International Journal of Retina (*IJRETINA*) 2023, Volume 6, Number 1.
P-ISSN. 2614-8684, E-ISSN.2614-8536

IJRETINA
International Journal of Retina

NEURODEVELOPMENTAL OUTCOMES AFTER ANTI-VEGF TREATMENT FOR RETINOPATHY OF PREMATURITY: A SYSTEMATIC REVIEW AND META-ANALYSIS

Nizma Permaisuari, Julie Dewi Barliana

Department of Ophthalmology, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta

Abstract

Introduction: *The objective of this study was to assess the neurodevelopmental outcomes in preterm infants who have undergone intravitreal anti-vascular endothelial growth factor (anti-VEGF), either as monotherapy or in combination with laser therapy, for treatment of retinopathy of prematurity (ROP). Secondary, efficacy of anti-VEGF was also evaluated.*

Methods: *Literature search was conducted using 7 online databases (CENTRAL, PubMed, ScienceDirect, SCOPUS, EBSCO, ProQuest, and JSTOR). Studies were selected based on the established inclusion and exclusion criteria. Primary outcomes were neurodevelopmental impairment (NDI), severe NDI (sNDI), neurodevelopmental scores, and cerebral palsy (CP) incidence. Secondary outcomes included impairment and severe impairment of each domain (motor, cognitive, and language) and retreatment of ROP.*

Result: *Seventeen studies were included. Random-effects model meta-analysis showed no differences were observed between anti-VEGF compared to control group in NDI (unadjusted odds ratio (uOR) 1.28; 95% confidence interval (CI) 0.85 to 1.94), sNDI (uOR 1.33; 95% CI 0.92 to 1.93), and CP outcomes . Meta-analysis showed insignificant result with lower overall scores, motor, cognitive, and language domains associated with anti-VEGF treatment. Secondary outcomes showed inferior cognitive impairment (OR 1.41; 95% CI: 1.03 to 1.92) and higher retreatment rate (OR 47.55; 95% CI: 12.35 to 183.09) in anti-VEGF group.*

Conclusion: *There were no differences in neurodevelopmental outcomes between anti-VEGF and control group. Despite not causing any adverse neurodevelopmental effect, clinicians should carefully weigh the benefits and risks of anti-VEGF injection for treating infants with ROP, since it has higher retreatment rate.*

Keywords: Anti–vascular endothelial growth factor, neurodevelopmental outcome, retinopathy of prematurity

Cite This Article: PERMAISUARI, Nizma; BARLIANA, Julie Dewi. NEURODEVELOPMENTAL OUTCOMES AFTER ANTI-VEGF TREATMENT FOR RETINOPATHY OF PREMATURITY: A SYSTEMATIC REVIEW AND META-ANALYSIS. International Journal of Retina, [S.l.], v. 6, n. 1, p. 30, mar. 2023. ISSN 2614-8536. Available at: <https://www.ijretina.com/index.php/ijretina/article/view/205>. Date accessed: 01 mar. 2023. doi: https://doi.org/10.35479/ijretina.2023.vol006.iss001.205..

Correspondence to:
Nizma Permaisuari,
Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta
permaisuari@gmail.com

INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder affecting premature infants that can lead to poor visual acuity and blindness in children.[1–3] ROP is a biphasic disease related to excessive supplemental oxygen administered during early postnatal period.[4] Phase 1 is characterized by relative hyperoxia and downregulation of vascular endothelial growth factor (VEGF), resulting in cessation of retinal vascular development that leads to hypoxic ischemia. This condition induces the release of VEGF,

with small pupil or presence of media opacities, and cause less refractive errors.[8,11] However, there is the uncertainty of long-term systemic side effects of anti-VEGF administration in premature population, especially its effects in neurodevelopment. VEGF plays an important role, not only for angiogenesis in the eye, but also in other vital organs such as the lungs, kidneys, and brain.[6,12] The possibility of systemic absorption after intravitreal anti-VEGF, may further decrease serum VEGF levels and have long-term effects on development of central nervous system and other systems.[13,14] Morin et al[15] reported increased odds of neurodevelopmental impairment (NDI) in preterm infants treated with IVB compared to laser treatment. Contrarily, Lien et al[14] reported no differences. Hence, a focused systematic review was conducted to evaluate the neurodevelopmental outcomes of preterm infants with ROP treated with intravitreal anti-VEGF.

METHODS

Eligibility Criteria

In this review, we included level 2-3 studies according to Oxford Centre for Evidence-Based Medicine.[16] We considered studies that enrolled preterm infants (< 37 weeks' gestation at birth) with ROP at enrolment for inclusion. Intervention group consisted of preterm infants with ROP treated with administration of VEGF inhibitors by intravitreal route. Intravitreal anti-VEGF is administered either as monotherapy or in combination with laser therapy in either eye. Anti-VEGF given is either bevacizumab, ranibizumab, aflibercept pegaptanib sodium, or conbercept. Control group is those with any stage of ROP who did not receive anti-VEGF therapy. It can receive laser therapy or who did not receive any form of treatment. Studies were included if they provide at least one of the primary outcomes. Primary outcomes included NDI; severe NDI (sNDI); neurodevelopmental scores including overall scores, motor, cognitive, and language scores; and cerebral palsy (CP) incidence. Secondary outcomes were also evaluated if available, such as impairment and severe impairment of each domain (motor, cognitive, and language), also efficacy of anti-VEGF (retreatment of ROP). The operational definitions of the terms used in this review are presented in **Table 1**.

The exclusion criteria were studies in non-human subjects, articles that could not be fully accessed, articles with only published abstracts, editorial publications, and articles published not in English. Duplications were also excluded.

Literature Search

We conducted a literature search in 7 electronic databases including Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE via PubMed, ScienceDirect, SCOPUS, EBSCO, ProQuest, and JSTOR. The detailed search strategies are presented in **Table 2.** The search was not time-limited in order to obtain all studies related to the objective of this literature review.

Table 1. Operational Definitions

Terms	Definition
Cerebral Palsy (CP)	CP is a spectrum of neurological deficits resulting from damage to the developing nervous system that affect a person's ability to move and maintain balance and posture.[19] CP can be determined based on Gross Motor Functional Classification System (GMFCS)[11,20,21] or the General Movement Assessment (GMA).[12] Definition of CP in present study is based on operational definition in each included studies.
Cognitive impairment	Defined as presence any of the following:[7,15,20,22–24] • BSID-III cognitive score <85, • BSID-II MDI score <70, • Any comparable score with validated tools.
Cognitive score	Cognitive score is measured by using cognitive domain in BSID-III or any comparable validated tools.[11,20–23]
Language impairment	Defined as presence any of the following:[7,15,22–24] • BSID-III language score <85, • BSID-II MDI score <70, • Any comparable score with validated tools.
Language Score	Language score is measured by using language domain in BSID-III or any comparable validated tools.[11,20–23]
Motor impairment	Defined as presence any of the following:[7,15,20,22–24] • BSID-III motor score <85, • BSID-II PDI score <70, • Any comparable score with validated tools.
Motor score	Motor score is measured by using motor domain in BSID-III or any comparable validated tools.[11,20–23]
Neurodevelopmental Impairment (NDI)	Definition of NDI in present study is based on operational definition in each included studies. It can be measured by using any neurodevelopmental tools or defined as presence of CP, visual impairment, or hearing impairment.[12,20–23,25,26]
Overall scores	Overall scores is measured by using any neurodevelopmental tools. Intelligence Quotient (IQ) or Developmental quotient (DQ) is derived from the tools. • IQ is a total score derived from a set of standardized tests or subtests designed to assess human intelligence.[27] • DQ is a score which describes the normal developmental proportion with child at that age.[28]
Retreatment	Defined as ROP recurrences requiring additional treatment after receiving anti-VEGF, laser, or cryotherapy.[29,30]
Severe cognitive impairment	Defined as presence any of the following:[20,22,25] • BSID-III cognitive score <70, • Any comparable score with validated tools.
Severe language impairment	Defined as presence any of the following:[20,22,25] • BSID-III language score <70, • Any comparable score with validated tools.
Severe motor impairment	Defined as presence any of the following:[20,22,25] • BSID-III motor score <70, • Any comparable score with validated tools.
Severe Neurodevelopmental Impairment (sNDI)	Definition of sNDI in present study is based on operational definition in each included studies. It can be measured by using any neurodevelopmental tools or defined as presence of CP, visual impairment, or hearing impairment.[7,15,20,22,23]

We also searched the reference lists of all studies identified for potential relevant sources.

Study Selection

Based on the search results above, articles were considered eligible based on the following characteristics: study population (preterm infants with ROP), study intervention (administration of intravitreal anti-VEGF drugs with or without laser therapy), study control (not receiving anti-VEGF therapy), study outcome (NDI), and study design (randomised controlled trials, cohort).

We reviewed the titles and abstracts of all identified studies. We retrieved and reviewed the full text of the article if we could not ascertain relevance by screening the title and the abstract. The full texts of all potentially eligible articles were then evaluated to ensure that the studies met the eligibility criteria The trial author was contacted by email correspondence for additional information or for clarification as necessary.

Data Collection and Extraction

We performed data extraction regarding study setting (year and country), study design, patient characteristics, study intervention and control, screening tools for neurodevelopmental evaluation, length of follow-up, risk of biases, and outcomes of interest were independently extracted for further analysis. For dichotomous outcomes, we extracted the total number of participants for each group and the number of participants experiencing an event. For continuous outcomes, we extracted mean, standard deviation (or data required to calculate this), and the total number of participants for each group.

Risk of Bias Assessment

Author assessed the risk of bias of articles included in this review using different tools according to the types of study. A revised Cochrane risk-of-bias tool for randomized trials (RoB 2) is the tool used to assess the risk of bias in randomized trials.[17] Meanwhile, to assess the risk of bias in non-randomized studies, we use Risk of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool.[18]

Table 1. Search Strategies in Each Database

Database	Search Strategy
CENTRAL	#1 MeSH descriptor : [Retinopathy of Prematurity] explode all trees #2 MeSH descriptor : [Bevacizumab] explode all trees) #3 MeSH descriptor : [Ranibizumab] explode all trees) #4 Aflibercept # 5 Pegaptanib #6 Conbercept #7 #2 OR #3 OR #4 OR #5 OR #6 #8 #1 AND #2
PubMed	(Retinopathy of Prematurity[MeSH Terms]) AND (((((Bevacizumab[MeSH Terms]) OR Ranibizumab[MeSH Terms]) OR Aflibercept) OR Pegaptanib) OR Conbercept)
ProQuest	ab(Retinopathy of Prematurity) AND ab(Bevacizumab OR Ranibizumab OR Aflibercept OR Pegaptanib OR Conbercept) AND ft(Neuro*)
SCOPUS	(ABS (retinopathy AND of AND prematurity) AND ABS (bevacizumab OR ranibizumab OR aflibercept OR pegaptanib OR conbercept) AND TITLE-ABS-KEY (neuro*))
ScienceDirect	(ABS (retinopathy AND of AND prematurity) AND ABS (bevacizumab OR ranibizumab OR aflibercept OR pegaptanib OR conbercept) AND TITLE-ABS-KEY (neuro*))
EBSCO	AB Retinopathy of Prematurity AND AB ((bevacizumab) or (ranibizumab) or (aflibercept) or (pegaptanib) or (conbercept)) AND neuro*
JSTOR	((Retinopathy of Prematurity) AND (Bevacizumab OR Ranibizumab OR Aflibercept OR Pegaptanib OR Conbercept))

Data Synthesis and Analysis

For dichotomous outcomes, comparative effect sizes were calculated as odds ratios (ORs), with 95% confidence intervals (CI), using the Mantel–Haenszel method. For continuous outcomes, mean difference (MD) was reported with 95% CI based on an inverse-variance, weighted meta-analysis.

If the study provided median, range, interquartile range, and standard error, these were converted into mean and standard deviation. Estimated mean was calculated based on the study from Luo et al[31] and Hozo et al,[32] meanwhile estimated standard deviation was acquired based on study by Wan et al.[33] RevMan calculator assisted in data entry of dichotomous, continuous and generic inverse variance outcome types If the outcomes expressed as a ratio, the analysis required use of the generic inverse-variance method in RevMan.[34] If available, the comparative effect sizes were also calculated using adjusted analysis.

A random effect model was performed for all outcomes. The meta-analysis for Randomized Controlled Trials (RCTs) and non-randomized studies was performed separately. Publication bias assessed by funnel plot asymmetry when there are at least 10 studies included in the meta-analysis. We evaluated forest plots qualitatively and used p for chi-square and I^2 values (derived from the chi-squared Q-statistic) for assessing heterogeneity. We considered significant statistical heterogeneity if p for chi-square <0.10 or I^2 values 75-100%.[34] All statistical analyses were performed using Review Manager 5.4.1 (Cochrane Collaboration, Nordic Cochrane Center, Copenhagen, Denmark).

RESULTS

By using the search in 7 electronic databases, we retrieved a total of 345 studies, of which 17 fulfilled the eligibility criteria and were included in the review. One study by Kang et al[30] was excluded in meta-analysis because no events found in both intervention and control group. **Figure 1** is the flowchart of the selection process based on PRISMA flow diagram.[35]

Study Characteristics

Table 3 presents the study characteristics which published between 2014 and 2021. All studies used anti-VEGF monotherapy for the treatment group, except for 4 studies that used laser combined with anti-VEGF for the treatment group. Cohort was the study design in all studies except one from Kennedy et al[20] which was an RCT. Intravitreal bevacizumab (IVB) was used in all studies, except for Kang et al,[30] which used ranibizumab. The bevacizumab dosage was 0.625 mg/0.025 mL in 11 of the included studies; the remaining studies did not specify the dosage. The dosage injected in ranibizumab administration was 0.25 mg/0.025 mL. Regarding the control groups, most studies used laser monotherapy as the control. Meanwhile, Natarajan et al[20] employed laser and/or cryotherapy, Chang et al[24] and Fan et al[7] enrolled ROP patients with ROP but requiring no treatment.

Risk of Bias Assessment

Kennedy et al[11] was assessed "low risk of bias" using RoB 2 tool. Other 16 studies were assessed by ROBINS-I tool and summarized in **Figure 2**. Nine studies were at serious risk of bias and 2 studies were at critical risk of bias. The detailed risk of bias assessment is provided in **Table 4**.

Effects of Intervention

Neurodevelopmental Impairment

Eight studies reported NDI incidence in their original reports. The result for this analysis was presented in the forest plot in **Figure 3.** NDI incidence did not differ significantly between the anti-VEGF and control groups, with an overall OR for NDI of 1.28 (95% CI: 0.85 to 1.94; test for overall effect: Z = 1.17, p = 0.24) with no heterogeneity (I^2 = 0%). The OR was the same under fixed-effect model. Adjusted analysis of NDI incidences was not significantly different (**Table 5**).

Severe Neurodevelopmental Impairment

Of the 9 studies included in the analysis of sNDI outcomes, the result was shown in **Figure 4**. The risk was similar in anti-VEGF and control groups with OR 1.33 (95% CI: 0.92 to 1.93; test for overall effect: Z = 1.53, p = 0.13). Mild heterogeneity was detected in this analysis (I^2 = 21%). Adjusted analysis of sNDI incidences was not significantly different as shown in **Table 5**.

Neurodevelopmental Scores

There are 14 included studies reporting the scores of neurodevelopmental tests. The meta-analysis showed lower scores for overall scores, motor, cognitive, and language domains associated with anti-VEGF treatment. Overall scores (MD = −1.74; 95% CI: −16.53 to 13.05; test for overall effect: Z = 0.23, p = 0.82; **Figure 5A**), motor scores (MD = −2.05; 95% CI: −5.09 to 0.98; test for overall effect: Z = 1.32, p = 0.19; **Figure 5B**), cognitive scores (MD −2.00; 95% CI −4.35 to 0.36; test for overall effect: Z = 1.66, p = 0.10; **Figure 5C**), and language scores (MD −1.87; 95% CI −4.61 to 0.87; test for overall effect: Z = 1.34, p = 0.18; **Figure 5D**) did not differ significantly between anti-VEGF and control groups. After performing subgroup analysis, the meta-analysis result of motor, cognitive, and language scores in non-randomised studies were still insignificant. Stratified analyses based on the risk of bias and sensitivity analysis with fixed-effect model application were done with insignificant result. When we restricted the analysis by eliminating study with critical risk of bias by Zayek et al,[23] the motor scores (MD = −3.32; 95% CI: −6.19 to -0.44; test for overall effect: Z = 2.26, p = 0.02) showed significant result.

Adjusted analysis of cognitive, language, and motor scores were not significantly different as shown in **Table 5**. Funnel plots for cognitive, language, and motor scores are shown in **Figure 6A-C**. The 3 plots were both relatively symmetrical, which indicated no evidence of publication bias.

Cerebral Palsy

CP risk was similar in anti-VEGF and control groups (OR = 1.32; 95% CI: 0.93 to 1.86; **Figure 7**). No heterogeneity was detected (I^2 = 0%; Chi^2 = 4.77, p = 0.57). In study by Morin et al,[15] the number of infants with CP in the anti-VEGF group was reported as "<5". We inserted "0 to 4" for the sensitivity analysis and found no difference. The results also remained the same during the sensitivity analysis when fixed-effect model was applied. Meta-analysis of 3 studies providing adjusted odds ratio also did not find significant differences between the groups (**Table 5**).

Motor, Language, and Cognitive Impairment

The meta-analysis showed significant increased odds of cognitive impairment associated with anti-VEGF treatment with OR 1.41 (95% CI: 1.03 to 1.92; Z = 2.14, p = 0.03; I^2 = 0%). No statistically significant differences were noted on unadjusted and adjusted analyses of impairment and severe impairment in motor and language domain (**Table 5**). A trend favoring the control group was observed in all analysis.

Efficacy of Anti-VEGF

The present study showed that the retreatment rate was higher following anti-VEGF treatment compared to control with OR 47.55 (95% CI: 12.35 to 183.09; Z = 5.61, p = <0.001; I^2 = 0%) (**Table 5**).

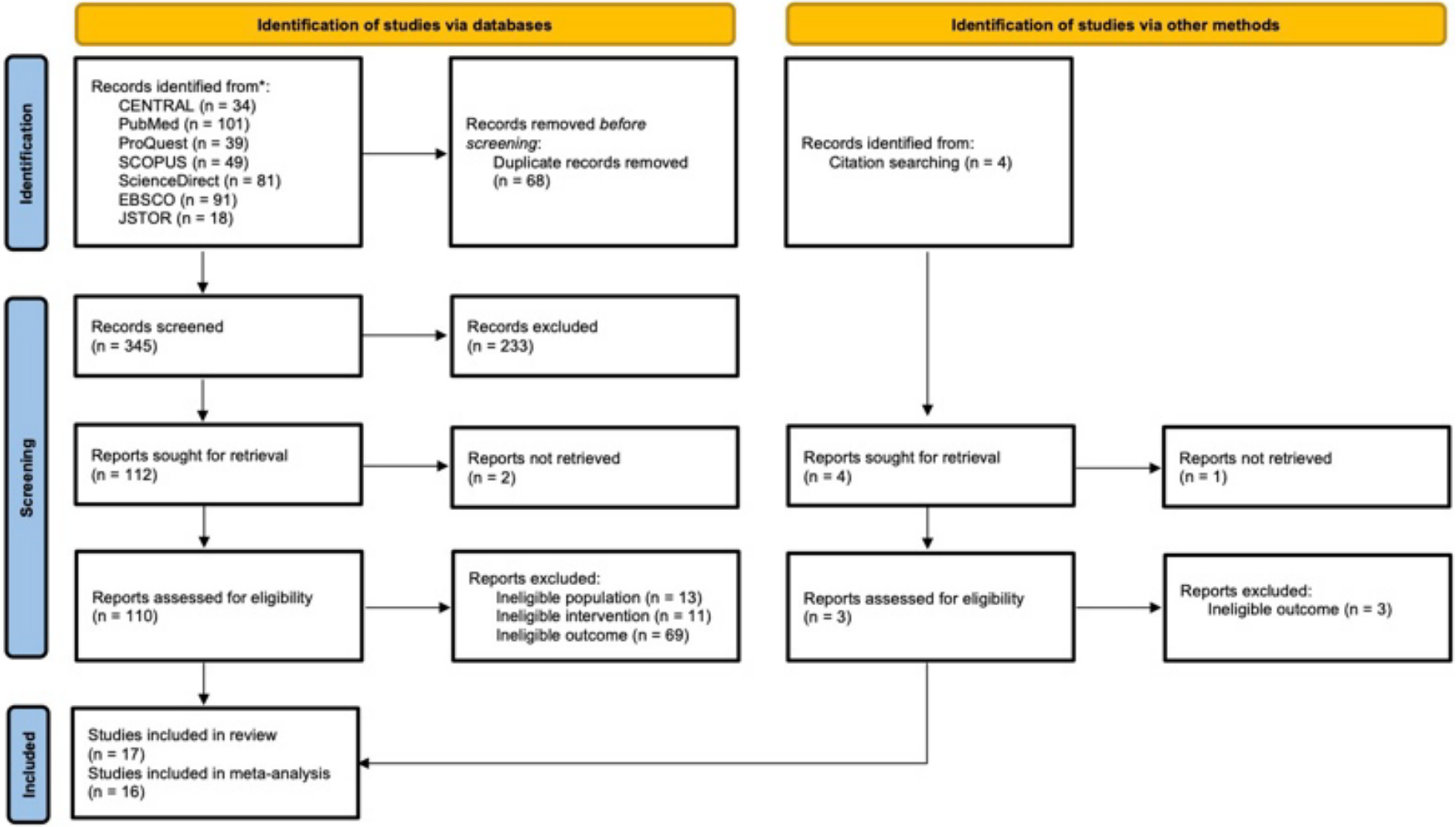


Figure 1. Study Flow Diagram

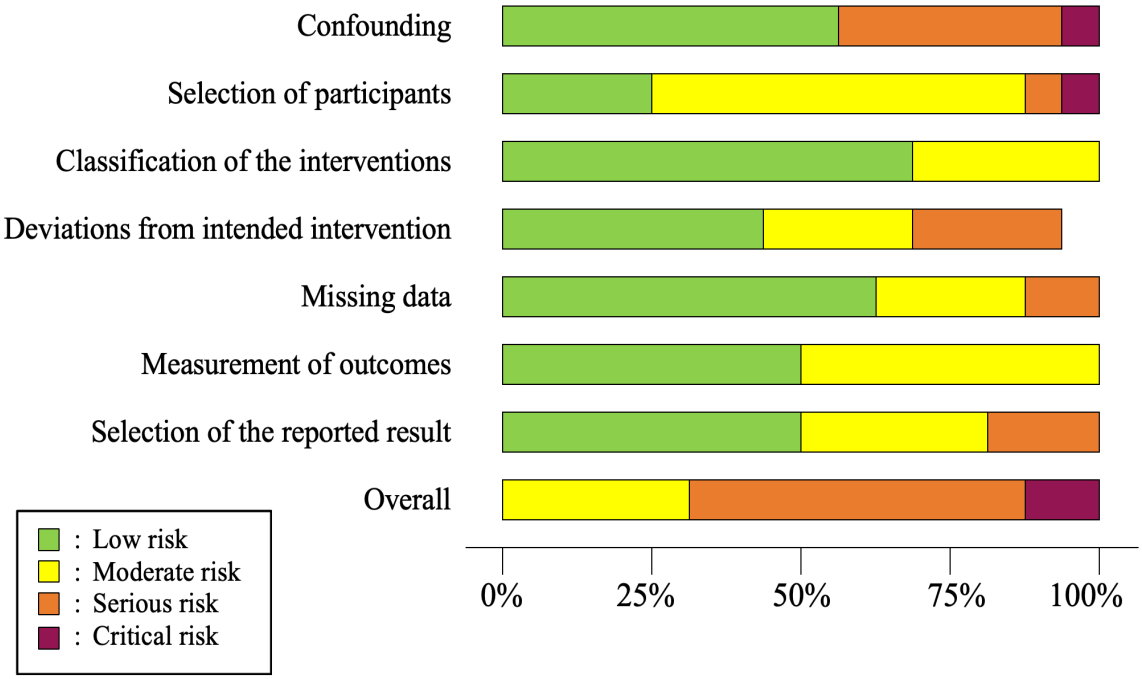


Figure 1. **Summary Plots of ROBINS-I**

Study or Subgroup	Anti-VEGF Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ahmed 2020	14	18	39	48	9.7%	0.81 [0.21, 3.04]
Celik 2021	10	22	19	32	14.3%	0.57 [0.19, 1.71]
Chang 2019	11	18	38	86	15.9%	1.98 [0.70, 5.61]
Morin 2016	21	27	55	98	17.4%	2.74 [1.02, 7.37]
Murakami 2021	3	12	3	14	5.1%	1.22 [0.20, 7.59]
Raghuram 2019	26	34	20	30	14.2%	1.63 [0.54, 4.87]
Rodriguez 2019	9	13	7	9	4.4%	0.64 [0.09, 4.58]
Zayek 2020	31	40	47	61	18.9%	1.03 [0.40, 2.66]
Total (95% CI)		**184**		**378**	**100.0%**	**1.28 [0.85, 1.94]**
Total events	125		228			

Heterogeneity: Tau² = 0.00; Chi² = 6.36, df = 7 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.17 (P = 0.24)

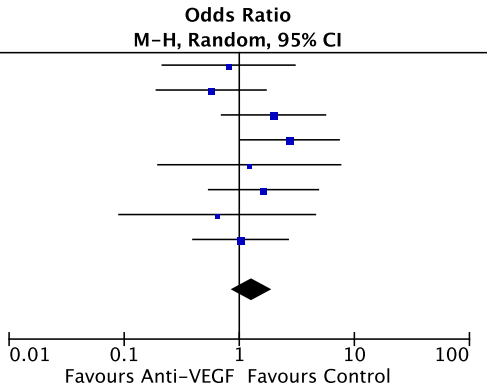


Figure 2**. Odds Ratio for Neurodevelopmental Impairment in ROP Infants Treated with Anti-VEGF Compared with Control**

Study or Subgroup	Anti-VEGF Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Celik 2021	6	22	10	32	8.1%	0.82 [0.25, 2.74]
Chang 2019	4	13	17	51	6.9%	0.89 [0.24, 3.31]
Fan 2019	11	38	2	31	4.9%	5.91 [1.20, 29.12]
Kong 2015	7	10	6	9	3.4%	1.17 [0.17, 8.09]
Morin 2016	14	27	28	98	13.6%	2.69 [1.12, 6.44]
Natarajan 2019	67	155	84	210	32.5%	1.14 [0.75, 1.74]
Raghuram 2019	19	34	11	30	10.9%	2.19 [0.80, 5.98]
Rodriguez 2019	6	13	5	9	4.3%	0.69 [0.12, 3.78]
Zayek 2020	18	40	30	61	15.4%	0.85 [0.38, 1.88]
Total (95% CI)		**352**		**531**	**100.0%**	**1.33 [0.92, 1.93]**
Total events	152		193			

Heterogeneity: Tau² = 0.06; Chi² = 10.07, df = 8 (P = 0.26); I² = 21%
Test for overall effect: Z = 1.53 (P = 0.13)

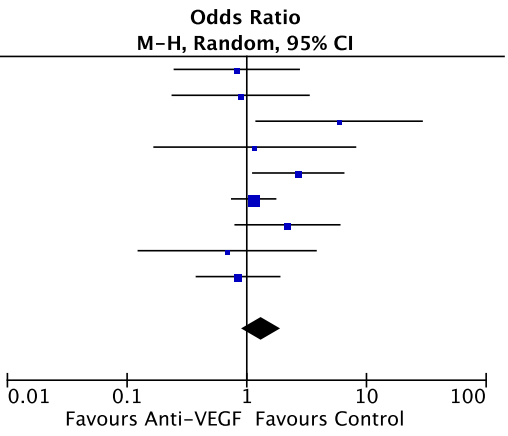


Figure 3. **Odds Ratio for Severe Neurodevelopmental Impairment in ROP Infants Treated with Anti-VEGF Compared with Control**

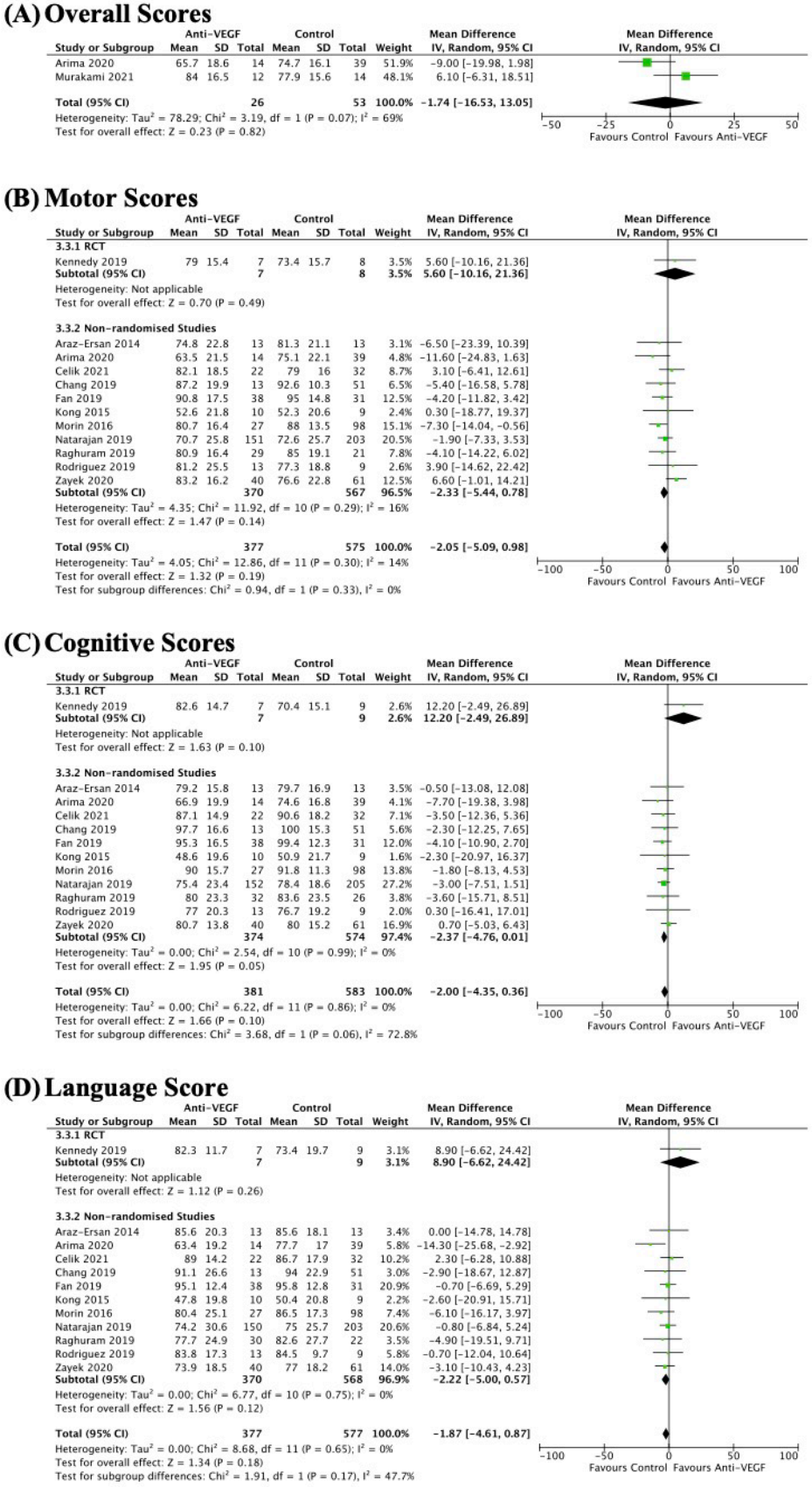
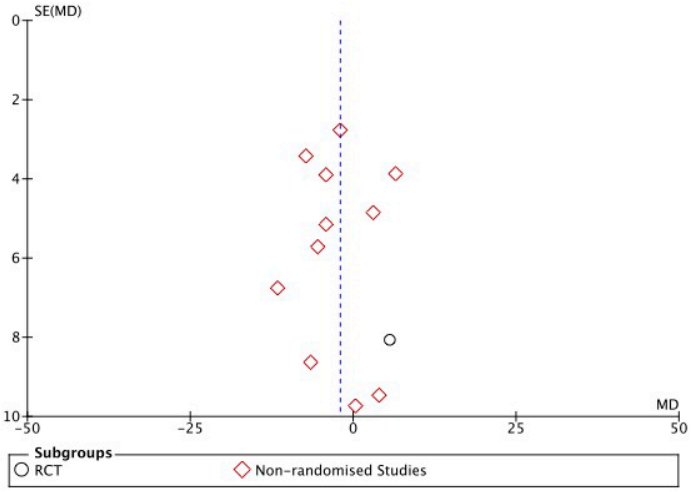
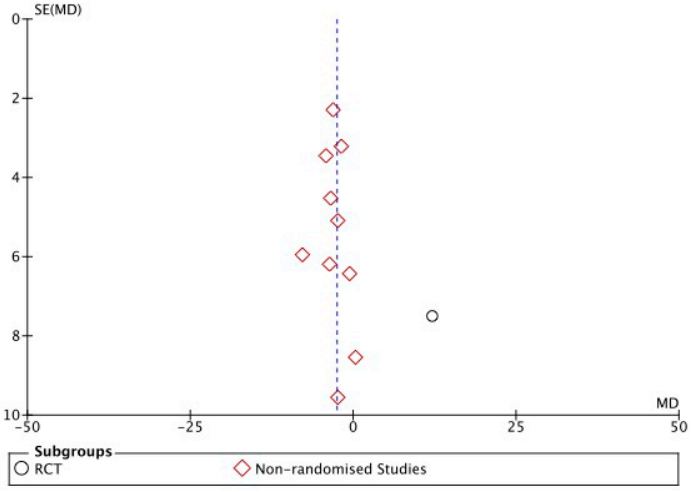


Figure 4**. Mean Differences of Neurodevelopmental Scores Between ROP Infants Treated with Anti-VEGF Compared with Control in Multiple Domains**

(A) Motor Scores



(B) Cognitive Scores



(C) Language Scores

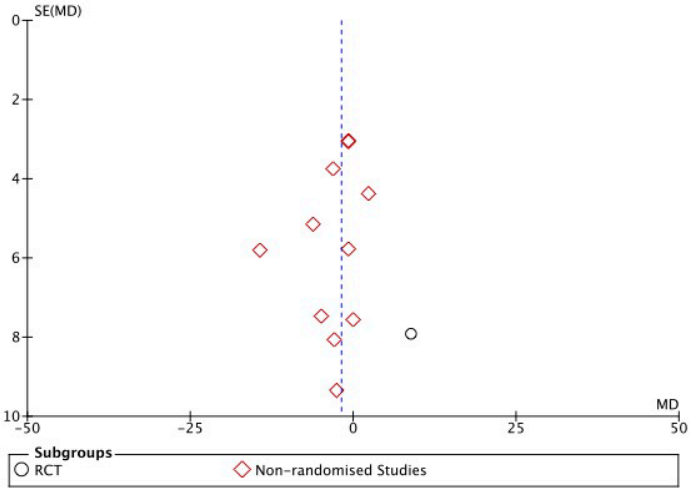


Figure 5**. Funnel Plot of Twelve Studies Reporting Mean Differences of Neurodevelopmental Scores in Multiple Domain**

Study or Subgroup	Anti-VEGF Events	Anti-VEGF Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
6.8.1 RCT						
Kennedy 2019	2	7	2	9	2.3%	1.40 [0.14, 13.57]
Subtotal (95% CI)		**7**		**9**	**2.3%**	**1.40 [0.14, 13.57]**
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
6.8.2 Non-randomised Studies						
Zayek 2020	14	40	22	61	17.0%	0.95 [0.41, 2.20]
Rodriguez 2019	6	41	9	35	8.9%	0.50 [0.16, 1.57]
Raghuram 2019	8	34	5	30	7.6%	1.54 [0.44, 5.34]
Natarajan 2019	46	154	45	209	51.8%	1.55 [0.96, 2.50]
Chang 2019	3	18	11	86	6.1%	1.36 [0.34, 5.48]
Celik 2021	6	12	9	32	6.3%	2.56 [0.65, 10.05]
Subtotal (95% CI)		**299**		**453**	**97.7%**	**1.32 [0.93, 1.86]**
Total events	83		101			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.77$, df = 5 (P = 0.45); $I^2 = 0\%$						
Test for overall effect: Z = 1.55 (P = 0.12)						
Total (95% CI)		**306**		**462**	**100.0%**	**1.32 [0.93, 1.86]**
Total events	85		103			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.77$, df = 6 (P = 0.57); $I^2 = 0\%$						
Test for overall effect: Z = 1.57 (P = 0.12)						
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.96), $I^2 = 0\%$						

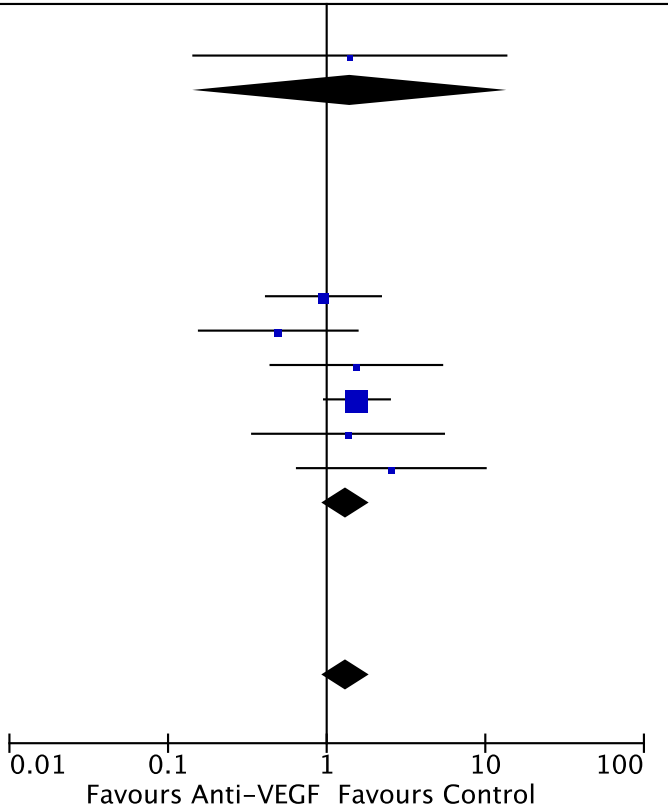


Figure 6**. Odds Ratio for Cerebral Palsy in ROP Infants Treated with Anti-VEGF Compared with Control**

Table 3. Summary of Study Characteristics of All Included Studies

Author(s)	Year	Country	Study Design	Study Population	Intervention Group			Control Group		Screening Tool(s)	Age at Evaluation (months)
					Sample (n)	Intervention(s)	Dose (mg)	Sample (n)	Control(s)		
Celik et al[22]	2021	Turkey	Cohort Retrospective	Preterm infants treated for ROP	22	IVB ± Laser	NA	32	Laser	BSID-III GMFCS	12 - 42
Murakami et al[29]	2021	Japan	Cohort Retrospective	Preterm infants treated for type 1 ROP	12	IVB	0.625	14	Laser	WISC IV/KSPD	60
Ahmed et al[26]	2020	USA	Cohort Retrospective	Preterm infants treated for type 1 ROP	18	IVB + Laser	NA	48	Laser	BSID-III	24
Arima et al[36]	2020	Japan	Cohort Retrospective	Preterm infants (GA < 32 weeks or BW < 1500 gr) treated for type 1 ROP	14	IVB	0.625	39	Laser	KSPD	18
Zayek et al[23]	2020	USA	Cohort Retrospective	Preterm infants (GA ≤ 26 weeks and BW < 1000 gr) treated for type 1 ROP or high-risk pre-threshold ROP	50	IVB	0.625	64	Laser	BSID-III GMFCS	18 - 24
Chang et al[24]	2019	Taiwan	Cohort Retrospective	Screened preterm infants with ROP	18	IVB	0.625	86	No treatment	BSID-II or BSID-III	24
Fan et al[7]	2019	Taiwan	Cohort Prospective	Screened preterm infants (GA <37 weeks) with ROP	38	IVB	0.625	31	No treatment	BSID-III	12 - 36
Kennedy et al[11]	2019	USA	RCT	Participants of BEAT-ROP trial in a single center (GA < 27 weeks)	7	IVB	0.625	9	Laser	BSID-III GMFCS	>18
Natarajan et al[20]	2019	USA	Cohort Retrospective	Extremely preterm infants (GA < 27 weeks) with severe ROP	181	IVB	NA	224	Laser and/or cryotherapy	BSID-III GMFCS	18 - 26
Raghuram et al[21]	2019	Canada	Cohort Retrospective	Preterm infants treated for ROP	34	IVB	0.625	30	Laser	BSID-III/ASQ GMFCS	18 - 24
Rodriguez et al[12]	2019	USA	Cohort Retrospective	Preterm infants (GA < 31 weeks and BW < 1500 gr) treated for ROP	13	IVB	NA	9	Laser	BSID-III GMA	24
Chen et al[37]	2018	USA	Cohort Retrospective	Preterm infants treated for TW-ROP	15	IVB	0.625	10	Laser	BSID-III Capute Scales	20.4
Kang et al[30]	2018	Korea	Cohort Retrospective	Preterm infants (GA < 32 weeks and BW < 1500 gr) treated for type 1 ROP	153	IVR	0.25	161	Laser	Denver	36.3 ± 31.9
Lien et al[14]	2016	Taiwan	Cohort Retrospective	ELBW infants (BW < 1000 gr) treated for type 1 ROP	28	IVB ± Laser	0.625	33	Laser	BSID-II	24
Morin et al[15]	2016	Canada	Cohort Retrospective	Preterm infants (GA < 29 weeks) treated for type 1 ROP	27	IVB	NA	98	Laser	BSID-III GMFCS	18
Kong et al[38]	2015	USA	Cohort Retrospective	Preterm infants treated for type 1 ROP or severe zone 3 ROP	10	IVB	0.625	9	Laser	RGDS Capute Scales	6 - 12
Araz-Ersan et al[25]	2014	Turkey	Cohort Retrospective	Type 1 ROP infants treated with IVB and matched controls	13	IVB + Laser	0.625	13	Laser	BSID-III	24

Abbreviations: ROP — retinopathy of prematurity, GA—gestational age (weeks), BW—birth weight (grams), BEAT-ROP — Bevacizumab Eliminates the Angiogenic Threat of ROP, ELBW—extremely low birth weight, IVB — Intravitreal bevacizumab, IVR — intravitreal ranibizumab, NA — not available, BSID — Bayley Scales of Infant Development, GMFCS — Gross Motor Functional Classification System, WISC — Wechsler Intelligence Scale for Children, KPSD — Kyoto Scale of Psychological Development, ASQ — Ages and Stages Questionnaires, GMA — General Movement Assessment

Table 4. Risk of Bias Summary for Each Included Study

Author(s)	Year	Confounding	Selection of Participants/ Randomization	Classification of Interventions	Deviations of Intended Intervention	Missing Data	Measurement of Outcomes	Selection of Reported Result	Overall
RCT[a]									
Kennedy et al[11]	2019		🟢		🟢	🟢	🟢	🟢	🟢
Non-randomised Studies[b]									
Celik et al[22]	2021	🟢	🟢	🟡	🟢	🟢	🟡	🟢	🟡
Murakami et al[29]	2021	🟠	🟡	🟢	🟠	🟢	🟢	🟢	🟠
Ahmed et al[26]	2020	🟢	🟡	🟡	🟢	🟢	🟢	🟢	🟡
Arima et al[36]	2020	🟠	🟢	🟢	?	🟡	🟡	🟡	🟠
Zayek et al[23]	2020	🟣	🟡	🟢	🟡	🟠	🟢	🟡	🟣
Chang et al[24]	2019	🟠	🟡	🟢	🟠	🟡	🟢	🟢	🟠
Fan et al[7]	2019	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟡
Natarajan et al[20]	2019	🟢	🟠	🟡	🟢	🟠	🟡	🟡	🟠
Raghuram et al[21]	2019	🟢	🟡	🟢	🟢	🟡	🟡	🟢	🟡
Rodriguez et al[12]	2019	🟠	🟡	🟡	🟡	🟢	🟡	🟢	🟠
Chen et al[37]	2018	🟢	🟣	🟢	🟠	🟢	🟡	🟠	🟣
Kang et al[30]	2018	🟠	🟡	🟢	🟠	🟢	🟡	🟢	🟠
Lien et al[14]	2016	🟢	🟡	🟢	🟢	🟡	🟢	🟠	🟠
Morin et al[15]	2016	🟢	🟢	🟡	🟡	🟢	🟢	🟢	🟡
Kong et al[38]	2015	🟠	🟡	🟢	🟡	🟢	🟡	🟡	🟠
Araz-Ersan et al[25]	2014	🟢	🟡	🟢	🟢	🟢	🟢	🟠	🟠

[a] : Risk of bias assessment using revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

[b] : Risk of bias assessment using Risk of Bias In Non-Randomized Studies - of Interventions (ROBINS-I)

🟢 : Low risk of bias

🟡 : Moderate risk of bias

🟠 : Serious risk of bias

🟣 : Critical risk of bias

? : Insufficient information provided to determine risk of bias

Table 5. Meta-analysis of Primary and Secondary Outcomes

Outcomes	Unadjusted Analysis	Adjusted Analysis
NDI	uOR 1.28; 95% CI: 0.85 to 1.94; Z = 1.17, p = 0.24; I^2 = 0% Eight studies; 562 participants	aOR 1.42; 95% CI: 0.87 to 2.33; Z = 1.39, p = 0.16; I^2 = 0% Five studies; 458 participants
sNDI	uOR 1.33; 95% CI: 0.92 to 1.93; Z = 1.53, p = 0.13; I^2 = 21% Nine studies; 883 participants	aOR 1.42; 95% CI: 0.79 to 2.57; Z = 1.17, p = 0.24; I^2 = 54% Six studies; 744 participants
Neurodevelopmental Scores		
Overall scores	MD -1.74; 95% CI: −16.53 to 13.05; Z = 0.23, p = 0.82; I^2 = 69% Two studies; 79 participants	NA
Motor scores	MD −2.05; 95% CI: −5.09 to 0.98; Z = 1.32, p = 0.19; I^2 = 14% Twelve studies; 952 participants	MD −1.91; 95% CI: −5.58 to 1.76; Z = 1.02, p = 0.31 I^2 = NA One study; 354 participants
Cognitive scores	MD −2.00; 95% CI: −4.35 to 0.36; Z = 1.66, p = 0.10; I^2 = 0% Twelve studies; 964 participants	MD −3.07; 95% CI: −6.46 to 0.33; Z = 1.77, p = 0.08; I^2 = NA One study; 357 participants
Language scores	MD −1.87; 95% CI: −4.61 to 0.87; Z = 1.34, p = 0.18; I^2 = 0% Twelve studies; 954 participants	MD −5.77; 95% CI: −17.82 to 6.29; Z = 0.94, p = 0.35; I^2 = 74% Two studies; 406 participants
Cerebral palsy	uOR 1.32; 95% CI: 0.93 to 1.86; Z = 1.57, p = 0.12; I^2 = 0% Eight studies; 868 participants	uOR 1.32; 95% CI: 0.72 to 2.43; Z = 0.90, p = 0.37; I^2 = 31% Three studies; 528 participants
Motor impairment	uOR 1.14; 95% CI: 0.67 to 1.94; Z = 0.48, p = 0.63; I^2 = 57% Six studies; 793 participants	aOR 1.31; 95% CI: 0.55 to 3.10; Z = 0.62, p = 0.54; I^2 = 77% Five studies; >635 participants
Severe motor impairment	uOR 1.06; 95% CI: 0.71 to 1.60; Z = 0.30, p = 0.76; I^2 = 0% Three studies; 434 participants	aOR 1.05; 95% CI: 0.65 to 1.70; Z = 0.20, p = 0.84; I^2 = NA One study; 354 participants
Cognitive impairment	**uOR 1.41; 95% CI: 1.03 to 1.92; Z = 2.14, p = 0.03; I^2 = 0% Six studies; 800 participants**	aOR 1.72; 95% CI: 0.95 to 3.08; Z = 1.81, p = 0.07; I^2 = 57% Six studies; >696 participants
Severe cognitive impairment	uOR 1.40; 95% CI: 0.91 to 2.16; Z = 1.54, p = 0.12; I^2 = 0% Three studies; 437 participants	aOR 1.53; 95% CI: 0.80 to 2.91; Z = 1.83, p = 0.07; I^2 = 0% Two studies; 437 participants
Language impairment	uOR 1.23; 95% CI: 0.72 to 2.13; Z = 0.76, p = 0.45; I^2 = 27% Five studies; 438 participants	aOR 1.72; 95% CI: 0.63 to 4.70; Z = 1.06, p = 0.29; I^2 = 61% Four studies; >280 participants
Severe language impairment	uOR 1.01; 95% CI: 0.66 to 1.52; Z = 0.03, p = 0.98; I^2 = 0% Three studies; 433 participants	aOR 1.03; 95% CI: 0.60 to 1.76; Z = 0.10, p = 0.92; I^2 = NA One study; 353 participants
Retreatment	**uOR 47.55; 95% CI: 12.35 to 183.09; Z = 5.61, p = <0.001; I^2 = 0% Two studies; 171 eyes**	NA

The details of the outcome definitions are provided in methods; the analyses highlighted in bold represent significant statistical differences between the groups.

Abbreviations: NDI — neurodevelopmental impairment, sNDI — severe neurodevelopmental impairment, uOR — unadjusted odds ratio, CI — confidence interval, aOR — adjusted odds ratio, MD — mean difference, NA — not available

DISCUSSION

Anti-VEGF have been used as an attractive therapeutic agent for ROP treatment. It has ability to block VEGF locally, thus inhibiting pathologic neovascularization and slowing the progression of the disease. Currently, available drugs for ROP treatment include bevacizumab, ranibizumab, aflibercept, pegaptanib, and conbercept.[39] In this review, bevacizumab is the most frequently used anti-VEGF for ROP treatment. It might be caused by its widespread availability, low cost, and effectivity.[8]

Unfortunately, systemic absorption and potential side effects of anti-VEGF agents raised some concerns. Increasing odds in cognitive impairment as shown in our study might support the hypothesis. Several studies have shown VEGF suppression following anti-VEGF administration in preterm infants. Kong et al[40] reported that serum bevacizumab was detected 2 days following IVB injection, peaked at 14 days, and persisted in the blood as long as 60 days with a half-life of 21 days. Wu et al[41] demonstrated that serum VEGF level was 379 pg/ml at baseline and decreased to 72 pg/mL 6 weeks following IVB treatment. Wu et al[42] also found that serum VEGF levels were less affected after intravitreal ranibizumab (IVR) treatment, compared with those who received IVB treatment. Huang et al[43] have sown further that VEGF levels in type 1 ROP infants were suppressed for 12 weeks after either IVB or intravitreal aflibercept (IVA) injection, but the suppression was more pronounced in IVB compared with IVA treatment.

VEGF plays an important role in neurogenesis in embryos and preterm newborns. Bagnard et al[44] found that VEGF can modulate migration, survival, and proliferation of neural progenitor cell line. Malik et al[45] showed that preterm delivery and room air exposure reduced VEGF expression in rabbit pups. However, significant neurogenesis continued in human preterm infants until 28 gestational weeks. This study might explain effects of VEGF deprivation in preterm infants on neurodevelopmental delay condition.

Blocking VEGF-A expression has been shown to impair brain vascularization. It may have long-term effects on the development of the central nervous system and other systems. Another possible reason for the inferior cognitive function reported by Morin et al[15] and Natarajan et al[20]might be the imbalance of baseline conditions between intervention and control group. Preterm infants treated with anti-VEGF in the study had severe systemic illnesses and more severe ROP statuses compared with control. More patients were also excluded from the control group in study by Morin et al[15] because of inability to undergo neurodevelopmental assessment and might have been associated with poorer outcomes. Neurologic outcome may be related with to the choice of intervention. Intravitreal anti-VEGF can be performed with lighter anesthesia than laser teraphy. Thus, in critical infants, anti-VEGF injection may be perceived as safer than ROP surgery, with the accompanying general anesthesia and intubation risks.

The variation in patient populations among included studies might lead to difference baseline. Seven studies[11,12,15,20,23,30,36] only included infants with small GA (SGA). Blencowe et al[46] reported that incidence of NDI increased from 5% among infants born at 32-36 weeks GA to 24.5% among those born at 28-31 weeks GA, and further to 52% among those born before 28 weeks. SGA infants were more likely to develop severe ROP. These extremely preterm infants were also at higher risk of developing aggressive posterior retinopathy of prematurity (AP-ROP), a severe and rare form of ROP which is more likely treated with anti-VEGF treatment. It is supported by Kang et al[30] where 100% preterm infants with AP-ROP were treated with IVR. In addition, 3 large neonatal networks

(the National Institute of Child Health and Development Neonatal Research Network,[47] the Vermont Oxford Network,[48] and the Canadian Neonatal Network)[49] showed that ELBW infants were at a higher risk for NDI. For ELBW infants, every 100-gram decrease in birth weight increased the risk of severe disability by 31%.[48] Therefore, GA and BW should be evaluated as potential confounders as we assess neurodevelopmental outcomes. Some included studies tried to adjust some confounders, however the adjustments were not consistent among those studies.

Clinical trial can be done in the future by stratifying the treatment based on the severity of ROP. According to Glass et al,[50] severe ROP is associated with abnormal white matter maturation and adverse neurodevelopmental outcome. Supplemental use of high concentration oxygen for a prolonged duration may play a more significant role in older and heavier babies.[51] Murakami et al[29] stated that protracted mechanical ventilation increased risk of neurodevelopmental disability. However, Altendahl et al[52] stated that poorer neurodevelopmental outcomes in preterm infants are not related with severity of ROP. Chang et al[24] and Fan et al[7] minimized the selection bias by choosing any ROP except type 1 ROP as controls, instead of laser therapy. They reported no difference in neurodevelopmental outcomes between ROP infants with and without treatment.

Anti-VEGF administration in this present study was showing a higher retreatment rate compared to control group. Meta-analysis performed by Li et al[53] also stated that retreatment incidence was significantly increased for anti-VEGF compared to the laser treatment with OR 2.52 (95% CI 1.37 to 4.66; $P = 0.003$). Changes of VEGF level might explain this phenomenon. Reduction of VEGF level in vitreous is noted following anti-VEGF administration. When the level of anti-VEGF in the vitreous reduced gradually and eventually was not in effective concentration anymore, increased levels of VEGF caused development of neovascularization and ROP progression. Xiang et al[54] demonstrated a compensatory mechanism. Other vascular growth factors of ROP including basic fibroblast growth factor (bFGF) and angiopoietin 1 (ANG1) were upregulated when VEGF was expressed at a low level.

Kang et al[30] stated that greater proportion of zone 1 ROP cases in ranibizumab-treated-group required more time to achieve full vascularisation after initial treatment. During an extended period of vascular growth, an elevation in VEGF levels may cause ROP reactivation requiring additional ranibizumab injections. Also concluded in the American Academy of Ophthalmology report,[6] eyes treated with anti-VEGF, mostly with ROP in zone I, may never completely vascularize and still need retreatment after 55 weeks of postmenstrual age. Meanwhile, retreatment or recurrences in laser therapy is caused by inadequate treatment. Decrease of retreatment rate over the years indicates a better quality of therapy by the clinician.

The weakness of our review was that the data mainly from nonrandomized studies. The choice of intervention in each participants was mostly based on clinician's preference. In some studies,[14,21,23,38] the chosen treatment was made by the agreement of the ophthalmologist and the parents after the off-label status, benefits, and risk of using anti-VEGF had been thoroughly explained. Chen et al[37] stated that they typically chose anti-VEGF over laser therapy in sicker infants. This selection bias might affect the result of neurodevelopmental outcomes.

Second, some studies did not report their dosage usage. Remaining studies with intravitreal bevacizumab used a dosage of 6.25 mg, half of the adult dosage, as recommended by the BEAT-ROP study. Kong et al[40] reported that systemic exposure of VEGF was variable among the participants and was dose dependent.

According to the calculation based on the volume of neonates' vitreous, the size-adjusted dosage of should be 0.4 mg.[55] Wallace et al[56] demonstrated that dose of bevacizumab as low as 0.031 mg was effective for premature infants with type 1 ROP and might reduce the risk for neurodevelopmental disability or detrimental effects on other organs. However, after after low-dose bevacizumab injection, many eyes received additional treatment. The effect of anti-VEGF on NDI might differ if using a lower dosage. In the other side, Raghuram et al[21] stated that systemic absorption of bevacizumab is too low to exert any significant clinical effects. We recommend a trial with varying concentrations of anti-VEGF to provide more evidence regarding dose-dependent effect of anti-VEGF on NDI.

Other limitation included the differences in definitions of each outcomes among the analyzed studies. This difference is caused by different ways of measuring the outcomes. Most included studies used BSID-III for outcome evaluations. BSID-III is considered to be the gold standard for the early detection of developmental delays in children.[25] It separates of the original mental development index (MDI) and psychomotor development index (PDI) from BSID-II into distinct cognitive, receptive language, expressive language, fine motor, and gross motor scales. These scales were converted further into 3 composite scores including cognitive, language, and motor composite scores.[7] There are a conversion formula to conver BSID-II scores to BSID-III scores to make it comparable. In addition, Bayley-III cognitive and language scores <85 had 99% agreement with MDI <70.[57] However, the results of the KSPD and BSID-II were comparable with only moderate correlation (r = 0.61-0.63).[58,59]

CONCLUSION

Nevertheless, the review is important as it summarizes the current and updated literature with some limitations. The search was broad across 7 databases and contained additional search methods. Anticipating the heterogeneity, we used the random-effects model, an appropriate method in the presence of heterogeneity. The results of the current meta-analysis which analyzed more than 700 infants, concluded that there was no difference in neurodevelopmental outcomes between anti-VEGF and control group. Increased odds of retreatment rate in preterm infants treated with anti-VEGF was also noted. We suggest that until high-quality evidence has been established, clinicians should carefully weigh the benefits and risks of anti-VEGF injection for treating infants with ROP.

REFERENCES

1. Hered RW, Lee KA, Archer SM, Lueder GT, Braverman RS, O'Hara MA, et al. Disorders of the Retina and Vitreous. In: Rapuano CJ, Stout JT, McCannel CA, editors. 2020-2021 Basic and Clinical Science Course: Pediatric Ophthalmology and Strabismus. San Fransisco: American Academy of Ophthalmology; 2020. p. 325–35.
2. Kaushal M, Razak A, Patel W, Pullattayil AK, Kaushal A. Neurodevelopmental outcomes following bevacizumab treatment for retinopathy of prematurity: a systematic review and meta-analysis. J Perinatol. 2021;41(6):1225–35.
3. Subramanian KS, Kern MD, Deegan WF. Retinopathy of Prematurity [Internet]. Medscape. 2021 [cited 2021 Dec 23]. Available from: https://emedicine.medscape.com/article/976220-overview#a4
4. Nicoară S. Indirect Diode Laser in the Treatment of Retinopathy of Prematurity. In: Ma Y, editor. Laser Technology and its Applications. Cluj-Napoca: IntechOpen; 2018. p. 107–22.

5. Quinn GE, Fielder AR. Retinopathy of prematurity. In: Lambert SR, Lyons CJ, editors. Taylor & Hoyt's Pediatric Ophthalmology and Strabismus. 5th ed. Edinburgh: Elsevier; 2017. p. 443–55.
6. VanderVeen DK, Melia M, Yang MB, Hutchinson AK, Wilson LB, Lambert SR. Anti-Vascular Endothelial Growth Factor Therapy for Primary Treatment of Type 1 Retinopathy of Prematurity: A Report by the American Academy of Ophthalmology. Ophthalmology. 2017;124(5):619–33.
7. Fan YY, Huang YS, Huang CY, Hsu JF, Shih CP, Hwang YS, et al. Neurodevelopmental Outcomes after Intravitreal Bevacizumab Therapy for Retinopathy of Prematurity: A Prospective Case-Control Study. Ophthalmology. 2019;126(11):1567–77.
8. Enríquez AB, Avery RL, Baumal CR. Update on anti-vascular endothelial growth factor safety for retinopathy of prematurity. Asia-Pacific J Ophthalmol. 2020;9(4):358–68.
9. Mutlu FM, Sarici SU. Treatment of retinopathy of prematurity: a review of conventional and promising new therapeutic options. Int J Ophthalmol. 2013;6(2):228.
10. Hartnett ME. VEGF Antagonit Therapy for ROP. Clin Perinatol. 2014;41(4):925.
11. Kennedy KA, Mintz-Hittner HA. Medical and Developmental Outcomes of Bevacizumab versus Laser for Retinopathy of Prematurity. J Am Assoc Pediatr Ophthalmol Strabismus. 2018;22(1):1971–2.
12. Rodriguez SH, Peyton C, Lewis K, Andrews B, Greenwald MJ, Schreiber MD, et al. Neurodevelopmental outcomes comparing bevacizumab to laser for type 1 ROP. Ophthalmic Surg Lasers Imaging Retin. 2019;50(6):337–43.
13. Tran KD, Cernichiaro-Espinosa LA, Berrocal AM. Management of retinopathy of prematurity-use of anti-VEGF therapy. Asia-Pacific J Ophthalmol. 2018;7(1):56–62.
14. Lien R, Yu MH, Hsu KH, Liao PJ, Chen YP, Lai CC, et al. Neurodevelopmental outcomes in infants with retinopathy of prematurity and bevacizumab treatment. PLoS One. 2016;11(1):1–12.
15. Morin J, Luu TM, Superstein R, Ospina LH, Lefebvre F, Simard MN, et al. Neurodevelopmental outcomes following bevacizumab injections for retinopathy of prematurity. Pediatrics. 2016;137(4):e20153128.
16. Howick J, Chalmers I, Greenhalgh T, Carl H, Liberati A, Moschetti I, et al. OCEBM Levels of Evidence [Internet]. Oxford Centre for Evidence-Based Medicine. 2011 [cited 2022 Jan 12]. Available from: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence
17. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:14898.
18. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355.
19. Jackson J, Castleberry C, Galli M, Arnoldi KA. Cerebral Palsy for the Pediatric Eye Care Team Part II: Diagnosis and Treatment of Ocular Motor Deficits. Am Orthopt J. 2006;56(1):86–96.
20. Natarajan G, Shankaran S, Nolen TL, Sridhar A, Kennedy KA, Hintz SR, et al. Neurodevelopmental Outcomes of Preterm Infants With Retinopathy of Prematurity by Treatment. Pediatrics. 2019;144(2):e20183537.

21. Raghuram K, Isaac M, Yang J, AlAli A, Mireskandari K, Ly LG, et al. Neurodevelopmental outcomes in infants treated with intravitreal bevacizumab versus laser. J Perinatol. 2019;39(9):1300–8.
22. Celik P, Ayranci Sucakli I, Kara C, Petricli IS, Kavurt S, Celik IH, et al. Bevacizumab and neurodevelopmental outcomes of preterm infants with retinopathy of prematurity: should we still worry? J Matern Neonatal Med. 2021;1–8.
23. 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. 2020;38(11):1158–66.
24. Chang YS, Chen YT, Lai TT, Chou HC, Chen CY, Hsieh WS, et al. Involution of retinopathy of prematurity and neurodevelopmental outcomes after intravitreal bevacizumab treatment. PLoS One. 2019;14(10):1–12.
25. Araz-Ersan B, Kir N, Tuncer S, Aydinoglu-Candan O, Yildiz-Inec D, Akdogan B, et al. Preliminary anatomical and neurodevelopmental outcomes of intravitreal bevacizumab as adjunctive treatment for retinopathy of prematurity. Curr Eye Res. 2015;40(6):585–91.
26. 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 Retin. 2020;51(4):220–4.
27. Kawabe K, Kondo S, Matsumoto M, Seo K, Ochi M, Oka Y, et al. Developmental quotient to estimate intelligence in autism spectrum disorder. Pediatr Int. 2016;58(10):963–6.
28. Wangke L, Victory W, Rampengan NH, Lestari H. External risk factors associated with language disorders in children. Paediatr Indones. 2021;61(3):133–40.
29. Murakami T, Sugiura Y, Okamoto F, Okamoto Y, Kato A, Hoshi S, et al. Comparison of 5-year safety and efficacy of laser photocoagulation and intravitreal bevacizumab injection in retinopathy of prematurity. Graefe's Arch Clin Exp Ophthalmol. 2021;259(9):2849–55.
30. Kang HG, Choi EY, Byeon SH, Kim SS, Koh HJ, Lee SC, et al. Intravitreal ranibizumab versus laser photocoagulation for retinopathy of prematurity: Efficacy, anatomical outcomes and safety. Br J Ophthalmol. 2018;0:1–5.
31. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018;27(6):1785–805.
32. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5(1):1–10.
33. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014 141. 2014;14(1):1–13.
34. JPT H, J T, J C, M C, T L, MJ P, et al. Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. JPT H, J T, J C, M C, T L, MJ P, et al., editors. Chichester: John Wiley & Sons; 2019.
35. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n71.
36. Arima M, Akiyama M, Fujiwara K, Mori Y, Inoue H, Seki E, et al. Neurodevelopmental outcomes following intravitreal bevacizumab injection in Japanese preterm infants with type 1 retinopathy of prematurity. PLoS One. 2020;15(3):1–7.

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 Retin. 2018;49(2):126–31.
38. Kong L, Dinh K, Schechet S, Coats D, Voigt R, Demny A, et al. Comparison of Ocular and Developmental Outcomes in Laser-and Bevacizumab-treated Infants with Retinopathy of Prematurity. Ophthalmol Res An Int J. 2015;3(1):13–22.
39. Eldweik L, Mantagos IS. Role of VEGF inhibition in the treatment of retinopathy of prematurity. Semin Ophthalmol. 2016;31(1–2):163–8.
40. Kong L, Bhatt AR, Demny AB, Coats DK, Li A, Rahman EZ, et al. Pharmacokinetics of bevacizumab and its effects on serum VEGF and IGF-1 in infants with retinopathy of prematurity. Invest Ophthalmol Vis Sci. 2015;56(2):956–61.
41. Wu WC, Lien R, Liao PJ, Wang NK, Chen YP, Chao AN, et al. Serum levels of vascular endothelial growth factor and related factors after intravitreous bevacizumab injection for retinopathy of prematurity. JAMA Ophthalmol. 2015 Apr 1;133(4):391–7.
42. Wu WC, Shih CP, Lien R, Wang NK, Chen YP, Chao AN, et al. Serum Vacular Endothelial Growth Factor after Bevacizumab or Ranibizumab Treatment for Retinopathy of Prematurity. Retina. 2017;37(4):694–701.
43. Huang CY, Lien R, Wang NK, Chao AN, Chen KJ, Chen TL, et al. Changes in systemic vascular endothelial growth factor levels after intravitreal injection of aflibercept in infants with retinopathy of prematurity. Graefes Arch Clin Exp Ophthalmol. 2018;256(3):479–87.
44. Bagnard D, Vaillant C, Khuth ST, Dufay N, Lohrum M, Püschel AW, et al. Semaphorin 3A-vascular endothelial growth factor-165 balance mediates migration and apoptosis of neural progenitor cells by the recruitment of shared receptor. J Neurosci. 2001;21(10):3332–41.
45. Malik S, Vinukonda G, Vose LR, Diamond D, Bhimavarapu BBR, Hu F, et al. Neurogenesis continues in the third trimester of pregnancy and is suppressed by premature birth. J Neurosci. 2013;33(2):411–23.
46. 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(Suppl 1):49.
47. Kono Y. Neurodevelopmental outcomes of very low birth weight infants in the Neonatal Research Network of Japan: importance of neonatal intensive care unit graduate follow-up. Clin Exp Pediatr. 2021;64(7):313–21.
48. Mercier CE, Dunn MS, Ferrelli KR, Howard DB, Soll RF. Neurodevelopmental Outcome of Extremely Low Birth Weight Infants from the Vermont Oxford Network: 1998–2003. Neonatology. 2010;97(4):329.
49. Vohr BR, Wright LL, Dusick AM, Mele L, Verter J, Steichen JJ, et al. Neurodevelopmental and Functional Outcomes of Extremely Low Birth Weight Infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993–1994. Pediatrics. 2000;105(6):1216–26.
50. Glass TJA, Chau V, Gardiner J, Foong J, Vinall J, Zwicker JG, et al. Severe retinopathy of prematurity predicts delayed white matter maturation and poorer neurodevelopment. Arch Dis Child Fetal Neonatal Ed. 2017 Nov 1;102(6):F532–7.
51. Kumawat D, Sachan A, Shah P, Chawla R, Chandra P. Aggressive posterior retinopathy of prematurity: a review on current understanding. Eye (Lond). 2021 Apr 1;35(4):1140–58.

52. Altendahl M, Sim MS, Kokhanov A, Gundlach B, Tsui I, Chu A. Severe Retinopathy of Prematurity Is Not Independently Associated With Worse Neurodevelopmental Outcomes in Preterm Neonates. Front Pediatr. 2021 Jun 10;9.
53. Li Z, Zhang Y, Liao Y, Zeng R, Zeng P, Lan Y. Comparison of efficacy between anti-vascular endothelial growth factor (VEGF) and laser treatment in Type-1 and threshold retinopathy of prematurity (ROP). BMC Ophthalmol. 2018;18(1):1–10.
54. Xiang N, Zhao MJ, Li XY, Zheng HH, Li GG, Li B. Redundant Mechanisms for Vascular Growth Factors in Retinopathy of Prematurity in vitro. Ophthalmic Res. 2011 Jan;45(2):92–101.
55. Spandau U. What is the optimal dosage for intravitreal bevacizumab for retinopathy of prematurity? Acta Ophthalmol. 2013;
56. Wallace DK, Kraker RT, Freedman SF, Crouch ER, Hutchinson AK, Bhatt AR, et al. Assessment of Lower Doses of Intravitreous Bevacizumab for Retinopathy of Prematurity: A Phase 1 Dosing Study. JAMA Ophthalmol. 2017 Jun 1;135(6):654–6.
57. Johnson S, Moore T, Marlow N. Using the Bayley-II to assess neurodevelopmental delay: which cut-off should be used? Pediatr Res. 2014;75(5):670–4.
58. Tatsuta N, Suzuki K, Sugawara T, Nakai K, Hosokawa T, Satoh H. Comparison of Kyoto Scale of Psychological Development and Bayley Scales of Infant Development second edition among Japanese Infants. J Spec Educ Res. 2013;2(1):17–24.
59. Janzen D, Delaney KA, Shapiro EG. Cognitive and adaptive measurement endpoints for clinical trials in mucopolysaccharidoses types I, II, and III: A review of the literature. Mol Genet Metab. 2017;121(2):57–69.