Cognitive Outcomes Following Intravitreal Bevacizumab for Retinopathy of Prematurity: 4- to 6-Year Outcomes in a Prospective Cohort

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• PURPOSE: To determine the long-term cognitive outcomes in children who underwent intravitreal bevacizumab (IVB) for retinopathy of prematurity (ROP).
• DESIGN: Prospective cohort study.
• METHODS: This single-center study enrolled 186 children between 3 and 6 years of age and included 101 children in the final analysis: premature without ROP (group 1), ROP not needing treatment (group 2), IVB monotherapy (group 3), IVB plus laser therapy (group 4), and laser monotherapy (group 5). The Full-Scale Intelligence Quotient (FSIQ) was evaluated by the Wechsler Preschool and Primary Scale of Intelligence Test at baseline and then annually for 1-2 years and compared among groups.
• RESULTS: The age at cognitive evaluation was 4.5-4.9 years at baseline and 6.1-7.0 years at the last follow-up. The FSIQ was comparable among the groups at both time points ($P = .08$ and .50, respectively). Severe cognitive impairment (FSIQ < 70) was more common in group 4 at baseline (4%, 22%, 13%, 33%, and 0% in groups 1-5, respectively; $P = .03$) but did not differ among the groups at the last follow-up (6%, 0%, 4%, 22%, and 0%; $P = .22$). After adjusting for sex, Apgar score, neonatal adverse events, and days on mechanical ventilation, IVB was not associated with FSIQ either at baseline or at the last follow-up.
• CONCLUSIONS: At 4.5 to beyond 6 years of age, children who underwent IVB monotherapy had comparable cognitive outcomes compared to the other premature children without prior IVB. Children who underwent IVB plus laser showed higher severe cognitive impairment at 4.5 years of age. (Am J Ophthalmol 2022;234: 59–70.

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RETINOPATHY OF PREMATURITY (ROP) IS A preventable blinding disease in preterm children worldwide, and the rate of ROP needing treatment is increasing.[1,2] Vascular endothelial growth factor (VEGF), a critical factor affecting the progression of ROP, is a therapeutic target.[3] Since the 1990s, laser ablation of the peripheral avascular retina to decrease the production of VEGF has been the gold standard treatment for severe ROP.[4]

In 2011, the Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity Study reported the efficacy of treating severe ROP with intravitreal injection of bevacizumab (IVB), an anti-VEGF agent, and demonstrated comparable results to conventional laser treatment for zone II disease and an additional benefit for zone I disease.[5] Treating ROP with bevacizumab was also associated with fewer refractive errors, better foveal development, and potentially less constricted visual fields.[5-7] Because of these advantages and the ease of performing the injections, bevacizumab treatment has gained popularity in recent decades.[8]

However, IVB is associated with systemic risks. Although medication was injected into the vitreous cavity, evidence has shown that it can spread into the systemic circulation, leading to systemic VEGF suppression for up to 8 weeks.[9,10] VEGF is important for organogenesis and neurodevelopment up to the third trimester of pregnancy, which is usually the time at which children with ROP receive anti-VEGF treatment.[11,12] Thus, whether the systemic suppression of VEGF affects neurodevelopmental outcomes in these IVB-treated children is a matter of concern.[6]

The current evidence regarding the influence of anti-VEGF agents on neurodevelopmental outcomes is inconsistent and has limitations.[13] The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), which is the assessment used in most studies, is an overly optimistic tool, especially for poorly performing children.[14,15] Moreover, most neurodevelopmental assessments were performed before 2 years of age, with the only 5-year report limited by its small sample size and single-arm design.[6,13,16] Notably, neurodevelopmental deficits can emerge at older ages in patients with previously normal performance at ages <3 years.[17,18] Therefore, the current study was conducted to determine the long-term cognitive outcomes in children who underwent IVB for ROP.

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METHODS

• **SUBJECTS AND GROUPING:** This was a prospective cohort study conducted in Chang Gung Memorial Hospital, Linkou, between April 2015 and November 2018. The study was approved by the Institutional Review Board (No. 201801566A3) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the children's parent(s) for the enrollment of their children in the study.

Premature children with or without ROP between the chronological ages of 3 and 6 years were invited to participate in this study. Demographics, neonatal events, and data on ROP were gathered from the medical records. Prematurity was defined as birth at <37 weeks' gestation. The severity of ROP was graded according to the Early Treatment for Retinopathy of Prematurity (ETROP) Study.[4]

Children who underwent vitrectomy for advanced ROP, received anti-VEGF agents other than bevacizumab, had cerebral palsy, or were unwilling or unable to complete the cognitive assessment were excluded. The enrolled children received a baseline cognitive assessment and a subsequent assessment at the end of year 1 and at the end of year 2 if the patient was followed for 2 years (Figure 1). In the analysis, we included subjects who received their last assessment when they were between 5 and 8 years.

The final cohort was divided into 5 groups according to their prior ROP status in the more severely affected eye: premature without ROP (group 1), ROP not needing treatment (group 2), IVB monotherapy (group 3), IVB + laser treatment (group 4), and laser monotherapy (group 5). Finally, the cognitive outcomes were compared among the groups.

• **INTRAVITREAL BEVACIZUMAB AND LASER TREATMENT:** The treatment for ROP was either primary IVB or laser photocoagulation, and the indication for treatment was type 1 ROP, as defined by the ETROP Study.[4] The risks and benefits of the treatments and the off-label use of bevacizumab were thoroughly explained to the parents. The parents chose the treatment method and signed an informed consent form.

The IVB procedure was performed as previously described.[19] In brief, IVB was administered in a neonatal intensive care unit under intravenous sedation. After antiseptic preparation, bevacizumab 0.625 mg (Avastin; Genentech Inc) was injected through the pars plicata with a 30-gauge needle. Levofloxacin 0.5% (Cravit; Santen) was applied for 7 days after the procedure, and patients were followed every 1-2 weeks until full vascularization or the absence of an active fibrovascular component of the retina.

For laser ablation, a conventional near-confluent 810-nm diode laser was applied to the entire avascular retina. The follow-up schedule was same as after IVB.

After the primary treatment, if there was an initial positive response but with later worsening of the ROP status, including recurrence or deterioration of neovascularization or plus disease,[20] additional IVB or laser therapy was administered based on the preference of the parents. If retinal detachment was present, vitrectomy was considered.

• **COGNITIVE OUTCOMES ASSESSMENT:** Cognitive abilities were assessed by the Chinese version of the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV; Chinese Behavioral Science Corporation) Test. The WPPSI-IV is composed of different subtests according to the test subject's age. From these subtests, raw scores can be calculated and converted to an age-corrected standard scaled score. Specific composite scores can be further derived from these scaled scores, including the Full-Scale Intelligence Quotient (FSIQ; mean = 100, SD = 15), which reflects the overall intelligence of a test subject. FSIQs of 70 to 84 (<1-2 SD) and <70 (<2 SD) were defined as borderline and severe cognitive impairment, respectively. In this study, an experienced pediatric psychiatrist (Y.-S.H.) performed all the assessments and was blinded to each patient's prior ophthalmic history and treatment.

• **STATISTICAL ANALYSES:** The normality of the distribution of numerical variables was tested with the Shapiro-Wilk test. A χ^2 test or Fisher exact test was performed to compare categorical variables. Analysis of covariance or Kruskal-Wallis tests were used to compare differences in numerical variables, and multiple comparisons were conducted. Cognitive scores were compared among groups and within the same group using McNemar test and paired *t* tests, respectively. Generalized estimating equations were used to analyze the change in FSIQ over time. Finally, multiple linear regression models were constructed by forward selection of all the recorded factors to explore the variables related to FSIQ. SAS, version 9.4 (SAS Inc) was used for analysis, and a P <.05 was considered statistically significant.

RESULTS

• **DEMOGRAPHICS AND CLINICAL FEATURES:** A total of 186 children were recruited and underwent the baseline WPPSI-IV assessment. Among these children, 126 (67.7%) were followed for 1 year or longer and underwent at least 1 follow-up assessment. After excluding the 25 children who had their last cognitive assessments outside of the target age band, 101 children were included in the final analyses (Figure 1).

Table 1 shows the demographics and neonatal events of the children. Group 1 had a significantly older gestational

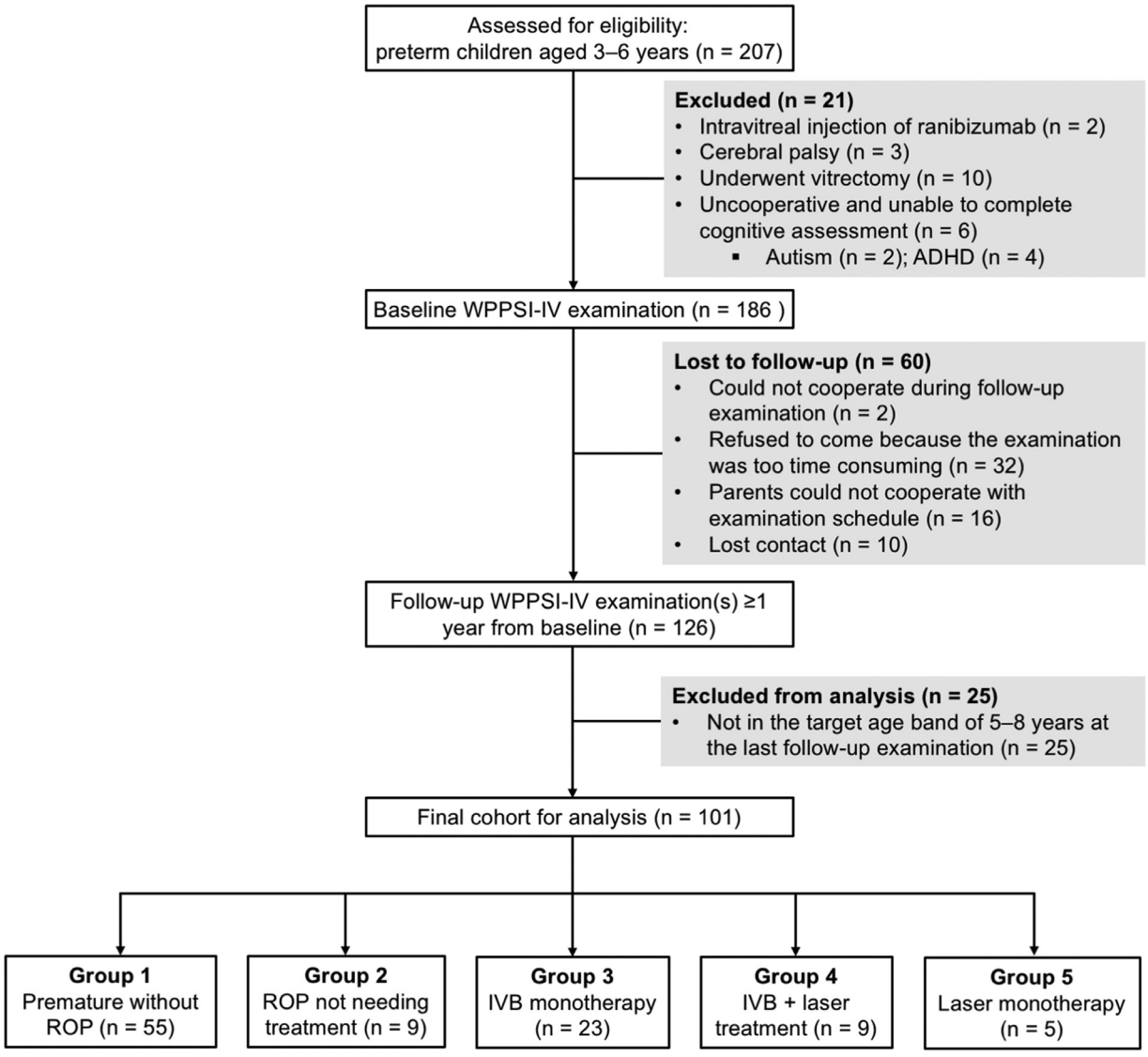

FIGURE 1. Study flowchart. ADHD = attention deficit/hyperactivity disorder, FSIQ = Full-Scale Intelligence Quotient, IVB = intravitreal injection of bevacizumab, ROP = retinopathy of prematurity, WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition.

age (GA), larger birth weight (BW), and higher Apgar scores at 1 and 5 minutes (all $P < .0001$), but those values were similar in groups 2 to 4. In group 1, significantly fewer children had sepsis ($P = .02$), patent ductus arteriosus ($P < .0001$), and respiratory distress syndrome ($P < .0001$), and they had fewer days on ventilation during infancy (median 10 days in group 1 compared with 84-93 days in groups 2-4; $P < .0001$). The factors in group 5 were comparable to those in groups 2 to 4 but showed no statistical significance when compared to those in group 1, likely because of the small number of cases in group 5. In addition, some imbalances were noted among the groups regarding the rates of antenatal corticosteroids, NEC, and intraventricular hemorrhage grade 3/4. Despite the heterogeneity among the groups, in general, the systemic condition in the neonatal period was significantly better in group 1 than in the other groups.

Table 2 compares the demographics and clinical features between the 101 included children and the 60 children who were lost to follow-up. Most of the factors were balanced, except significantly more children were inborn (95%) and had a higher proportion with NEC (15%) for those who were lost to follow-up. The detailed comparison between the included children and those lost to follow-up in the respective study groups is listed in Supplementary Tables S1 to S4.

• **COGNITIVE OUTCOMES AT BASELINE AND THE LAST FOLLOW-UP:** Table 3 shows the cognitive outcomes at the 2 time points. The mean age at baseline and the last follow-

TABLE 1. Demographics and Clinical Characteristics Between the Study Groups

	Group 1: Premature Without ROP (n = 55)	Group 2: ROP Not Needing Treatment (n = 9)	Group 3: IVB Monotherapy (n = 23)	Group 4: IVB + Laser Treatment (n = 9)	Group 5: Laser Monotherapy (n = 5)	*P* Value
Male	29 (53)	4 (44)	15 (65)	8 (89)	2 (40)	.19[a]
GA, wk, median (IQR)	32.6 (30.0, 34.0)	26.7[b] (26.0, 27.9)	25.9[b] (24.6, 26.7)	25.1[b] (25.1, 25.7)	26 (26.0, 26.0)	<.0001[c]
BW, g, median (IQR)	1675 (1340, 2100)	770[b] (705, 1010)	794[b] (730, 1020)	797[b] (750, 860)	700 (670, 795)	<.0001[c]
Apgar score, 1 min, median (IQR)	8 (7, 8)	4[b] (3, 5)	5[b] (4, 8)	4[b] (3, 5)	5 (4, 6)	<.0001[c]
Apgar score, 5 min, median (IQR)	9 (8, 9)	7[b] (6, 8)	7[b] (7, 9)	6[b] (6, 7)	8 (6, 8)	<.0001[c]
Inborn	45 (82)	7 (78)	15 (65)	8 (89)	2 (40)	.14[a]
Use of antenatal corticosteroids	30 (55)	8 (89)	12 (52)	8 (89)	5 (100)	.03[a]
Patent ductus arteriosus	4 (8)	7 (78)	15 (65)	4 (44)	5 (100)	<.0001[a]
Necrotizing enterocolitis	0 (0)	1 (11)	0 (0)	0 (0)	1 (20)	.04[a]
Sepsis	8 (15)	4 (44)	11 (48)	3 (33)	1 (20)	.02[a]
IVH, grade 3 or 4	1 (2)	0 (0)	4 (17)	0 (0)	1 (20)	.048[a]
Periventricular leukomalacia	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	>.99[a]
Respiratory distress syndrome	25 (48)	9 (100)	22 (96)	9 (100)	5 (100)	<.0001[a]
Days on mechanical ventilation, median (IQR)	10.0 (1.0, 30.0)	84.0[b] (65.0, 86.0)	93.0[b] (67.0, 103.0)	86.0[b] (77.0, 101.5)	56 (52.0, 87.0)	<.0001[c]
ROP stage[d]						<.0001[e]
No ROP	55 (100)	N/A	N/A	N/A	N/A	
1	N/A	4 (44)	0 (0)	0 (0)	0 (0)	
2	N/A	5 (56)	1 (4)	0 (0)	1 (20)	
3	N/A	0 (0)	22 (96)	9 (100)	4 (80)	
ROP zone[d]						.051[e]
I	N/A	0 (0)	1 (4)	3 (33)	1 (20)	
II	N/A	8 (89)	22 (96)	6 (67)	4 (80)	
III	N/A	1 (11)	0 (0)	0 (0)	0 (0)	
Plus disease[d]						<.0001[e]
Yes	N/A	0 (0)	23 (100)	9 (100)	4 (80)	
No	55 (100)	9 (100)	0 (0)	0 (0)	1 (20)	

BW = birth weight, GA = gestational age, IQR = interquartile range, IVH = intraventricular hemorrhage, ROP = retinopathy of prematurity.
[a] *P* values were calculated by Fisher exact test.
[b] Significant difference between the current group and group 1 by the post hoc test.
[c] *P* values were calculated by Kruskal-Wallis test, and post hoc tests were performed by Dunn test.
[d] As defined in the Early Treatment for Retinopathy of Prematurity Study.[4] The worst recorded ROP grading in the more severely affected eye of each subject is shown.
[e] *P* values were calculated by Fisher exact test while comparing between groups 2, 3, 4, and 5.
Unless otherwise noted, values are n (%).

up examination were 4.5-4.9 years and 6.1-7.0 years, respectively, which were comparable among groups 1 to 4 but older in group 5. Compared to group 1, groups 2 to 5 had nonsignificantly lower mean FSIQ scores at baseline ($P = .08$). Similarly, the scores at the last follow-up tended to be slightly lower in the latter groups, but the difference was not significant ($P = .50$).

Severe cognitive impairment (FSIQ < 70) at baseline was more common in groups 2 (22%), 3 (13%), and 4 (33%) than in groups 1 and 5 (4% and 0%, respectively; $P = .03$). This significance disappeared at the last follow-up (6%, 0%, 4%, 22%, and 0% in groups 1-5, respectively; $P = .33$). The proportion of patients with borderline cognitive impairment (FSIQ between 70 and 84) was not significantly different among the 5 study groups.

• **CHANGES IN COGNITIVE SCORES:** Compared to the baseline, the FSIQ scores at the last follow-up had improved in all groups, and the improvement was significant in groups 2, 3, and 5 ($P = .06$, .009, .0006, .24, and .01 in groups 1-5, respectively). The proportion of patients with severe cognitive impairment also decreased from baseline to the last follow-up in groups 2, 3, and 4 but was nonsignificant ($P =$ N/A, .16, and .56, respectively). The proportion of patients with borderline cognitive impairment decreased in all groups and was significant in group 3 ($P = .32$, .08, .046, >.99, and .16 in groups 1−5, respectively).

TABLE 2. Demographics and Clinical Characteristics Between the Included Children and the Children Who Were Lost to Follow-up

	Included (n = 101)	Lost to Follow-up (n = 60)	*P* Value
Groups			.08[a]
Group 1: Premature without ROP	55 (54.5)	33 (55.0)	
Group 2: ROP not needing treatment	9 (8.9)	10 (16.7)	
Group 3: IVB monotherapy	23 (22.8)	16 (26.7)	
Group 4: IVB + laser treatment	9 (8.9)	1 (1.7)	
Group 5: Laser monotherapy	5 (5.0)	0 (0.0)	
Male	58 (57.4)	37 (61.7)	.60[b]
GA, wk, median (IQR)	29.4 (26.0, 33.0)	29.7 (27.1, 32.4)	.86[c]
BW, g, median (IQR)	1180 (797.0, 1750.0)	1202.5 (893.0, 1567.5)	.85[c]
Apgar score, 1 min, median (IQR)	7 (4, 8)	6 (5, 8)	.66[c]
Apgar score, 5 min, median (IQR)	8 (7, 9)	8 (7, 9)	.84[c]
Inborn	77 (76)	57 (95)	.002[b]
Use of antenatal corticosteroids	63 (62.4)	41 (68.3)	.44[b]
Patent ductus arteriosus	35 (35.7)	22 (36.7)	>.99[b]
Necrotizing enterocolitis	2 (2.0)	9 (15.0)	.003[a]
Sepsis	27 (27.6)	10 (16.7)	.13[b]
IVH, grade 3 or 4	6 (6.3)	6 (10.0)	.54[b]
Periventricular leukomalacia	2 (2.1)	0 (0.0)	.52[a]
Respiratory distress syndrome	70 (71.4)	48 (80.0)	.26[b]
Days on mechanical ventilation, median (IQR)	45 (8, 85)	45 (20, 83)	.71[c]
ROP stage[d]			.53[a]
No ROP	55 (54.5)	34 (56.7)	
1	4 (4.0)	5 (8.3)	
2	7 (6.9)	5 (8.3)	
3	35 (34.7)	16 (26.7)	
ROP zone[d]			.20[a]
No ROP	55 (54.5)	34 (56.7)	
I	5 (5.0)	3 (5.0)	
II	40 (39.6)	19 (31.7)	
III	1 (1.0)	4 (7.7)	
Plus disease[d]			.06[b]
Yes	36 (35.6)	13 (21.7)	
No	65 (64.4)	47 (78.3)	
Age at baseline WPPSI-IV examination, y, mean ± SD	4.5 ± 0.9	3.9 ± 0.6	<.0001[e]
Baseline WPPSI-IV FSIQ, mean ± SD	89.2 ± 15.6	91.5 ± 16.8	.37[e]
Severe cognitive impairment at baseline (FSIQ < 70)	10 (9.9)	7 (11.7)	.72[b]
Borderline cognitive impairment at baseline (FSIQ 70-84)	26 (30.2)	12 (23.1)	.36[b]

BW = birth weight, FSIQ = Full-Scale Intelligence Quotient, GA = gestational age, IQR = interquartile range, IVH = intraventricular hemorrhage, ROP = retinopathy of prematurity, WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition.

[a] *P* values were calculated by Fisher exact test.

[b] *P* values were calculated by χ^2 test.

[c] *P* values were calculated by Wilcoxon 2-sample test.

[d] As defined in the Early Treatment for Retinopathy of Prematurity Study.[4] The worst recorded ROP grading in the more severely affected eye of each subject is shown.

[e] *P* values were calculated by 2-sample *t* test.

Unless otherwise noted, values are n (%).

Furthermore, generalized estimating equations were used to compare the changes in FSIQ over the follow-up period (Figure 2). Although there were no significant differences in the mean FSIQ at baseline and at the last follow-up among the groups, the changes in the FSIQ over time were significantly greater in group 2 and group 3 than in group 1 ($P = .03$ and .01, respectively; Supplementary Table S5).

• **FACTORS ASSOCIATED WITH COGNITIVE OUTCOMES:** At baseline, univariate analysis demonstrated that IVB

TABLE 3. Cognitive Outcomes at Baseline and the Last Follow-up Between ROP Groups.

	Group 1: Premature Without ROP (n = 55)	Group 2: ROP Not Needing Treatment (n = 9)	Group 3: IVB Monotherapy (n = 23)	Group 4: IVB + Laser Treatment (n = 9)	Group 5: Laser Monotherapy (n = 5)	*P* Value
Chronological age at examination, y, mean ± SD						
Baseline	4.5 ± 0.7	4.5 ± 1.0	4.6 ± 0.8	4.6 ± 1.2	4.9 ± 1.0	.77[a]
Last follow-up	6.1 ± 0.6[b]	6.2 ± 0.6[c]	6.4 ± 0.7	6.3 ± 0.9	7.0 ± 1.0[b,c]	.04[a]
WPPSI-IV FSIQ, mean ± SD						
Baseline	94.7 ± 13.6	84.7 ± 16.5	83.5 ± 16.9	78.0 ± 16.1	82.8 ± 4.6	.08[d]
Last follow-up	97.7 ± 16.6	94.9 ± 14.2	91.6 ± 15.1	83.2 ± 14.5	90.0 ± 6.3	.50[d]
WPPSI-IV FSIQ change between the last follow-up and baseline[e], median (IQR)	3.0 (−5.0, 10.0)	6.0 (5.0, 12.0)	8.0 (2.0, 16.0)	3.0 (−6.0, 18.0)	7 (3.0, 9.0)	.20[f]
Severe cognitive impairment (FSIQ < 70)						
Baseline	2 (4)	2 (22)	3 (13)	3 (33)	0 (0)	.03[g]
Last follow-up	3 (6)	0 (0)	1 (4)	2 (22)	0 (0)	.33[g]
Borderline cognitive impairment (FSIQ 70-84)						
Baseline	11 (21)	3 (43)	8 (40)	2 (33)	2 (67)	.15[g]
Last follow-up	8 (15)	2 (22)	6 (27)	3 (43)	1 (20)	.24[g]

FSIQ = Full-Scale Intelligence Quotient, IQR = interquartile range, ROP = retinopathy of prematurity, WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition.

[a] *P* values were calculated by analysis of variance, and post hoc test was calculated by Fisher least significant difference test.

[b] Significant difference between groups 1 and 5.

[c] Significant difference between groups 2 and 5.

[d] *P* values were calculated by analysis of covariance while gestational age, Apgar score at 5 minutes, patent ductus arteriosus, and days on mechanical ventilation were covariates.

[e] Calculated by subtracting FSIQ at baseline from the last follow-up.

[f] *P* values were calculated by Kruskal-Wallis test.

[g] *P* values were calculated by Fisher exact test.

Unless otherwise noted, values are n (%).

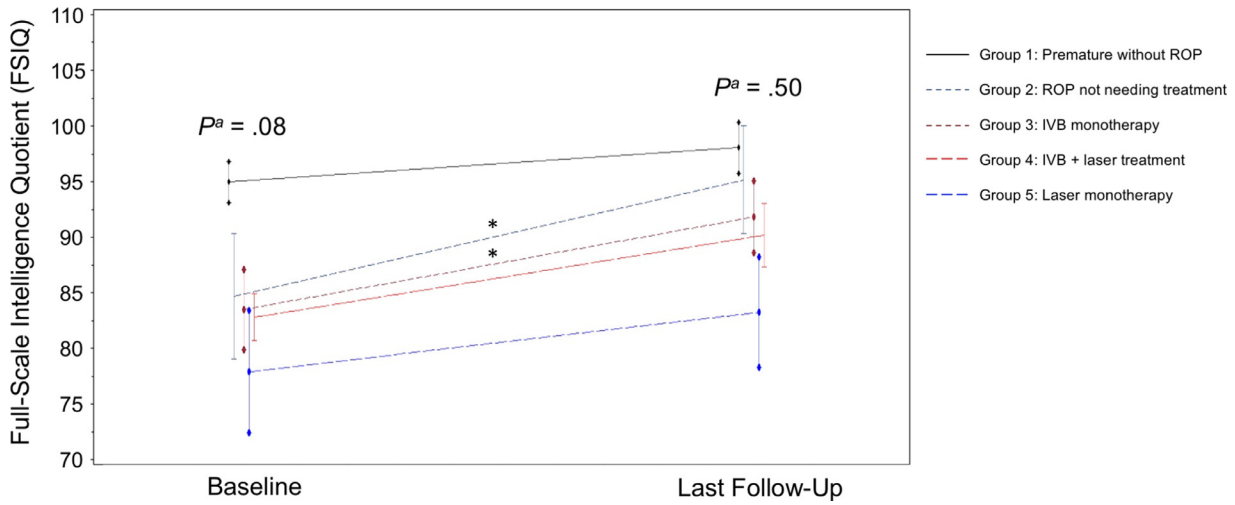

FIGURE 2. Changes in cognitive scores from baseline to the last follow-up. Compared to group 1, the changes in the Full-Scale Intelligence Quotient (FSIQ) were significantly greater in groups 2 and 3 (asterisks). The FSIQ was evaluated by the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV) Test. The change in the FSIQ was analyzed using generalized estimating models and adjusted for gestational age, the Apgar score at 5 minutes, patent ductus arteriosus, and days on mechanical ventilation. IVB = intravitreal injection of bevacizumab, ROP = retinopathy of prematurity. *P < .05. [a]P values comparing the scores among the 5 groups at baseline and the last follow-up, respectively, were calculated with analysis of covariance with the same covariates as in the generalized estimating models.

treatment, male sex, patent ductus arteriosus, and days on mechanical ventilation were negatively associated with the FSIQ, whereas GA and BW had positive associations (Table 4). Only male sex ($P = .01$) and days on ventilation ($P = .0001$) were significant factors with a negative association in the multivariable model.

At the last follow-up, both IVB treatment and days on ventilator were found to be negatively related to the FSIQ. However, after adjustments for the related demographic and systemic factors, only days on mechanical ventilation remained to have a negative influence on the FSIQ at the last follow-up ($P = .01$). The adjusted R^2 was 0.29 for the constructed model at baseline and decreased to 0.13 at the last follow-up, implying that the included factors affected cognitive outcome to a lesser degree as the children grew.

DISCUSSION

This prospective observational study demonstrates that children who underwent IVB had cognitive scores comparable to preterm children who did not undergo IVB at 4.5 and 6 years of age. Severe cognitive impairment at age 4.5 years was significantly more common in children who underwent IVB + laser combination treatment, but this difference decreased by the time the children were 6 years old. Moreover, after adjusting for sex, Apgar score at 1 minute, inborn status, use of antenatal corticosteroids, patent ductus arteriosus, necrotizing enterocolitis (NEC), sepsis, high-grade intraventricular hemorrhage, periventricular leukomalacia, and days on mechanical ventilation, IVB was not associated with FSIQ at either age.

Table 5 lists the current studies on neurodevelopmental outcomes after IVB. Most of these studies only followed the treated children up to 26 months' corrected age and used Bayley-III or II (Second Edition) as the assessment tool. The Bayley scales are designed to evaluate infants and toddlers up to 42 months of age. Compared to the Denver Developmental Screening Test, Second Edition, Bayley-III is a more comprehensive and detailed screening test[21] and is used widely in current clinical practice. However, the Bayley-III test was found to underestimate neurodevelopmental impairment,[22] thus rendering these Bayley-III–tested children at risk of being overlooked.

The WPPSI-IV test is targeted at an older and broader age band of 2 years 6 months to 7 years 7 months. For the WPPSI-IV composite FSIQ, the reliability analysis showed excellent internal consistency with a reliability coefficient of .96 and a test-retest correlation of .93.[23] The broad age band and the high validity of the WPPSI-IV test ensured the reliability of the current long-term longitudinal study.

At a corrected age of 1.5 years, Morin and associates[24] and Arima and associates[25] reported that the Bayley-III assessment showed a greater likelihood of severe neurodevelopmental disabilities and delay in the language-social domain in children who received IVB than in children who received laser treatment (Table 5). However, their studies were limited by the retrospective design, unbalanced groups,[26,27] and, in the latter study, a lack of reporting important risk factors.

A recent multicenter prospective study reviewed 181 children who received IVB and 224 children who underwent laser or cryotherapy and compared the Bayley-III scores at corrected ages of 18-26 months.[28] The results demonstrated that although the likelihood of neurodevelopmental impairment was comparable, the IVB group had a significantly higher mortality rate and likelihood of a cognitive score <85. However, as the authors mentioned, the IVB group had a slightly but significantly smaller BW and longer time on oxygen support, which could indicate that the children in this group were more severely ill.[29]

Conversely, a recent retrospective study on 61 children who underwent IVB and 85 who underwent laser treatment concluded that IVB did not affect either mortality or neurodevelopment.[30] In agreement with their findings, our previous studies[27,31] and other studies[32-37] also found no significant association between IVB and poor neurodevelopmental outcomes in children up to 2 years of age (Table 5). Similarly, a recent meta-analysis concluded that IVB did not increase the risk of developing severe neurodevelopmental impairment, although the quality of the currently available evidence was low.[13]

The development of cognitive function in preterm children is affected by multiple factors. In general, preterm children have lower IQ scores than full-term children, and a younger GA and lower BW are correlated with a lower cognitive score.[38] Male sex, birth at an external site, and neonatal events, including bronchopulmonary dysplasia, NEC, sepsis, ROP, high-grade intraventricular hemorrhage, periventricular leukomalacia, and postnatal corticosteroids, were also associated with cognitive impairment.[39-42] In the present study, in groups 2 to 5, the median GA (25.1-26.7 weeks) and BW (700-797 g) were categorized as extremely preterm and extremely low birth weight, respectively. When comparing groups 1 to groups 2 to 5, the former had a significantly older GA (32.6 weeks) and heavier BW (1675 g); thus, it is not surprising that cognitive scores tended to be numerically lower in the latter groups.

Among the ROP groups with similar demographics at birth (groups 2-5), the laser monotherapy group (group 5) was the ideal group to compare with the IVB monotherapy group (group 3). Although limited by the small case numbers in group 5 (n = 5), the rate of cognitive impairment was not significantly different between groups 3 and 5 at baseline (severe impairment, 13% vs 0%; borderline impairment, 40% vs 67%). Similarly, comparable low rates were observed at the follow-up examination (severe impairment, 4% vs 0%).

Furthermore, when comparing the IVB monotherapy group to the ROP not needing treatment group (group 2), the rates of cognitive impairment were also compara-

TABLE 4. Univariate and Multivariable Regression Analysis for Factors Associated With Cognitive Outcomes[a]

	FSIQ at Baseline				FSIQ at the Last Follow-up			
	Univariate		Multivariable[b]		Univariate		Multivariable[b]	
	β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value
IVB treatment[c]	−10.6 (−16.9, −4.2)	.001[d]	−3.6 (−11.5, 4.3)	.37	−7.5 (−14.1, −0.9)	.03[d]	−3.2 (−12.0, 5.7)	.48
Male sex	−6.6 (−12.8, −0.5)	.03[d]	−7.3[b] (−13.1, −1.5)	.01[d]	−4.1 (−10.4, 2.3)	.21	−5.2[a] (−11.8, 1.3)	.11
Gestational age, y	1.3 (0.5, 2.1)	.002[d]	—	—	0.8 (−0.04, 1.6)	.06	—	—
Birth weight, g	0.007 (0.002, 0.01)	.005[d]	—	—	0.004 (−0.001, 0.01)	.14	—	—
Apgar score, 1 min	0.9 (−0.5, 2.3)	.19	−1.7 (−3.4, 0.1)	.06	0.4 (−1.1, 1.8)	.61	−1.7 (−3.6, 0.3)	.10
Apgar score, 5 min	1.1 (−0.8, 3.0)	.27	—	—	0.5 (−1.4, 2.5)	.57	—	—
Inborn (reference: outborn)	−1.3 (−8.6, 6.0)	.72	5.9 (−1.7, 13.6)	.13	−4.8 (−12.2, 2.5)	.19	—	—
Use of antenatal corticosteroids	−1.2 (−7.6, 5.2)	.72	4.7 (−1.5, 11.0)	.14	−1.1 (−7.6, 5.4)	.75	5.1 (−1.9, 12.1)	.15
Patent ductus arteriosus	−6.5 (−13.0, −0.01)	.05[d]	5.1 (−3.1, 13.3)	.22	−3.6 (−10.3, 3.1)	.29	4.2 (−4.9, 13.3)	.36
Necrotizing enterocolitis	−5.0 (−27.5, 17.5)	.66	−12.8 (−33.1, 7.4)	.21	−5.8 (−28.7, 17.1)	.62	−16.9 (−39.5, 5.8)	.14
Sepsis	−4.5 (−11.5, 2.6)	.21	—	—	−3.0(−10.2, 4.3)	.42	−1.9 (−9.4, 5.4)	.60
IVH, grade 3 or 4 (reference: no IVH)	−6.1 (−19.3, 7.1)	.36	—	—	−10.3 (−23.7, 3.0)	.13	−4.9 (−18.3, 8.4)	.46
Periventricular leukomalacia	−6.0 (−28.5, 16.5)	.60	—	—	−14.0 (-36.7, 8.8)	.23	−13.4 (−35.0, 8.2)	.22
Respiratory distress syndrome	−8.1[a] (−15.0, −1.3),	.02	—	—	−1.9 (−9.1, 5.2)	.59	—	—
Days on mechanical ventilation	−0.2 (−0.2, −0.1)	<.0001[f]	−0.2[c] (−0.4, −0.1)	.0001[e]	−0.1 (−0.2, −0.05)	.001[d]	−0.2[a] (−0.4, −0.1)	.01[d]
Adjusted R^2	–		0.294		–		0.128	

FSIQ = Full-Scale Intelligence Quotient, IVB = intravitreal injection of bevacizumab, IVH = intraventricular hemorrhage.

[a]FSIQ was evaluated by the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV) test.

[b]Forward selection.

[c]Including children who underwent IVB monotherapy and IVB + laser. The reference group included preterm children without prior ROP, children not needing treatment for ROP, and those who underwent laser monotherapy.

[d]$P < .05$.

[e]$P < .001$.

[f]$P < .0001$.

TABLE 5. Publications on Neurodevelopmental Outcomes of Preterm Children After Intravitreal Injection of Bevacizumab

Author	Publication Year	Study Design	Age at Assessment	Assessment Tool	Patient Groups and Numbers	Findings
Martínez-Castellanos et al[16]	2013	Prospective, single-arm	Up to 60 mo	DDST-II	IVB (n = 13)	All except 1 critically ill patient showed normal neurodevelopmental scores.
Araz-Ersan et al[35]	2015	Retrospective, case-control	Up to 24 mo	Bayley-III	IVB + laser (n =13), laser (n = 13)	No significant difference was found in the Bayley scores.
Morin et al[24]	2016	Retrospective, comparative	18 mo	Bayley-III	IVB (n = 27), laser (n = 98)	Higher odds of severe neurodevelopmental disabilities in the IVB group.
Lien et al[31]	2016	Retrospective, comparative	6, 12, 18, and 24 mo	Bayley-II	IVB (n = 12), laser (n = 33), IVB + laser (n = 16)	Similar neurodevelopmental outcomes in the IVB and the laser monotherapy group. The IVB + laser group had a higher incidence of mental and psychomotor impairment than the laser monotherapy group.
Kennedy et al[32]	2018	Prospective, randomized	18-22 mo	Bayley-III	IVB (n = 7), laser (n = 9)	No significant differences in body weight, length, head circumference, cerebral palsy, or Bayley scores.
Chen et al[37]	2018	Retrospective, comparative	Up to 20 mo	Bayley-III or an equivalent test	IVB (n = 15), laser (n = 9)	No significant difference in neurodevelopmental delay.
Fan et al[27]	2019	Prospective, case-control	12-36 mo	Bayley-III	IVB (n = 38); premature, no ROP (n = 79); ROP, no treatment (n = 31)	No significant difference in Bayley scores and the risks for poor neurodevelopmental outcomes.
Raghuram et al[33]	2019	Retrospective, comparative	18-24 mo	Bayley-III	IVB (n = 34), laser (n = 30)	No significant differences in neurodevelopmental impairment or severe neurodevelopmental impairment.
Natarajan et al[28]	2019	Multicenter prospectively collected data	18-26 mo	Bayley-III	IVB (n = 155), surgery for ROP (n = 210)	No significant differences were identified in severe neurodevelopmental impairment, but IVB group had a higher mortality rate and likelihood of a cognitive score < 85.
Chang et al[34]	2019	Retrospective, comparative	Up to 24 mo	Bayley-II or Bayley-III	IVB (n = 18), any ROP (n = 86)	No significant differences in body weight and neurodevelopmental outcomes.
Arima et al[25]	2020	Retrospective, comparative	18 mo	KSPD	IVB (n = 14), laser (n = 39)	IVB was significantly associated with neurodevelopmental delay in the language-social domain.
Zayek et al[30]	2020	Retrospective, comparative	18-24 mo	Bayley-III	IVB (n = 61), laser (n = 85)	IVB did not affect survival and severe neurodevelopmental impairment.
Ahmed et al[36]	2020	Retrospective, comparative	Up to 24 mo	Bayley-III	IVB + laser (n = 18), laser (n = 48)	No significant difference in neurodevelopmental delay.
Chou et al	Current study	Single-center prospectively collected data	4.5-4.9 and 6.1-7.0 y	WPPSI-IV	Premature, no ROP (n = 55); ROP not needing treatment (n = 9); IVB (n = 23); IVB + laser (n = 9); laser (n = 5)	At 4.5 to beyond 6 years of age, children who underwent IVB monotherapy had comparable cognitive outcomes compared to the other premature children without prior IVB. Children who underwent IVB plus laser showed higher severe cognitive impairment at 4.5 y of age.

Bayley-II = Bayley Scales of Infant and Toddler Development, Second Edition, Bayley-III = Bayley Scales of Infant and Toddler Development, Third Edition, DDST-II = Denver Developmental Screening Test, Second Edition, IVB = intravitreal injection of bevacizumab, KSPD = Kyoto Scale of Psychological Development, ROP = retinopathy of prematurity, WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition.

ble. Last, the mean FSIQ was very similar among groups 2, 3, and 5, which was 84.7, 83.5, and 82.8 at baseline and 94.9, 91.6, and 90.0 at the last follow-up. The above observations indicated that no significant difference in cognitive outcomes was found among children treated with IVB or laser monotherapy and children without ROP treatment.

Notably, the children who underwent IVB + laser (group 4) had a significantly higher rate (33%) of severe cognitive impairment at baseline. These children were different from the IVB monotherapy group, as eyes with recurrence of ROP after the primary treatment were mostly sicker children with worse systemic and ocular conditions, and they tended to undergo ROP treatment at earlier ages.[20] In line with this, group 4 underwent IVB at a significantly younger postmenstrual age of 33.2 ± 2.4 weeks compared with the IVB monotherapy group of 36.1 ± 1.6 weeks in the current study ($P = .005$). Furthermore, group 4 consisted of mainly boys (89%) and had the lowest GA among all groups, and both of these factors were strongly and independently associated with poorer cognitive outcomes.[38,40] Therefore, to determine the effect of IVB on this group of children, the above factors should be adjusted.

In the unadjusted correlation analysis, there was a negative association between IVB treatment and FSIQ at both baseline and the follow-up examination (Table 4). However, the "IVB treatment" factor included the IVB monotherapy and the IVB + laser groups, and the reference group contained not only those who received laser monotherapy but also those with a better neonatal condition, the premature without ROP group.

To adjust for these clinical differences, multivariable models were constructed, and the significant association found between IVB and FSIQ in the univariate analysis turned nonsignificant after adding the days on mechanical ventilation factor to the model. In fact, there was a significant difference in the duration on ventilation between the children who underwent IVB (median 92 days) and those who did not (median 22 days, $P < .001$). The effect of mechanical ventilation on cognitive function was reported to be –0.43 IQ points per day of ventilation.[43] In agreement with their findings, the detrimental effect of ventilation on the FSIQ was noted in this study.

The importance of long-term follow-up of the neurodevelopment of preterm children was emphasized because not all aspects of cognition can be accurately predicted in early childhood.[17,18] Borderline cognitive impairment in toddlerhood was associated with definite deficits at school age, and emotional and behavioral problems may emerge at older ages.[44,45] In children who were born extremely preterm, severe neurodevelopmental impairment is present in 11% to 28% when they reach 6.5-10 years of age.[39,41,46] In our study, 22% to 33% of our extremely preterm children in groups 2 to 4 had severe cognitive impairment at 4.5 years, but there was no increase from 4.5 to 6 years of age. Interestingly, severe cognitive impairment decreased and the mean FSIQ increased as the children aged.

Similar to our findings, investigators have found that cognitive test scores improved over time in very-low-birthweight and extremely preterm children.[47,48] Whether this change over time is truly an actual improvement is still under debate,[49] but studies did find that socioeconomic factors, including higher parental educational level, caregiver employment, and living in the same household with both parents, were associated with a greater improvement in cognitive score across preschool years,[50] as the negative influence of male sex on neonates became less relevant in the longer term.[51]

This study has several limitations. First, this was a nonrandomized single-center study with a small number of enrolled patients. Second, because a significant number of children might have been lost to follow-up by the time they were eligible for this study, selection bias could have existed. However, our institution is a tertiary referral center and receives patients from a broad area, and the cohort had been followed for years and tended to stay in our clinic.[27,31]

Third, neurodevelopmental impairment is typically defined as the presence of cognitive, neurologic, and/or sensory deficits. Here, only the cognitive outcomes were evaluated. Last, cognitive development is complicated and is influenced by a broad range of factors. Although we documented various recognized factors, other unrecorded variables may also have a significant role. Despite these limitations, this study is important because of its prospective, longitudinal study design, which provides valuable long-term data from this special cohort.

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REFERENCES

1. Blencowe H, Lawn JE, Vazquez T, Fielder A, Gilbert C. Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. *Pediatr Res*. 2013;74(1):35–49 suppl.
2. Kang EY, Lien R, Wang NK, et al. Retinopathy of prematurity trends in Taiwan: a 10-year nationwide population study. *Invest Ophthalmol Vis Sci*. 2018;59(8):3599–3607.
3. Alon T, Hemo I, Itin A, Pe'er J, Stone J, Keshet E. Vascular endothelial growth factor acts as a survival factor for newly

formed retinal vessels and has implications for retinopathy of prematurity. *Nat Med*. 1995;1(10):1024–1028.
4. Early Treatment for Retinopathy of Prematurity Cooperative GroupRevised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol*. 2003;121(12):1684–1694.
5. Mintz-Hittner HA, Kennedy KA, Chuang AZ. BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med*. 2011;364(7):603–615.
6. Sankar MJ, Sankar J, Chandra P. Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity. *Cochrane Database Syst Rev*. 2018;1(1):Cd009734.
7. Lee YS, See LC, Chang SH, et al. Macular structures, optical components, and visual acuity in preschool children after intravitreal bevacizumab or laser treatment. *Am J Ophthalmol*. 2018;192:20–30.
8. Kang EY, Hsu KH, Chu SM, et al. Ten-year epidemiology of retinopathy of prematurity treatment in Taiwan. *Retina*. 2020;40(9):1804–1811.
9. Sato T, Wada K, Arahori H, et al. Serum concentrations of bevacizumab (Avastin) and vascular endothelial growth factor in infants with retinopathy of prematurity. *Am J Ophthalmol*. 2012;153(2):327–333 e321.
10. Wu WC, Lien R, Liao PJ, et al. Serum levels of vascular endothelial growth factor and related factors after intravitreous bevacizumab injection for retinopathy of prematurity. *JAMA Ophthalmol*. 2015;133(4):391–397.
11. 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.
12. 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.
13. Tsai CY, Yeh PT, Tsao PN, Ella Chung YC, Chang YS, Lai TT. Neurodevelopmental outcomes after bevacizumab treatment for retinopathy of prematurity—a meta-analysis. *Ophthalmology*. 2020;128(6):877–888.
14. Vohr BR, Stephens BE, Higgins RD, et al. Are outcomes of extremely preterm infants improving? Impact of Bayley assessment on outcomes. *J Pediatr*. 2012;161(2):222–228 e223.
15. Anderson PJ, Burnett A. Assessing developmental delay in early childhood—concerns with the Bayley-III scales. *Clin Neuropsychol*. 2017;31(2):371–381.
16. Martinez-Castellanos MA, Schwartz S, Hernandez-Rojas ML, et al. Long-term effect of antiangiogenic therapy for retinopathy of prematurity up to 5 years of follow-up. *Retina*. 2013;33(2):329–338.
17. Potharst ES, Houtzager BA, van Sonderen L, et al. Prediction of cognitive abilities at the age of 5 years using developmental follow-up assessments at the age of 2 and 3 years in very preterm children. *Dev Med Child Neurol*. 2012;54(3):240–246.
18. Aylward GP. Neurodevelopmental outcomes of infants born prematurely. *J Dev Behav Pediatr*. 2014;35(6):394–407.
19. Wu WC, Yeh PT, Chen SN, Yang CM, Lai CC, Kuo HK. Effects and complications of bevacizumab use in patients with retinopathy of prematurity: a multicenter study in Taiwan. *Ophthalmology*. 2011;118(1):176–183.
20. Ling KP, Liao PJ, Wang NK, et al. Rates and risk factors for recurrence of retinopathy of prematurity after laser or intravitreal anti-vascular endothelial growth factor monotherapy. *Retina*. 2020;40(9):1793–1803.
21. Jeong SU, Kim GC, Jeong HJ, et al. The validity of the Bayley-III and DDST-II in preterm infants with neurodevelopmental impairment: a pilot study. *Ann Rehabil Med*. 2017;41(5):851–857.
22. Acton BV, Biggs WS, Creighton DE, et al. Overestimating neurodevelopment using the Bayley-III after early complex cardiac surgery. *Pediatrics*. 2011;128(4):e794–e800.
23. Syeda MM, Climie EA. Test review: Wechsler Preschool and Primary Scale of Intelligence–fourth edition. *J Psychoeduc Assess*. 2014;32(3):265–272.
24. Morin J, Luu TM, Superstein R, et al. Neurodevelopmental outcomes following bevacizumab injections for retinopathy of prematurity. *Pediatrics*. 2016;137(4).
25. Arima M, Akiyama M, Fujiwara K, et al. Neurodevelopmental outcomes following intravitreal bevacizumab injection in Japanese preterm infants with type 1 retinopathy of prematurity. *PLoS One*. 2020;15(3):e0230678.
26. Blair MP, Shapiro MJ. Re: Good: Bevacizumab for retinopathy of prematurity: Treatment when pathology is embedded in a normally developing vascular system (Ophthalmology. 2016;123:1843-1844). *Ophthalmology*. 2017;124(10):e74–e75.
27. 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.
28. Natarajan G, Shankaran S, Nolen TL, et al. Neurodevelopmental outcomes of preterm infants with retinopathy of prematurity by treatment. *Pediatrics*. 2019;144(2):e20183537.
29. Rodriguez SH, Blair MP, Shapiro MJ, et al. Neurodevelopmental outcomes of preterm infants with retinopathy of prematurity by treatment. *Pediatrics*. 2020;31 Published online March 31. doi:10.1542/peds.2020-0056A [Epub ahead of print].
30. Zayek M, Parker K, Rydzewska M, Rifai A, Bhat R, Eyal F. Bevacizumab for retinopathy of prematurity: 2-year neurodevelopmental follow-up. *Am J Perinatol*. 2021;38(11):1158–1166.
31. 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.
32. Kennedy KA, Mintz-Hittner HA, Group BEAT-ROP Cooperative. Medical and developmental outcomes of bevacizumab versus laser for retinopathy of prematurity. *J AAPOS*. 2018;22(1):61–65 e61.
33. Raghuram K, Isaac M, Yang J, et al. Neurodevelopmental outcomes in infants treated with intravitreal bevacizumab versus laser. *J Perinatol*. 2019;39(9):1300–1308.
34. Chang YS, Chen YT, Lai TT, et al. Involution of retinopathy of prematurity and neurodevelopmental outcomes after intravitreal bevacizumab treatment. *PLoS One*. 2019;14(10):e0223972.
35. Araz-Ersan B, Kir N, Tuncer S, et al. Preliminary anatomical and neurodevelopmental outcomes of intravitreal bevacizumab as adjunctive treatment for retinopathy of prematurity. *Curr Eye Res*. 2015;40(6):585–591.

36. Ahmed K, Ali AS, Delwadia N, Greven MA. Neurodevelopmental outcomes following intravitreal bevacizumab with laser versus laser photocoagulation alone for retinopathy of prematurity. *Ophthalmic Surg Lasers Imaging Retina*. 2020;51(4):220–224.
37. Chen TA, Schachar IH, Moshfeghi DM. Outcomes of intravitreal bevacizumab and diode laser photocoagulation for treatment-warranted retinopathy of prematurity. *Ophthalmic Surg Lasers Imaging Retina*. 2018;49(2):126–131.
38. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA*. 2002;288(6):728–737.
39. Kuban KC, Joseph RM, O'Shea TM, et al. Girls and boys born before 28 weeks gestation: risks of cognitive, behavioral, and neurologic outcomes at age 10 years. *J Pediatr*. 2016;173:69–75 e61.
40. Linsell L, Johnson S, Wolke D, et al. Cognitive trajectories from infancy to early adulthood following birth before 26 weeks of gestation: a prospective, population-based cohort study. *Arch Dis Child*. 2018;103(4):363–370.
41. Cheong JLY, Lee KJ, Boland RA, et al. Changes in long-term prognosis with increasing postnatal survival and the occurrence of postnatal morbidities in extremely preterm infants offered intensive care: a prospective observational study. *Lancet Child Adolesc Health*. 2018;2(12):872–879.
42. Synnes A, Luu TM, Moddemann D, et al. Determinants of developmental outcomes in a very preterm Canadian cohort. *Arch Dis Child Fetal Neonatal Ed*. 2017;102(3):F235–f234.
43. Breeman LD, Jaekel J, Baumann N, Bartmann P, Wolke D. Neonatal predictors of cognitive ability in adults born very preterm: a prospective cohort study. *Dev Med Child Neurol*. 2017;59(5):477–483.
44. Dewey DG, Crawford SG, Creighton DE, Sauve RS. Long-term neuropsychological outcomes in very low birth weight children free of sensorineural impairments. *J Clin Exp Neuropsychol*. 1999;21(6):851–865.
45. Burnett A, Davey CG, Wood SJ, et al. Extremely preterm birth and adolescent mental health in a geographical cohort born in the 1990s. *Psychol Med*. 2014;44(7):1533–1544.
46. Serenius F, Ewald U, Farooqi A, et al. Neurodevelopmental outcomes among extremely preterm infants 6.5 years after active perinatal care in Sweden. *JAMA Pediatr*. 2016;170(10):954–963.
47. Ment LR, Vohr B, Allan W, et al. Change in cognitive function over time in very low-birth-weight infants. *JAMA*. 2003;289(6):705–711.
48. Stålnacke SR, Tessma M, Böhm B, Herlenius E. Cognitive development trajectories in preterm children with very low birth weight longitudinally followed until 11 years of age. *Front Physiol*. 2019;10:307.
49. Doyle LW. Are neurodevelopmental outcomes of infants born extremely preterm improving over time? *Pediatrics*. 2018;141(5):e20174009.
50. Manley BJ, Roberts RS, Doyle LW, et al. Social variables predict gains in cognitive scores across the preschool years in children with birth weights 500 to 1250 grams. *J Pediatr*. 2015;166(4):870–876 e871-872.
51. 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.