsis, grade 3 or 4 intraventricular hemorrhage, periventricular leukomalacia, and year of birth.

Because the participants in our analyses were required to have corrected ages of 18 to 24 months, we used inverse probability weights (IPWs) to correct for potential selection bias in this group as an additional sensitivity analysis. IPW reweights study participants so that the participants who are similar to those lost to follow-up after discharge are given

a higher weight. IPWs were obtained from a logistic regression model including all participants with ROP examinations at baseline and similar selection criteria to those used in this analysis (n = 4874).[24] Factors used in IPWs were sex, patent ductus arteriosus, intraventricular hemorrhage, respiratory distress syndrome, use of antenatal steroid, mechanical ventilator care, hearing problem, GA, Apgar score 1 minute, and year of birth.

All reported *P* values were 2-sided, and the significance level was set at .05. All analyses were performed using STATA version 15 (StataCorp LP, College Station, TX, USA).

RESULTS

• **DEMOGRAPHICS:** The number of VLBWIs who underwent ROP examinations was 3231 from January 1, 2013, to December 31, 2015. We then excluded participants who had meningitis (n = 11) or severe congenital anomalies (n = 88) at baseline, resulting in 3132 patients in the final sample (2039 no ROP, 644 non-TR-ROP, and 449 TR-ROP patients). The mean (SD) GA and birth weight of the study participants was 28.5 (2.6) weeks and 1094.3 (264.0) g, respectively. The proportion of infants in the non−TR-ROP and TR-ROP groups was 20.6% (n = 644) and 14.3% (n = 449), respectively. Infants in the TR-ROP (vs no ROP and non−TR-ROP) group had a shorter GA ($P < .01$), lower birth weight, and lower Apgar scores ($P < .01$), experienced more neonatal problems including BPD ($P < .01$) and NEC ($P < .01$), and were more likely to receive mechanical ventilator care ($P < .01$) (Tables 1 and 2).

• **NEURODEVELOPMENTAL OUTCOMES BY ROP SEVERITY:** At the corrected ages of 18 to 24 months, 1179 participants (37.6%) had at least 1 neurodevelopmental impairment. The proportion of neurodevelopmental impairment in infants in the no ROP, non−TR-ROP, and TR-ROP groups was 31.5% (644), 43.0% (277), and 57.5% (258), respectively. Compared to the no ROP group, the fully-adjusted OR for any neurodevelopmental impairment in the non−TR-ROP, and TR-ROP groups was 1.13 (95% CI = 0.92-1.39) and 1.72 (95% CI = 1.33-2.21), respectively (Table 3). According to the domain of the neurodevelopmental impairment, the TR-ROP group showed an elevated risk of mental (OR = 1.62, 95% CI =1.25-2.09), social (OR = 1.61, 95% CI =1.24-2.07), and motor impairment (OR = 1.69, 95% CI =1.31-2.18) compared to the no ROP group. The IPW weighted and unweighted results were similar (data not shown).

• **ANALYSIS BY GA, BIRTH WEIGHT FOR GA, AND TYPE OF ROP TREATMENT:** When we evaluated whether the association between ROP and neurodevelopmental impairment differed in prespecified subgroups according to GA and birth weight for GA, a positive association between ROP and neurodevelopmental impairment was seen in all subgroups analyzed ($P = .51$ for interaction with GA [Table 4] and $P = .63$ for interaction of birth weight with GA [Table 5]), except for the mental domain among those of SGA.

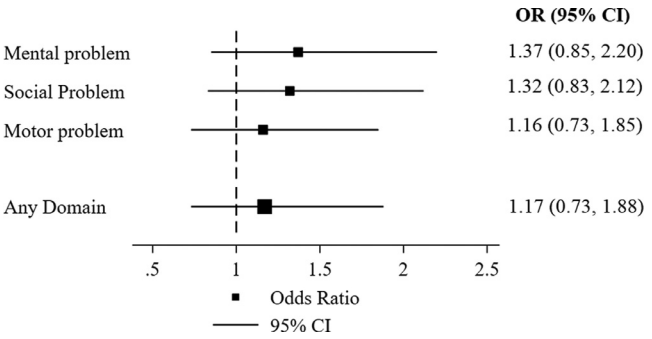

FIGURE 1. Comparison of neurodevelopmental impairment in up to 2 years of follow-up in infants with retinopathy of prematurity (ROP) who received ROP treatment (odds ratio [OR] of laser treatment group [n = 120] and anti−vascular endothelial growth factor (anti-VEGF) therapy group [n = 258] as reference). Adjusted ORs were calculated by multivariable logistic regression adjusted for gestational age, moderate-to-severe bronchopulmonary dysplasia, necrotizing enterocolitis, sepsis, grade 3 or 4 intraventricular hemorrhage, periventricular leukomalacia, and year of birth. Neurodevelopmental impairment was defined as one of the following: (1) Bayley Scales of Infant and Toddler Development−2nd Edition (Bayley-II) or 3rd Edition (Bayley-III) scores of <70; Korean Developmental Screening Test below −1 SD; Korean Ages and Stages Questionnaire "below the threshold"; and Gross Motor Function Classification System (GMFCS) level 2 or above. If the infants were recorded to have cerebral palsy (CP) or disability indicating an unlikely probability of being able to sit alone or walk 10 steps independently, they were regarded as being GMFCS level 2 or above. The definition of each domain is described in Supplemental Table 1. Infants with unspecified treatment (n = 71) were excluded from the analysis. Infants with both treatments (n = 60) were included in the anti-VEGF group.

In the analysis of the type of treatment in the TR-ROP group, the risk of neurodevelopmental impairment in patients in the laser treatment therapy (n = 120) did not differ from those who received anti-VEGF therapy (n = 258) (OR = 1.17, 95% CI = 0.73-1.88) (Figure 1). Infants with unspecified treatment (n = 71) were excluded from the analysis. Infants with both treatments (n = 60) were included in the anti-VEGF group. Baseline characteristics of the infants who were included in the ROP treatment subgroup analysis are presented in Supplemental Table 2.

• **OPHTHALMOLOGIC OUTCOME BY ROP:** At the corrected ages of 18 to 24 months, infants in the TR-ROP group were the most likely to be prescribed glasses (0.7% vs 1.6% vs 9.4% for no ROP, non−TR-ROP, and TR-ROP groups, re-

TABLE 2. Comorbidities of the Very-Low-Birth-Weight Infant Participants

Characteristic	Retinopathy of Prematurity[a]				*P* Value[b]	*P* Value[c]
	Total (N = 3132) n (%)	No ROP (n = 2039) n (%)	Non−TR-ROP (n = 644) n (%)	TR-ROP (N = 449)		
n (%)						
Patent ductus arteriosus	1099 (35.1)	582 (28.5)	271 (42.1)	246 (54.8)	<.01	<.01
Moderate-to-severe Bronchopulmonary dysplasia	948 (30.3)	397 (19.5)	263 (40.8)	288 (64.1)	<.01	<.01
Sepsis	602 (19.2)	273 (13.4)	160 (24.8)	169 (37.6)	<.01	<.01
Intraventricular Hemorrhage					<.01	<.01
No	1837 (58.7)	1368 (67.1)	303 (47)	166 (37)		
Grade 1 or 2	1101 (35.2)	609 (29.9)	287 (44.6)	205 (45.7)		
Grade 3 or 4	194 (6.2)	62 (3)	54 (8.4)	78 (17.4)		
Necrotizing Enterocolitis					<.01	<.01
No	2988 (95.4)	1993 (97.7)	598 (92.9)	397 (88.4)		
Yes	143 (4.6)	45 (2.2)	46 (7.1)	52 (11.6)		
Unknown	1 (0.0)	1 (0.1)	0	0		
Neonatal seizure	185 (5.9)	42 (2.1)	54 (8.4)	89 (19.8)	<.01	<.01
Periventricular leukomalacia	218 (7.0)	95 (4.7)	70 (10.9)	53 (11.8)	<.01	<.01
Respiratory distress syndrome	2488 (79.4)	1455 (71.4)	600 (93.2)	433 (96.4)	<.01	<.01
Hearing Problems					<.01	<.01
No	2452 (78.3)	1663 (81.6)	495 (76.9)	294 (65.5)		
Yes	433 (13.8)	252 (12.4)	88 (13.7)	93 (20.7)		
Unknown	247 (7.9)	124 (6.1)	61 (9.5)	62 (13.8)		

ROP = retinopathy of prematurity.

[a]Study participants were divided into 3 groups according to the presence and treatment of ROP: no ROP, ROP with no treatment required (non−TR-ROP), and ROP with treatment required (TR-ROP).

[b]Result of analysis of covariance among the no ROP, non−TR-ROP, and TR-ROP groups.

[c]Result of analysis of covariance between the TR-ROP groups vs no ROP, and non-TR-ROP.

spectively; $P < .01$) and to have cataracts (0% vs 0.2% vs 0.7%, $P = .03$) and blindness (0.1% vs 0.2%, vs 2.4%, $P = .01$) (Supplemental Table 3).

DISCUSSION

This prospective nationwide cohort study exploring the independent association between ROP and neurodevelopmental impairment revealed that infants who developed treatment-indicated ROP and received treatment had a higher risk of neurodevelopmental impairment than those who developed less severe ROP not needing treatment. The risk for neurodevelopmental impairment did not differ according to the type of ROP treatment received.

The subgroup analysis results showed an increased risk of neurodevelopmental impairment in all TR-ROP subgroups classified by GA (<25 or >25 weeks) and birth weight for GA (SGA/normal/LGA), except for the mental domain among those of SGA, suggesting that TR-ROP independently increased the risk of neurodevelopmental impairment.

Although the neurodevelopment of VLBWIs is associated with various factors, most of the comorbidities are strongly related to GA. Therefore, after adjusting for GA, other confounding factors were carefully selected as covariates. BPD has been considered to have a significant impact on poor development in preterm children,[25] as well as NEC.[26] Sepsis is also significantly contributed to neurodevelopmental impairment in preterm infants, independent of other risk factors.[27,28] Because brain injury is directly related to neurodevelopmental impairment, the common neonatal morbidities that strongly predict the risk of neurosensory impairment,[29] intraventricular hemorrhage, and periventricular leukomalacia proved by ultrasonography were included. In addition, as the survival rate of VLBWIs has increased year by year in Korea,[30] adjustment for the year of birth was also made to eliminate the effect of the survival difference between years.

Another report showed a strong association between the development of severe ROP (defined as unilateral or bilat-

TABLE 3. Adjusted Odds Ratios by Multivariable Logistic Regression for Neurodevelopmental Impairment in Up to 2 Years of Follow-up by Severity of Retinopathy of Prematurity Among Very-Low-Birth-Weight Infants (N = 3132)

	Retinopathy of Prematurity[b]		
Neurodevelopmental Outcome[a]	No ROP	Non−TR-ROP Adjusted OR[c] (95% CI)	TR-ROP Adjusted OR[c] (95% CI)
Any neurodevelopmental impairment	Reference	1.13 (0.92-1.39)	1.72 (1.33-2.21)
Neurodevelopmental Impairment by Domain			
Mental domain	Reference	1.08 (0.88-1.33)	1.62 (1.25-2.09)
Social domain	Reference	0.95 (0.77-1.18)	1.61 (1.24-2.07)
Motor domain	Reference	1.05 (0.85-1.29)	1.69 (1.31-2.18)

OR = odds ratio; ROP = retinopathy of prematurity.

[a]Neurodevelopmental impairment was defined as one of following: Bayley Scales of Infant and Toddler Development−2nd Edition (Bayley-II) or 3rd Edition (Bayley-III) scores of <70; Korean Developmental Screening Test below −1 SD; Korean Ages and Stages Questionnaire "below the threshold"; and Gross Motor Function Classification System (GMFCS) of level 2 or above. If the infants were recorded to have cerebral palsy or disability indicating an unlikely probability of being able to sit alone or walk 10 steps independently, they were regarded as being GMFCS level 2 or above. The definition of each domain is described in Supplemental Table 1.

[b]Study participants were divided into 3 groups according to the presence and treatment of ROP: no ROP, ROP with no treatment required (non−TR-ROP), and ROP with treatment required (TR-ROP).

[c]Adjusted for gestational age, moderate-to-severe bronchopulmonary dysplasia, necrotizing enterocolitis, sepsis, grade 3 or 4 intraventricular hemorrhage, periventricular leukomalacia, and year of birth.

TABLE 4. Adjusted Odds Ratios by Multivariable Logistic Regression for Neurodevelopmental Impairment in Up to 2 Years of Follow-up by Severity of Retinopathy of Prematurity Among Very-Low-Birth-Weight Infants by Gestational Age Groups (N = 3132)

	Retinopathy of Prematurity[a]		
	No ROP	Non−TR-ROP Adjusted OR[c] (95% CI)	TR-ROP Adjusted OR[c] (95% CI)
Gestational age	*P* for interaction = .51[d]		
Gestational Age ≤25 wk (n = 465)			
Any neurodevelopmental impairment[b]	Reference	1.51 (0.82-2.78)	2.11 (1.16-3.82)
Neurodevelopmental impairment by domain			
Mental domain	Reference	1.47 (0.80-2.72)	2.03 (1.12-3.67)
Social domain	Reference	1.32 (0.70-2.47)	1.93 (1.06-3.54)
Motor domain	Reference	1.53 (0.82-2.86)	2.16 (1.18-3.97)
Gestational Age >25 wk (n = 2667)			
Any neurodevelopmental impairment[b]	Reference	1.07 (0.85-1.34)	1.52 (1.11-2.15)
Neurodevelopmental impairment by domain			
Mental domain	Reference	1.01 (0.81-1.28)	1.41 (1.03-1.93)
Social domain	Reference	0.89 (0.70-1.13)	1.48 (1.08-2.04)
Motor domain	Reference	0.98 (0.77-1.23)	1.56 (1.13-2.13)

OR = odds ratio; ROP = retinopathy of prematurity.

[a]Study participants were divided into 3 groups according to the presence and treatment of ROP: no ROP, ROP with no treatment required (non−TR-ROP), and ROP with treatment required (TR-ROP).

[b]Neurodevelopmental impairment was defined as one of following: Bayley Scales of Infant and Toddler Development−2nd Edition (Bayley-II) or 3rd Edition (Bayley-III) scores of <70; Korean Developmental Screening Test below −1 SD; Korean Ages and Stages Questionnaire "below the threshold"; and Gross Motor Function Classification System (GMFCS) level 2 or above. If the infants were recorded to have cerebral palsy or disability indicating an unlikely probability of being able to sit alone or walk 10 steps independently, they were regarded as being GMFCS level 2 or above. The definition of each domain is described in Supplemental Table 1.

[c]Adjusted for gestational age, moderate-to-severe bronchopulmonary dysplasia, necrotizing enterocolitis, sepsis, grade 3 or 4 intraventricular hemorrhage, periventricular leukomalacia, and year of birth

[d]*P* value for interaction between gestational age ≤25 wk and gestational age >25 wk.

TABLE 5. Adjusted Odds Ratios by Multivariable Logistic Regression for Neurodevelopmental Impairment in Up to 2 Years of Follow-up by Severity of Retinopathy of Prematurity Among Very-Low-Birth-Weight Infants by Small/Normal/Large for Gestational Age Groups (N = 3132)

	Retinopathy of Prematurity[a]		
	No ROP	Non−TR-ROP Adjusted OR[c] (95% CI)	TR-ROP Adjusted OR[c] (95% CI)
Birth weight for gestational age	*P* for interaction = .63[d]		
SGA (n = 513)			
Any neurodevelopmental impairment[b]	Reference	1.13 (0.64-1.99)	2.26 (1.08-4.75)
Neurodevelopmental impairment by domain			
Mental domain	Reference	1.05 (0.60-1.86)	2.01 (0.96-4.18)
Social domain	Reference	0.99 (0.55-1.77)	2.27 (1.10-4.70)
Motor domain	Reference	1.14 (0.64-2.01)	2.35 (1.12-4.89)
Normal (n = 2298)			
Any neurodevelopmental impairment[b]	Reference	1.08 (0.85-1.36)	1.43 (1.07-1.90)
Neurodevelopmental impairment by domain			
Mental domain	Reference	1.03 (0.81-1.30)	1.41 (1.06-1.88)
Social domain	Reference	0.89 (0.70-1.14)	1.36 (1.02-1.82)
Motor domain	Reference	0.97 (0.76-1.24)	1.42 (1.06-1.89)
LGA (n = 321)			
Any neurodevelopmental impairment[b]	Reference	1.12 (0.65-1.94)	2.20 (1.22-3.97)
Neurodevelopmental impairment by domain			
Mental domain	Reference	1.07 (0.62-1.85)	1.95 (1.09-3.50)
Social domain	Reference	1.08 (0.62-1.88)	1.97 (1.09-3.54)
Motor domain	Reference	1.16 (0.67-2.02)	2.16 (1.20-3.89)

LGA = large for gestational age; OR = odds ratio; ROP = retinopathy of prematurity; SGA = small for gestational age.

[a]Study participants were divided into 3 groups according to the presence and treatment of ROP: no ROP, ROP with no treatment required (non−TR-ROP), and ROP with treatment required (TR-ROP).

[b]Neurodevelopmental impairment was defined as one of following: Bayley Scales of Infant and Toddler Development−2nd Edition (Bayley-II) or 3rd Edition (Bayley-III) scores of <70; Korean Developmental Screening Test below −1 SD; Korean Ages and Stages Questionnaire "below the threshold"; and Gross Motor Function Classification System (GMFCS) level 2 or above. If the infants were recorded as having cerebral palsy or disability indicating an unlikely probability of being able to sit alone or walk 10 steps independently, they were regarded as being GMFCS level 2 or above. The definition of each domain is described in Supplemental Table 1.

[c]Adjusted for gestational age, moderate-to-severe bronchopulmonary dysplasia, necrotizing enterocolitis, sepsis, grade 3 or 4 intraventricular hemorrhage, periventricular leukomalacia, and year of birth,

[d]*P* value for the interaction of any developmental impairment with SGA, normal, and LGA.

eral stage 4 or 5 disease or as receipt of retinal therapy in at least 1 eye, which is similar to TR-ROP in this study) and the presence of nonvisual disabilities (ie, cognitive impairment, behavioral problems, poor general health, severe hearing loss) at 5 years of age.[9] This research showed outcomes similar to those in our study, but the analyzed data were from infants born between 1999 to 2004, more than 15 years earlier. As the survival rate of preterm infants has increased due to improvements in peri- and neonatal care,[31] the number of infants with severe ROP who survived has also markedly increased. Therefore, there was a difference in the proportion of infants with severe ROP included in that study compared to our study (6.0% in Scimidt et al.[9] vs 14.3% in this study), although the definition of severe ROP was similar. Also, there has been a reduction in the incidence of infants with a significant visual impairment from ROP over time in developed countries due to progress in the clinical management of ROP.[32] These are factors that could critically affect the results of the analysis of the association between ROP and neurodevelopment. Our results have clinical importance because they reflect more recent trends in the incidence of severe ROP, ocular disorders, hearing impairment and loss, and neurodevelopment.

Todd et al[10] reported that the developmental outcomes were not different between infants with stage 3 ROP and infants with stage 1, 2, or no ROP when GA and sex were matched. However, infants with stage 3 ROP tend to have lower GA and BW compared to those of stage 1, 2, or no ROP, and infants with lower GA and BW tend to have higher comorbidities. When GA was matched between 2 groups, the infants with stage 3 ROP with lower GA or BW might be excluded from the analysis, which would cause an underestimation of the risk of neurodevelopmental impairment in the stage 3 ROP group. In the present study, we could perform subgroup analysis according to GA because KNN is a nationwide cohort of VLBWIs in South Korea

with a large number of participants. We found that TR-ROP was significantly associated with neurodevelopmental impairment both in lower GA of the group 25 weeks or less and higher GA in the group more than 25 weeks (odds ratio [OR] = 2.11, CI = 1.16-3.82, and OR = 1.52, CI = 1.11-2.15, respectively) (Table 4).

The underlying mechanism of an association between neurodevelopmental impairment and TR-ROP is unclear. TR-ROP could have a negative effect on neurodevelopment because of visual dysfunction. However, only 2.4% of the infants in the TR-ROP group showed blindness, and other ophthalmologic diseases occurred even less frequently (glaucoma 0.2%, cataracts 0.7%). Hence, visual dysfunction could not fully explain our observations. The association between brain structure deficits and severe ROP has been reported.[33,34] These findings suggest that the development of ROP and delayed maturation of the brain might share a common pathophysiology. Although VEGF is important in the development of ROP,[35] insulin-like growth factor 1 (IGF-1) is known to be an important modifier in the circulatory levels of VEGF and early postnatal low-serum IGF-1 levels were associated with the development of ROP.[36] Also, IGF-1 was found to be closely associated with brain maturation and central nervous system development in animal studies,[37] and postnatal IGF concentrations were positively associated with brain volumes in very preterm infants.[38] Increases in circulating IGF-1 were associated with a decreased risk of neurodevelopmental impairment.[39] This evidence suggests that low postnatal IGF-1 levels might be the underlying mechanism causing severe ROP and neurodevelopmental impairment.

Anti-VEGF therapy did not show an elevated risk of neurodevelopmental impairment compared to laser treatment in our study. Concerns for the systemic effects of anti-VEGF have persisted[40,41] because of the important role of VEGF in the neurodevelopment of infants.[42,43] Several previous multicenter studies reported the superiority of laser therapy over anti-VEGF in terms of neurodevelopmental outcome. A study from the Canadian Neonatal Network reported that patients with anti-VEGF therapy showed worse neurodevelopmental outcomes than those who underwent laser treatment,[44] and similar results were reported from a multicenter cohort of preterm infants in the United States.[45] To the best of our knowledge, our research was the first nationwide multicenter cohort study showing that anti-VEGF treatment did not have worse effects on neurodevelopment than laser therapy. A retrospective study with small sample size (n = 33 in the laser group, n = 12 in the anti-VEGF group) from Taiwan reported no difference in neurodevelopment between participants who received only bevacizumab vs those who had only laser treatment.[46] In a prospective single-center study by Fan et al, ROP infants who received anti-VEGF treatment showed similar neurodevelopmental outcomes compared to infants with a history of ROP without treatment.[11] Our nationwide multicenter study with large sample size supports previous reports (with smaller sample sizes) that noted no difference in neurodevelopmental outcomes in infants treated with anti-VEGF therapy compared to laser.

Our study had certain limitations. First, detailed ophthalmologic examinations such as visual acuity or refractive error were not included in the cohort data. We cannot exclude the possibility that the TR-ROP group of infants had poor visual acuity that contributed to more frequent neurodevelopmental impairment. However, clinically significant ophthalmologic problems such as blindness, cataract, and glaucoma were recorded in the data. In addition, age 18 to 24 months is too young to test other ophthalmologic features. Second, the accuracy of ROP diagnosis and level of neonatal care can vary among centers in Korea. There are issues regarding discrepancies in the diagnosis for ROP staging[47] as well as discrepancies in the diagnosis of plus disease,[48] even among experts. We tried to overcome the problem using the presence of treatment as the standard for severity classification. However, as we could not review the medical records or fundus photography, there remains the possibility of diagnostic inaccuracy. Third, regarding the registry-based analysis, there could be a limitation regarding the accuracy of the variable measurements. The institutions used various neurodevelopmental assessment tools. With the intent to use all data to avoid selection bias, we developed a composite score by combining the scores from each tool. There have been issues with the Bayley-III tests overestimating neurodevelopment[17] and underestimating developmental delay[49] compared to the Bayley-II test, and also there have been issues of matching the cutoff values between the Bayley-II and Bayley-III tests.[50,51] However, as no agreement has yet been established, conventional interpretation was applied in this study (ie, scores <70 indicated developmental problems). In this study, 37.6% of the enrolled infants showed neurodevelopmental impairment measured by the composite outcome of the various assessment tools. This was a rate similar to those reported in previous studies.[52,53] As the value was comparable, the validity of the neurodevelopmental evaluation method used in this study could be assured. Fourth and last, as nearly the entire population of South Korea is composed of only 1 race, application to other populations needs to be made with caution. However, ruling out ethnic factors might be seen as an advantage of this study.

The strength of our study was that the database used was a prospective nationwide registry that included the majority of the VLBWIs in South Korea. The KNN database contains information on VLBWIs in the NICUs of 69 medical centers in South Korea,[54] and more than 2000 VLBWIs are registered annually, which covers about 70% of the VLBWIs born in South Korea in 1 year.[13] It was reported that two-thirds of all VLBWI in South Korea were registered in the KNN during the study period (2013-2015).[55] Therefore, we could assume that the included data were representative of information on VLBWIs in South Korea.

In conclusion, treated ROP was associated with higher rates of neurodevelopmental impairment in early childhood. Estimating the risk of neurodevelopmental impairment is important for consultation with the parents. The results of this study suggest that clinicians need to consider the severity of ROP when estimating the risk of neurodevelopmental impairment in VLBWIs. This finding should diminish the ambiguity of the effects of ROP on neurodevelopment raised from previous inconsistent results. Furthermore, as approaches to neuroprotection in preterm infants have been proposed,[56] this study might help to identify treated ROP infants as the proper candidates for early intervention. In addition, the type of ROP treatment (anti-VEGF or laser treatment) did not affect neurodevelopmental impairment in the TR-ROP group. Although there are concerns about the systemic adverse effects of anti-VEGF on the neurodevelopment of premature infants,[41] physicians should choose the optimal ROP treatment modality based on the status of the disease itself, according to our results. Future study is required to evaluate the neurodevelopmental outcomes of these infants in late childhood, adolescence, and adulthood.

Funding/Support: This work was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI19C0481 and HC19C0142), and a National Research Foundation of Korea grant funded by the Korean government's Ministry of Education (NRF-2021R1C1C1007795; Seoul, Korea) (to D.H.L.). Financial Disclosures: The authors report no financial disclosures or conflicts of interest. All authors attest that they meet the current ICMJE criteria for authorship. Author contributions: D.H.L. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: D.H.L., S.J.K.
Acquisition, analysis, or interpretation of data: D.K., J.C., E.G., Y.C., W.S.P.
Drafting of the manuscript: G.H., D.H.L., D.K.
Critical revision of the manuscript for important intellectual content: D.H.L., J.C., E.G., T.-Y.C., S.J.K.
Statistical analysis: D.K.
Obtained funding: D.H.L., T.Y.C.
Supervision: S.J.K., W.S.P.

REFERENCES

1. Shah PS, Lui K, Sjors G, et al. Neonatal outcomes of very low birth weight and very preterm neonates: an international comparison. *J Pediatr*. 2016;177:144–152. doi:10.1016/j.jpeds.2016.04.083.
2. Jarjour IT. Neurodevelopmental outcome after extreme prematurity: a review of the literature. *Pediatr Neurol*. 2015;52(2):143–152. doi:10.1016/j.pediatrneurol.2014.10.027.
3. Synnes A, Hicks M. Neurodevelopmental outcomes of preterm children at school age and beyond. *Clin Perinatol*. 2018;45(3):393–408. doi:10.1016/j.clp.2018.05.002.
4. Bonifacio SL, Glass HC, Chau V, et al. Extreme premature birth is not associated with impaired development of brain microstructure. *J Pediatr*. 2010;157(5):726–732. doi:10.1016/j.jpeds.2010.05.026.
5. Patel RM. Short- and long-term outcomes for extremely preterm infants. *Am J Perinatol*. 2016;33(3):318–328. doi:10.1055/s-0035-1571202.
6. Singer L, Yamashita T, Lilien L, Collin M, Baley J. A longitudinal study of developmental outcome of infants with bronchopulmonary dysplasia and very low birth weight. *Pediatrics*. 1997;100(6):987–993. doi:10.1542/peds.100.6.987.
7. Hickey M, Georgieff M, Ramel S. Neurodevelopmental outcomes following necrotizing enterocolitis. *Semin Fetal Neonatal Med*. 2018;23(6):426–432. doi:10.1016/j.siny.2018.08.005.
8. Msall ME, Phelps DL, DiGaudio KM, et al. Severity of neonatal retinopathy of prematurity is predictive of neurodevelopmental functional outcome at age 5.5 years. On behalf of the Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Pediatrics*. 2000;106(5):998–1005. doi:10.1542/peds.106.5.998.
9. Schmidt B, Davis PG, Asztalos EV, Solimano A, Roberts RS. Association between severe retinopathy of prematurity and nonvisual disabilities at age 5 years. *JAMA*. 2014;311(5):523–525. doi:10.1001/jama.2013.282153.
10. Todd DA, Goyen TA, Smith J, Rochefort M. Developmental outcome in preterm infants <29 weeks gestation with </= stage 3 retinopathy of prematurity (ROP): relationship to severity of ROP. *J Dev Orig Health Dis*. 2012;3(2):116–122. doi:10.1017/S2040174411000766.
11. Fan YY, Huang YS, Huang CY, et al. Neurodevelopmental outcomes after intravitreal bevacizumab therapy for retinopathy of prematurity: a prospective case-control study. *Ophthalmology*. 2019;126(11):1567–1577. doi:10.1016/j.ophtha.2019.03.048.
12. Linsell L, Malouf R, Morris J, Kurinczuk JJ, Marlow N. Prognostic factors for poor cognitive development in children born very preterm or with very low birth weight: a systematic review. *JAMA Pediatr*. 2015;169(12):1162–1172. doi:10.1001/jamapediatrics.2015.2175.
13. Chang YS, Park H-Y, Park WS. The Korean Neonatal Network: an overview. *J Korean Med Sci*. 2015;30(suppl 1) S3-S11. doi:10.3346/jkms.2015.30.S1.S3.
14. Chang YS, Ahn SY, Park WS. The establishment of the Korean Neonatal Network (KNN). *Neonatal Med*. 2013;20(2):169–178. doi:10.5385/nm.2013.20.2.169.
15. Good WV. Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc*. 2004;102:233–248 discussion 248-250.
16. Johnson S, Marlow N. Developmental screen or developmental testing? *Early Hum Dev*. 2006;82(3):173–183. doi:10.1016/j.earlhumdev.2006.01.008.
17. Acton BV, Biggs WSG, Creighton DE, et al. Overesti-

mating neurodevelopment using the Bayley-III after early complex cardiac surgery. *Pediatrics*. 2011;128(4):e794. doi:10.1542/peds.2011-0331.
18. Moon JS LS, Eun BL, Kim SW, et al. One-year evaluation of the national health screening program for infants and children in Korea. *Korean J Pediatr*. 2010;53(3):307–313.
19. Yim CH, Kim GH, Eun BL. Usefulness of the Korean Developmental Screening Test for infants and children for the evaluation of developmental delay in Korean infants and children: a single-center study. *Korean J Pediatr*. 2017;60(10):312–319. doi:10.3345/kjp.2017.60.10.312.
20. Jang CH, Kim SW, Jeon HR, et al. Clinical usefulness of the Korean Developmental Screening Test (K-DST) for developmental delays. *Ann Rehabil Med*. 2019;43(4):490–496. doi:10.5535/arm.2019.43.4.490.
21. Kim CY, Jung E, Lee BS, Kim KS, Kim EA. Validity of the Korean Developmental Screening Test for very-low-birth-weight infants. *Korean J Pediatr*. 2019;62(5):187–192. doi:10.3345/kjp.2018.07381.
22. Heo KH SJ, Lee SY, Lee JS. *Korean Ages and Stages Questionnaires: a parent completed development screening tool*. Seoul Community Rehabilitation Center; 2006.
23. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol*. 1997;39(4):214–223. doi:10.1111/j.1469-8749.1997.tb07414.x.
24. Gassett AJ, Sheppard L, McClelland RL, et al. Risk factors for long-term coronary artery calcium progression in the multi-ethnic study of atherosclerosis. *J Am Heart Assoc*. 2015;4(8):e001726. doi:10.1161/JAHA.114.001726.
25. DeMauro SB. The impact of bronchopulmonary dysplasia on childhood outcomes. *Clin Perinatol*. 2018;45(3):439–452. doi:10.1016/j.clp.2018.05.006.
26. Adams-Chapman I. Necrotizing enterocolitis and neurodevelopmental outcome. *Clin Perinatol*. 2018;45(3):453–466. doi:10.1016/j.clp.2018.05.014.
27. Alshaikh B, Yusuf K, Sauve R. Neurodevelopmental outcomes of very low birth weight infants with neonatal sepsis: systematic review and meta-analysis. *J Perinatol*. 2013;33(7):558–564. doi:10.1038/jp.2012.167.
28. Cai S, Thompson DK, Anderson PJ, Yang JY. Short- and long-term neurodevelopmental outcomes of very preterm infants with neonatal sepsis: a systematic review and meta-analysis. *Children (Basel)*. 2019;6(12). doi:10.3390/children6120131.
29. Schmidt B, Asztalos EV, Roberts RS, et al. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. *JAMA*. 2003;289(9):1124–1129. doi:10.1001/jama.289.9.1124.
30. Shim JW, Jin HS, Bae CW. Changes in survival rate for very-low-birth-weight infants in Korea: comparison with other countries. *J Korean Med Sci*. 2015;30(suppl 1):S25–S34. doi:10.3346/jkms.2015.30.S1.S25.
31. Stoelhorst GM, Rijken M, Martens SE, et al. Changes in neonatology: comparison of two cohorts of very preterm infants (gestational age <32 weeks): the Project On Preterm and Small for Gestational Age Infants 1983 and the Leiden Follow-Up Project on Prematurity 1996-1997. *Pediatrics*. 2005;115(2):396–405. doi:10.1542/peds.2004-1497.
32. Tan Z, Chong C, Darlow B, Dai S. Visual impairment due to retinopathy of prematurity (ROP) in New Zealand: a 22-year review. *Br J Ophthalmol*. 2015;99(6):801–806. doi:10.1136/bjophthalmol-2014-305913.
33. Drost FJ, Keunen K, Moeskops P, et al. Severe retinopathy of prematurity is associated with reduced cerebellar and brainstem volumes at term and neurodevelopmental deficits at 2 years. *Pediatr Res*. 2018;83(4):818–824. doi:10.1038/pr.2018.2.
34. Glass TJA, Chau V, Gardiner J, et al. Severe retinopathy of prematurity predicts delayed white matter maturation and poorer neurodevelopment. *Arch Dis Child Fetal Neonatal Ed*. 2017;102(6):F532–F537. doi:10.1136/archdischild-2016-312533.
35. Kwinta P, Bik-Multanowski M, Mitkowska Z, Tomasik T, Pietrzyk JJ. The clinical role of vascular endothelial growth factor (VEGF) system in the pathogenesis of retinopathy of prematurity. *Graefes Arch Clin Exp Ophthalmol*. 2008;246(10):1467–1475. doi:10.1007/s00417-008-0865-9.
36. Hellstrom A, Engstrom E, Hard AL, et al. Postnatal serum insulin-like growth factor I deficiency is associated with retinopathy of prematurity and other complications of premature birth. *Pediatrics*. 2003;112(5):1016–1020. doi:10.1542/peds.112.5.1016.
37. Fernandez AM, Torres-Aleman I. The many faces of insulin-like peptide signalling in the brain. *Nat Rev Neurosci*. 2012;13(4):225–239. doi:10.1038/nrn3209.
38. Hansen-Pupp I, Hovel H, Hellstrom A, et al. Postnatal decrease in circulating insulin-like growth factor-I and low brain volumes in very preterm infants. *J Clin Endocrinol Metab*. 2011;96(4):1129–1135. doi:10.1210/jc.2010-2440.
39. Hansen-Pupp I, Hovel H, Lofqvist C, et al. Circulatory insulin-like growth factor-I and brain volumes in relation to neurodevelopmental outcome in very preterm infants. *Pediatr Res*. 2013;74(5):564–569. doi:10.1038/pr.2013.135.
40. Jalali S, Balakrishnan D, Zeynalova Z, Padhi TR, Rani PK. Serious adverse events and visual outcomes of rescue therapy using adjunct bevacizumab to laser and surgery for retinopathy of prematurity. The Indian Twin Cities Retinopathy of Prematurity Screening Database report number 5. *Arch Dis Child Fetal Neonatal Ed*. 2013;98(4):F327–F333. doi:10.1136/archdischild-2012-302365.
41. Käll A. Is Avastin the right choice of treatment for retinopathy of prematurity? *Acta Paediatr*. 2012;101(8):796–798. doi:10.1111/j.1651-2227.2012.02757.x.
42. Malik S, Vinukonda G, Vose LR, et al. Neurogenesis continues in the third trimester of pregnancy and is suppressed by premature birth. *J Neurosci*. 2013;33(2):411–423. doi:10.1523/JNEUROSCI.4445-12.2013.
43. Breier G, Albrecht U, Sterrer S, Risau W. Expression of vascular endothelial growth factor during embryonic angiogenesis and endothelial cell differentiation. *Development*. 1992;114(2):521–532.
44. Morin J, Luu TM, Superstein R, et al. Neurodevelopmental outcomes following bevacizumab injections for retinopathy of prematurity. *Pediatrics*. 2016;137(4). doi:10.1542/peds.2015-3218.
45. Natarajan G, Shankaran S, Nolen TL, et al. Neurodevelopmental outcomes of preterm infants with retinopathy of prematurity by treatment. *Pediatrics*. 2019;144(2). doi:10.1542/peds.2018-3537.

46. Lien R, Yu MH, Hsu KH, et al. Neurodevelopmental outcomes in infants with retinopathy of prematurity and bevacizumab treatment. *PLoS One*. 2016;11(1):e0148019. doi:10.1371/journal.pone.0148019.
47. Campbell JP, Ryan MC, Lore E, et al. Diagnostic discrepancies in retinopathy of prematurity classification. *Ophthalmology*. 2016;123(8):1795–1801. doi:10.1016/j.ophtha.2016.04.035.
48. Hewing NJ, Kaufman DR, Chan RV, Chiang MF. Plus disease in retinopathy of prematurity: qualitative analysis of diagnostic process by experts. *JAMA Ophthalmol*. 2013;131(8):1026–1032. doi:10.1001/jamaophthalmol.2013.135.
49. Anderson PJ, De Luca CR, Hutchinson E, Roberts G, Doyle LW. Victorian Infant Collaborative Group. Underestimation of developmental delay by the new Bayley-III Scale. *Arch Pediatr Adolesc Med*. 2010;164(4):352–356. doi:10.1001/archpediatrics.2010.20.
50. Johnson S, Moore T, Marlow N. Using the Bayley-III to assess neurodevelopmental delay: which cut-off should be used? *Pediatr Res*. 2014;75(5):670–674. doi:10.1038/pr.2014.10.
51. Silveira RC, Filipouski GR, Goldstein DJ, O'Shea TM, Procianoy RS. Agreement between Bayley Scales second and third edition assessments of very low-birth-weight infants. *Arch Pediatr Adolesc Med*. 2012;166(11):1075–1076. doi:10.1001/archpediatrics.2012.732.
52. Kono Y, Yonemoto N, Nakanishi H, Kusuda S, Fujimura M. Changes in survival and neurodevelopmental outcomes of infants born at <25 weeks' gestation: a retrospective observational study in tertiary centres in Japan. *BMJ Paediatr Open*. 2018;2(1):e000211. doi:10.1136/bmjpo-2017-000211.
53. Younge N, Goldstein RF, Bann CM, et al. Survival and neurodevelopmental outcomes among periviable infants. *N Engl J Med*. 2017;376(7):617–628. doi:10.1056/NEJMoa1605566.
54. Lee A, Gilbert RM. Epidemiology of Parkinson disease. *Neurol Clin*. 2016;34(4):955–965. doi:10.1016/j.ncl.2016.06.012.
55. Lee JH, Noh OK, Chang YS. Neonatal outcomes of very low birth weight infants in Korean Neonatal Network from 2013 to 2016. *J Korean Med Sci*. 2019;34(5).
56. Fleiss B, Gressens P. Neuroprotection of the preterm brain. *Handb Clin Neurol*. 2019;162:315–328. doi:10.1016/b978-0-444-64029-1.00015-1.