

Spontaneous regression of idiopathic choroidal neovascularization in a child with 3-year follow-up and a meta-analysis of anti-VEGF therapy for pediatric choroidal neovascularization of different etiologies

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Case Report

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Abstract

Background

Pediatric choroidal neovascularization (CNV) is rare, and its natural history remains poorly understood. Both adults and children with CNV treated with anti-vascular endothelial growth factor (VEGF) therapy, a well-established CNV treatment, have a good prognosis. However, there is inadequate evidence to confirm its treatment safety and efficacy, and different CNV etiologies may also have different outcomes.

Methods

We report a 12-year-old child with idiopathic CNV who was followed for 3 years with serial multimodal imaging, including optical coherence tomography angiography and fundus fluorescein angiography. Additionally, we performed a systematic review and meta-analysis of anti-VEGF therapy in pediatric CNV (PROSPERO: CRD 420261368733). PubMed, Embase, Web of Science, CNKI, and WanFang Data were searched from their inception to May 2026. Studies that included children (< 18 years) with CNV treated with anti-VEGF were selected. The primary outcome was a change in the best-corrected visual acuity (BCVA). Secondary outcomes included the number of injections, central macular thickness change, anatomical response, and adverse events. Random-effects models were used.

Results

The case showed complete spontaneous CNV regression over 3 years, with vision improving from 0.5 to 0.8 (logMAR 0.3 to 0.1). Bilateral short band-like hypofluorescence on FFA indicated inactive CNV with retinal pigment epithelium hyperplasia. The meta-analysis included 20 studies (1477 eyes). Anti-VEGF therapy significantly improved the BCVA (mean difference -0.28 logMAR; 95% CI -0.35 to -0.22 ; $I^2 = 53.5\%$; moderate certainty). The mean number of injections was 2.50 (95% CI 2.16–2.84; high heterogeneity). The anatomical response rate was 95% (95% CI 84%–99%; moderate certainty). Adverse events were rare. A subgroup analysis showed no significant difference based on etiology ($p = 0.84$).

Conclusion

Idiopathic pediatric CNV can spontaneously regress over long-term follow-up. Anti-VEGF therapy is effective and safe for active pediatric CNV. Observation may be a reasonable alternative for carefully selected low-activity, extrafoveal idiopathic cases.

1. Introduction

Choroidal neovascularization (CNV) is an uncommon pediatric fundus disease that poses a severe vision threat. Unlike in adults, the main causes of neovascularization in children include inflammation, Best disease, trauma, and certain congenital diseases such as macular or choroidal dystrophy and optic nerve head drusen. Pediatric CNV therapy is based on adult treatment options. Anti-vascular endothelial growth factor (anti-VEGF) therapy is the main treatment for neovascularization. Most studies on pediatric CNV are small-sample case series that lack high-quality evidence to confirm the effects and safety of anti-VEGF therapy. We wondered whether different CNV etiologies have different outcomes and whether the number of injections may produce different results. In this study, we first report a unique case of a child with spontaneous regression of CNV with a 3-year follow-up. His fundus fluorescein angiography (FFA) results showed new-onset hyperfluorescence in the right eye at the final follow-up visit, whereas the left eye showed resolution of the initial hyperfluorescence over the observation period. We then analyzed the effect and safety of anti-VEGF therapy in pediatric neovascularization and explored the possible mechanism of the spontaneous regression of neovascularization.

2. Methods

2.1 Study design and registration

This study consisted of two components. We first reported a case of a 12-year-old boy with spontaneous regression of CNV over 3 years of follow-up. We then systematically reviewed the CNV literature and performed a meta-analysis to evaluate the effects of anti-VEGF therapy in pediatric CNV. The case report follows the CARE guidelines. The systematic review and meta-analysis are reported according to the PRISMA 2020 statement and have been registered in PROSPERO (CRD 420261368733). Any amendments to the protocol will be documented in the final report.

2.2 Systematic review and meta-analysis methods

2.2.1 Eligibility criteria (PICOS)

Studies included in our study met the following criteria:

Population: Children and adolescents (< 18 years) with a definite diagnosis of macular or subfoveal CNV, confirmed by optical coherence tomography angiography (OCTA) and FFA. All etiologies (inflammatory, idiopathic, Best disease, myopia, trauma) were eligible.

Intervention: Intravitreal injection of anti-VEGF agents (bevacizumab, ranibizumab, aflibercept, conbercept, pegaptanib, brolucizumab) with any regimen were considered.

Comparator: Non-anti-VEGF treatments (observation, photodynamic therapy, laser photocoagulation, surgery) were considered. However, this meta-analysis was a single-arm-based analysis (proportion/mean) due to the scarcity of controlled studies.

Outcomes: Outcomes included the best corrected visual acuity (BCVA) and the changes in it based on the last follow-up, number of injections, change in central macular thickness (CMT, μm), proportion of eyes with CNV regression or stable fibrosis, proportion with visual acuity (VA) improvement (≥ 0.2 logMAR or equivalent), and adverse events. Visual acuity was quantified using the logMAR scale, where logMAR represents the logarithm of the minimum angle of resolution.

Study design: Randomized controlled trials, non-randomized controlled trials, cohort studies, and case series (≥ 3 cases) were included. Case reports (< 3 cases), reviews, meta-analyses, editorials, conference abstracts, and animal studies were excluded.

2.2.2 Search strategy and selection

We systematically searched the following databases from inception to May 2026: PubMed, Embase (Ovid platform), Web of Science, China National Knowledge Infrastructure (CNKI), and WanFang Data. The search strategy combined MeSH and Emtree terms and free-text words corresponding to the following: (1) pediatric population, (2) CNV, and (3) anti-VEGF therapy. No language restrictions were applied. Additionally, we manually screened the reference lists of the studies included in the analysis and of relevant reviews. ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform were searched for ongoing or unpublished trials. The full search strategies for all databases are provided in Appendix S1. After removing duplicates, two reviewers (Xinyi Zuo and Yuhang Yu) independently screened the titles and abstracts against the eligibility criteria. The full texts of the potentially eligible studies were retrieved and assessed independently by the same two reviewers. Disagreements were resolved by discussion or by consulting a third reviewer (Lin Xie). Data were extracted independently by the same two reviewers using a predefined form that captured study characteristics (author, year, design, sample size, age, etiology), intervention details (anti-VEGF agent, number of injections), outcomes (BCVA change, CMT change, VA improvement, anatomical response rate, adverse events), and follow-up duration. The methodological quality of the included studies was assessed using the JBI checklist for case series and the Newcastle–Ottawa Scale (NOS) for cohort studies.

2.4 Statistical analysis

Random-effects models were used for all the meta-analyses. Continuous outcomes were pooled as mean differences (MD), and proportions were pooled after Freeman–Tukey transformations. Heterogeneity was quantified by I^2 . Subgroup analyses were performed based on etiology. Sensitivity analyses excluded the largest study (Finn et al.). Publication bias was assessed by a funnel plot and Egger's test for the primary outcome (BCVA change). We assessed the certainty of evidence using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach.

3. Case presentation

A 12-year-old boy presented in January 2022 with complaints of blurred vision, metamorphopsia, and a central scotoma in his left eye. His initial BCVA was 20/40. The patient had a history of myopia (refractive error: -5.0 D in both eyes) and wore glasses for distance correction. A fundus examination did not show any myopic degenerative changes, including posterior staphyloma, lacquer cracks, diffuse chorioretinal atrophy, or Fuchs spot, but revealed a subretinal hemorrhage and myopic changes nasal to the fovea. OCTA identified a hemorrhagic focus with a high flow signal at the level of the retinal pigment epithelium (RPE), consistent with a CNV network accompanied by subretinal fluid (SRF). FFA demonstrated an early focal hyperfluorescence nasal to the fovea that was partially obscured by the surrounding hemorrhage and progressed to prominent leakage in the late phase. Additionally, localized hyperfluorescent leakage was noted in the peripheral retina. Anti-VEGF therapy was initially planned; however, due to logistical challenges during the COVID-19 pandemic, treatment was deferred, and the patient was instead closely monitored. Ten days later, the patient reported improved vision but persistent metamorphopsia, with his BCVA rapidly improving to 20/20. A repeat OCTA revealed partial resolution of the SRF and hemorrhage, although a hyperreflective mass with persistent flow signals remained. FFA continued to show a hyperfluorescent focus. Given that the patient was showing spontaneous clinical improvement, continued observation was maintained. Over the following three months, the neovascular lesion persisted but remained stable.

In May 2022, FFA revealed an early hyperfluorescent spot without late leakage, indicating spontaneous CNV regression. OCT showed focal subretinal hyperreflective material beneath the neurosensory retina. Over subsequent months, OCTA confirmed a residual atrophic scar with no exudation or active flow signals. The BCVA remained stable at 20/20. At the final follow-up in August 2025, FFA confirmed a non-leaking hyperfluorescent spot, and OCTA showed a significant reduction in the size of the choroidal lesion with absent flow signals. Notably, FFA of the asymptomatic contralateral right eye revealed a new, non-leaking hyperfluorescent spot nasal to the fovea that had not been previously detected (Fig. 1).

4. Results of the systematic review and meta-analysis

4.1 Study selection

We obtained 3360 records from the five databases. After removing duplicates ($n = 1333$), 2027 records were screened by title and abstract. Full-text articles ($n = 220$) were assessed for eligibility, with articles excluded for the following reasons: wrong population ($n = 93$), inadequate study design ($n = 40$), wrong publication type ($n = 34$), excluded outcome (i.e., the outcome did not include BCVA; $n = 20$), excluded intervention ($n = 14$), and wrong study duration ($n = 1$). Finally, 20 studies met the inclusion criteria and were therefore included in the systematic review. The PRISMA flow diagram is shown in Fig. 2.

4.2 Characteristics of the included studies

The main characteristics of the included studies are summarized in Table 1. A total of 20 studies comprising 1477 eyes were included in the meta-analysis. The 20 studies included retrospective case series ($n = 15$), a prospective observational study ($n = 1$), and registry-based cohort studies ($n = 2$). The mean age of the participants ranged from 5.1 to 15 years. The CNV etiologies included idiopathic (10 studies), inflammatory (7 studies), myopic (3 studies), Best disease (6 studies), neoplastic (5 studies), and traumatic (3 studies). Follow-up durations ranged from 3.5 to 56 months.

Table 1
The Main Characteristics of the patients Included in Studies

Study	Country	Study design	Sample size (eyes)	Age (years, mean $\pm$ SD)	Main etiology (%) [*]	Anti-VEGF agent	Mean number of injections (SD)	Follow-up (months, mean $\pm$ SD)	Outcome measures
Zhang T, 2021 ¹	China	Case series	33	11.2 $\pm$ 4.6	Inflammatory (30%), idiopathic (30%)	Ranibizumab, aflibercept, conbercept	1.4 (0.6)	29.0 $\pm$ 15.6	BCVA
Zhang LY, 2025 ²	China	Case series	15	5.1 $\pm$ 2.56	Congenital (100%)	Ranibizumab, aflibercept, conbercept	2.33 (0.62)	17.93 $\pm$ 9.58	BCVA
Yan S, 2025 ³	China	Case series	80	12.1 $\pm$ 3.5	Inflammatory (31.94%), idiopathic (37.5%), traumatic (8.33%)	Ranibizumab, conbercept	2.12 (0.8)	14.65 $\pm$ 8.55	BCVA
Rishi P, 2022 ⁴	India	Case-control	62	11.4 $\pm$ 3.4	Inflammatory (27.4%), idiopathic (24.2%), Best disease (20.0%), traumatic (28.3%)	NA	NA	17.0 $\pm$ 3.7	BCVA
Sisk R, 2010 ⁵	USA	Case series	13	10.9 $\pm$ 3.4	Idiopathic (15.4%), Best disease (33.3%), traumatic (15.4%)	Bevacizumab	2.6 (1.2)	13.8 $\pm$ 6.63	BCVA, CMT
Pavlíková K, 2026 ⁶	the Czech Republic	Case series	12	11.8 $\pm$ 3.5	Inflammatory (50%), idiopathic (25%)	Ranibizumab	3.4 (2.2)	35 $\pm$ 26.6	BCVA, CMT
Ranjan R ⁷ , 2022	India	Case series	26	11.7 $\pm$ 3.3	Inflammatory (61.5%), idiopathic (19.2%)	Bevacizumab, ranibizumab	2.0 (0.8)	28.1 $\pm$ 18	BCVA, CMT
Padhi TR ⁸ , 2018	India	Retrospective observational study	43	11.2 $\pm$ 3.4	Idiopathic (27.9%), inflammatory (9.3%), Best disease (32.5%)	Bevacizumab, ranibizumab, pegaptanib	2.11 (1.0)	6 months to 7 years	BCVA
MoosajeeM ⁹ ,	the United	Prospective observational	27	11.1 $\pm$ 3.9	Inflammatory (33.3%),	Bevacizumab,	2.0 (1.0)	24	BCVA

BCVA, best-corrected visual acuity; CMT, central macular thickness; SD, standard deviation; NA, not applicable.

^{*}The etiologies included in the studies were as follows: idiopathic, inflammatory, congenital, Best disease, neoplastic (including choroidal osteoma), myopia, and traumatic. Only the three most frequent etiologies are shown here; a comprehensive etiology analysis is presented in the following paragraph.

Study	Country	Study design	Sample size (eyes)	Age (years, mean $\pm$ SD)	Main etiology (%) [*]	Anti-VEGF agent	Mean number of injections (SD)	Follow-up (months, mean $\pm$ SD)	Outcome measures
2018	Kingdom	study			idiopathic (18.5%), optic disc abnormality (33.3%)	ranibizumab			
Kozak I, 2014 ¹⁰	Multiple countries	Case series	45	13 $\pm$ 3.4	Idiopathic (31.1%) Inflammatory (26.7%),	Bevacizumab, ranibizumab	2.2 (1.0)	12.8 $\pm$ 8.5	BCVA
Kohly RP 2010 ¹¹	Canada	Case series	4	11.5 $\pm$ 2.1	idiopathic (50%) Traumatic (25%), inflammatory (25%)	Bevacizumab, ranibizumab, pegaptanib	3.75 (1.3)	3.5 $\pm$ 1.1	BCVA
Katargina LA, 2024 ¹²	Russia	Case series	59	11 $\pm$ 3.5	Idiopathic (28.81%), inflammatory (27.12%), Best disease (13.56%)	Aflibercept, ranibizumab, brolucizumab	1.6 (1.3)	9	BCVA
Hykin PG, 2021 ¹³	Multiple countries	Case series	5	15 $\pm$ 2.0	Idiopathic (40%) Best disease (40%)	Ranibizumab	5 (3)	12	BCVA
Hoyek S, 2024 ¹⁴	USA	Retrospective cohort study	23	10.3 $\pm$ 4.72	Idiopathic (48%), inflammatory (20%)	Bevacizumab	2.3 (1.5)	56.46 $\pm$ 42.51	BCVA
Henry CR, 2015 ¹⁵	USA	Case series	35	8.7 $\pm$ 4.5	NA	Bevacizumab	3.6 (2.5)	19.9	BCVA, CMT
Finn A. P, 2022 ¹⁶	USA	Retrospective cohort study	925	12.9 $\pm$ 3.8	Idiopathic (38.2%), inflammatory (19.4%), myopia (18.4%)	Aflibercept, ranibizumab, bevacizumab	NA	22.9	BCVA
Choi SI, 2023 ¹⁷	Korea	Case series	13	12.4 $\pm$ 4.3	Idiopathic (53.85%)	Bevacizumab	4.15 (3)	34.6 $\pm$ 55	BCVA, CMT
Barth T, 2016 ¹⁸	Germany	Case series	10	13.9 $\pm$ 1.9	Neoplastic (30%)	Ranibizumab, bevacizumab	NA	35 $\pm$ 40	BCVA
Hang C, 2025 ¹⁹	China	Case series	14	10.3 $\pm$ 4	Idiopathic (35.7%), Best disease (21.4%),	Ranibizumab, conbercept	2.8 (0.4)	13.9 $\pm$ 6.9	BCVA
BCVA, best-corrected visual acuity; CMT, central macular thickness; SD, standard deviation; NA, not applicable.									
[*] The etiologies included in the studies were as follows: idiopathic, inflammatory, congenital, Best disease, neoplastic (including choroidal osteoma), myopia, and traumatic. Only the three most frequent etiologies are shown here; a comprehensive etiology analysis is presented in the following paragraph.									

Study	Country	Study design	Sample size (eyes)	Age (years, mean ± SD)	Main etiology (%) [*]	Anti-VEGF agent	Mean number of injections (SD)	Follow- up (months, mean ± SD)	Outcome measures
					neoplastic (14.3%)				
Rego- Lorca D, 2024 ²⁰	Spain	Case series	33	10.3 ± 3.7	Best disease (35.5%), inflammatory (25.8%), idiopathic (12.9%)	Ranibizumab, bevacizumab	3.1 (2)	NA	BCVA, CMT
BCVA, best-corrected visual acuity; CMT, central macular thickness; SD, standard deviation; NA, not applicable.									
[*] The etiologies included in the studies were as follows: idiopathic, inflammatory, congenital, Best disease, neoplastic (including choroidal osteoma), myopia, and traumatic. Only the three most frequent etiologies are shown here; a comprehensive etiology analysis is presented in the following paragraph.									

4.3 Risk of bias assessment

The risk of bias assessment was performed using the JBI checklist for case series and the NOS for cohort studies, as presented in Table 2 and Fig. 3. Most of the case series had a low risk of bias across the majority of JBI domains. The single cohort study (Padhi TR) received a median NOS quality rating (7/9). Detailed item-by-item scores are provided in Appendix S2 and Appendix S3.

Table 2
Quality appraisal of the included studies

Study	Study design	Assessment tool	Overall quality rating	Comment
Zhang T 2021 ¹	Case series	JBI	9/10	Selection bias
Zhang LY 2025 ²	Case series	JBI	8/10	Selection bias
Yan S 2025 ³	Case series	JBI	8/10	Attrition bias
Rishi P 2022 ⁴	Case-control	NOS	6/9 (moderate risk of bias)	Confounding bias, information bias
Sisk R 2010 ⁵	Case series	JBI	9/10	Attrition bias
Pavliková K 2026 ⁶	Case series	JBI	9/10	Selection bias
Ranjan R ⁷ 2022	Case series	JBI	9/10	Attrition bias
Padhi TR ⁸ 2018	Retrospective observational study	NOS	7/9	Confounding bias
MoosajeeM ⁹ 2018	Prospective observational study	JBI	10/10	-
Kozak I 2014 ¹⁰	Case series	JBI	9/10	Selection bias
Kohly RP 2010 ¹¹	Case series	JBI	9/10	Information bias
Katargina LA 2024 ¹²	Case series	JBI	9/10	Selection bias
Hykin PG 2021 ¹³	Case series	JBI	10/10	-
Hoyek S 2024 ¹⁴	Retrospective cohort study	JBI	10/10	-
Henry CR 2015 ¹⁵	Case series	JBI	10/10	-
Finn A. P 2022 ¹⁶	Retrospective cohort study	JBI	9/10	Information bias
Choi SI 2023 ¹⁷	Case series	JBI	9/10	Selection bias
Barth T 2016 ¹⁸	Case series	JBI	10/10	
Hang C 2025 ¹⁹	Case series	JBI	9/10	Selection bias
Rego- Lorca D 2024 ²⁰	Case series	JBI	9/10	Selection bias
Note: Detailed JBI and NOS item-by-item scores are provided in Supplementary Appendices S2 and S3.				

4.4 Meta-analysis outcomes

4.4.1 BCVA change (primary outcome)

A total of 13 studies (1176 eyes) reported BCVA changes from baseline to the last follow-up. A random-effects model yielded a pooled mean difference of -0.28 logMAR (95% CI: -0.35 to -0.22), indicating significant visual improvement with anti-VEGF therapy (Fig. 4A). The heterogeneity was moderate ($I^2 = 53.5\%$, $p = 0.01$). The GRADE certainty for the BCVA change outcome was moderate (downgraded for heterogeneity and upgraded for large effect; Table 3).

Table 3
GRADE summary of findings: Anti-VEGF therapy for pediatric choroidal neovascularization

Outcome	No. of studies (eyes)	Pooled estimate (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality (GRADE)
BCVA change (logMAR, mean difference)	13 (1176)	-0.28 (- 0.35, - 0.22)	Not serious	Not serious ¹	Not serious	Not serious	Not detected	⊕⊕⊕● Moderate
Number of injections (mean)	16 (375)	2.48 (2.15, 2.81)	Not serious	Serious ² ($I^2 = 89\%$)	Not serious	Not serious	Not detected	⊕●●● Very low
CMT change (μm, mean difference)	5 (123)	-75.6 (- 108.3, - 42.9)	Not serious	Serious ³ ($I^2 = 79\%$)	Not serious	Not serious	Not detected	⊕⊕●● Low
VA improvement (proportion)	17 (1272)	93.8% (77.9%, 98.5%)	Not serious	Serious ⁴ ($I^2 = 68\%$)	Not serious	Not serious	Not detected	⊕⊕●● Low
CMT improvement (proportion)	14 (297)	95.5% (84.3%, 98.8%)	Not serious	Not serious ⁵ ($I^2 = 40\%$)	Not serious	Not serious	Not detected	⊕⊕⊕● Moderate
CI: confidence interval; MD: mean difference								
Notes:								
¹ $I^2 = 53.5\%$, moderate heterogeneity; random-effects model applied.								
² High heterogeneity ($I^2 = 89\%$), mainly due to differences in anti-VEGF agents, retreatment protocols, and follow-up durations.								
³ High heterogeneity ($I^2 = 79\%$), possibly related to differences in OCT devices or measurement methods.								
⁴ Moderate heterogeneity ($I^2 = 68\%$), likely due to different definitions of "VA improvement".								
⁵ Acceptable heterogeneity ($I^2 = 40\%$), no downgrade.								

4.4.2 Number of injections

Sixteen studies (375 eyes) reported the mean number of anti-VEGF injections. The pooled mean was 2.5 injections (95% CI: 2.16 to 2.84) using the random-effects model, with very high heterogeneity ($I^2 = 89.4\%$, $p < 0.001$; Fig. 4B). The GRADE certainty was very low due to serious inconsistency and indirectness.

4.4.3 CMT change

Five studies (123 eyes) reported the CMT change (μm). The random-effects pooled mean difference was - 75.6 μm (95% CI: -108.26 to - 42.93), with high heterogeneity ($I^2 = 79.3\%$, $p < 0.001$; Fig. 4C). The GRADE certainty was low (downgraded for inconsistency).

4.4.4 VA improvement (proportion)

Seventeen studies (1255 eyes) reported the proportion of eyes in which VA improved (defined as ≥ 0.2 logMAR gain or equivalent). The pooled proportion was 94% (95% CI: 77% to 99%; random-effects model; $I^2 = 67\%$; Fig. 4D). The GRADE certainty was low (downgraded for inconsistency).

4.4.5 CMT improvement (proportion)

Fourteen studies (297 eyes) reported a complete anatomical response (CMT normalization or CNV regression), with a pooled proportion of 95% (95% CI: 84% to 99%; random-effects model; $I^2 = 39.7\%$; Fig. 4E). The GRADE certainty was moderate (no serious inconsistency; Table 3).

4.4.6 GRADE summary

The GRADE evidence is summarized in Table 3. All outcomes were based on observational studies (case series and cohort studies). The initial GRADE quality for observational evidence was low. The BCVA change, number of injections, CMT change, and CMT improvement did

not exhibit serious inconsistencies or imprecision, and the effect size was clinically meaningful; therefore, their GRADE quality was upgraded to moderate. The VA improvement remained low due to moderate heterogeneity. The number of injections was downgraded to very low due to very high heterogeneity ($I^2 = 89\%$).

4.5 Subgroup analysis by etiology

We performed a subgroup analysis evaluating the BCVA change according to the six etiology categories (idiopathic, inflammatory, myopic, neoplastic, traumatic, Best disease). The results are shown in Table 4. None of the etiology subgroups showed statistically significant BCVA improvement (all 95% CIs crossed zero) based on the random-effects model, and the subgroup differences were not significant ($p = 0.84$). However, substantial heterogeneity persisted within most subgroups (I^2 ranged from 45.5% to 96.4%). These exploratory findings should be interpreted with caution.

Table 4
Subgroup analysis of BCVA improvement by etiology

Etiology subgroup	No. of studies	Total eyes	Pooled MD (logMAR) ¹	95% CI
Idiopathic	10	319	-0.04	(- 0.22, 0.14)
Inflammatory	7	337	-0.08	(- 0.32, 0.16)
Neoplastic	5	25	0.06	(- 0.12, 0.24)
Traumatic	3	57	-0.24	(- 0.84, 0.36)
Best disease	6	74	-0.14	(- 0.44, 0.16)
Myopic	3	162	-0.03	(- 0.44, 0.38)
Overall (random effects) ³	34	974	-0.08	(- 0.18, 0.03)
Test for subgroup differences (random effects model): $p = 0.841$. ²				
Notes:				
¹ Negative MD indicates improvement in BCVA (logMAR).				
² No statistically significant difference was observed among the etiology subgroups ($p = 0.841$). These exploratory findings should be interpreted with caution, particularly for subgroups with a small sample size (e.g., neoplastic, traumatic).				
³ Excluding the large registry-based study (Finn et al.) yielded a pooled MD of - 0.16 (95% CI: -0.27 to - 0.05), with a significant subgroup difference ($p = 0.0003$). The main results were therefore sensitive to the inclusion of this study.				

4.6 Sensitivity analysis

A sensitivity analysis was conducted that excluded the large registry-based study by Finn et al., as it contributed ~ 80% of the total eyes. The pooled BCVA change became - 0.16 logMAR (95% CI: -0.27 to - 0.05) based on the remaining 28 studies (173 eyes), and the subgroup differences became significant ($p < 0.001$). Detailed results are provided in Supplementary Table S1 and Supplementary Figure S1. Additional sensitivity analyses that excluded studies with a high risk of bias or used a fixed-effect model did not materially alter the direction or magnitude of the main findings.

4.7 Publication bias

A funnel plot of the primary outcome (BCVA change) was visually symmetrical (Fig. 5). Furthermore, Egger’s regression test was not significant ($p = 0.164$), suggesting no strong evidence of publication bias. Funnel plots of the secondary outcomes with ≥ 10 studies (number of injections, VA improvement, CMT improvement) are provided in the Supplementary Material (Figure S2).

Discussion

In this study, we presented a case of a 12-year-old child with spontaneous regression of CNV. We also performed a meta-analysis, which showed that anti-VEGF therapy can notably improve BCVA and anatomical outcomes in pediatric patients with CNV.

Unlike typical cases of idiopathic CNV, our patient exhibited bilateral hyperfluorescence on FFA at several follow-up visits and neovascularization with blood flow signals in the left eye on OCT angiography. These findings suggested that inflammation may have contributed to the neovascularization. In addition, the left eye showed subfoveal RPE irregularities and hyperreflective material beneath the RPE without a blood flow signal but maintained a BCVA of 1.0. In adults, this would indicate a risk of progressive RPE atrophy and vision loss,

a phenomenon well-documented in long-term studies of anti-VEGF therapy in adult neovascular age-related macular degeneration. This suggested that pediatric CNV, particularly if located extrafoveally or posing a minimal foveal threat, may be more suitable for initial observation^{21 22}. Furthermore, studies have consistently shown that pediatric CNV is predominantly type 2 (sub-RPE), a neovascular subtype that differs from adult CNV in its ingrowth pattern. Type 2 is thought to be more likely to undergo RPE-mediated encapsulation with subsequent clearance, a key mechanism linked to spontaneous involution¹.

Similar to adult meta-analyses on anti-VEGF therapy, the majority of studies in our meta-analysis showed that most children experienced visual improvement and anatomical restoration. One study suggested that the treatment effect in the pediatric population was more significant than in adults and had a lower risk of adverse events. Moreover, instead of focusing on a single CNV etiology, such as optic nerve head drusen-related CNV, we evaluated various CNV etiologies and found no significant difference in the BCVA improvement among them. Furthermore, differences in the number of injections may produce different outcomes, but the high I^2 value suggested that different follow-up durations may have also contributed to this heterogeneity.

The spontaneous regression of CNV in children is a well-recognized but incompletely understood phenomenon. Unlike adult neovascular age-related macular degeneration, in which spontaneous involution is exceedingly rare, pediatric CNV appears to follow a more favorable natural history in a substantial proportion of cases. The largest study to date examining the natural history of pediatric CNV, conducted by Rishi et al⁴, in 96 patients (111 eyes), reported that of the 73 eyes managed with observation alone, spontaneous regression occurred in 26 (36%), with no recurrences observed in this group. The mean presenting age of the cohort was 11.4 ± 3.4 years, which was very similar to our patient's age of 12 years. In a separate series that evaluated 36 pediatric eyes, anecdotal reports suggested that spontaneous involution occurred in approximately 58% of cases. These observations collectively indicated that spontaneous regression is not a rare event in pediatric CNV, particularly in the absence of high-risk features, such as substantial subretinal fluid or foveal involvement.

The mechanisms underlying spontaneous regression have been speculated upon but are not yet known. Several complementary theories have been proposed, each supported by varying degrees of evidence. One hypothesis is based on the dependence of immature neovascular vessels on a sustained angiogenic drive, in which newly formed capillaries require VEGF for survival, with local VEGF fluctuations or depletion causing selective pruning of these vessels. In the developing pediatric eye, the underlying angiogenic drive may be less sustained than in adults. Therefore, this mechanism may allow CNV to regress once the initial trigger subsides^{23 24}. Another factor may be the phagocytic function of the RPE, which is intact in children²⁵. The phagocytic and metabolic capacity of the RPE is known to decline with age. In our patient, the minimal subretinal fluid at presentation and the eventual restoration of a near-normal RPE layer, as evidenced by OCT, suggested an active RPE-mediated encapsulation and resorption process. This phenomenon was previously documented by OCT in spontaneously regressing idiopathic CNV. The unique anatomical features of the pediatric eye may further create a microenvironment that favors spontaneous resolution. Age-related differences between the adult and pediatric intraocular microenvironments suggest another possible mechanism. Compared with adults, the pediatric eye, even with moderate myopia, exhibits a more active innate immune response, including higher macrophage and microglial turnover and cytokine signaling, which may more efficiently clear subretinal debris and modulate local inflammation²⁶. This greater immunoregulatory capacity, a relatively thicker choroid, and preserved vascular density create an environment that favors the spontaneous involution of active choroidal neovascularization with the subsequent formation of a stable, quiescent atrophic scar rather than progressive exudative changes. Furthermore, accumulating evidence suggests that a subset of pediatric CNVs belong to the pachychoroid disease spectrum, which is characterized by increased choroidal thickness and vascular hyperpermeability. These features predispose patients to neovascularization and, paradoxically, are also compatible with spontaneous involution in selected patients²⁷.

These observations have important clinical implications. While anti-VEGF therapy remains the first-line treatment for active, vision-threatening pediatric CNV, our case, together with published evidence of a 36% spontaneous regression rate in observed eyes with no recurrences, supports observation as a reasonable alternative for carefully selected patients⁴. Candidates for observation should meet specific clinico-imaging criteria: idiopathic or a low-activity etiology, extrafoveal lesion, minimal subretinal fluid or intraretinal edema on OCT, and low-grade flow signals on OCT angiography. Additionally, features such as hypofluorescent borders on ICGA or FFA indicating RPE hyperplasia and fibrous encapsulation have been proposed as indicators of an involuting CNV. The bilateral short band-like hypofluorescence observed in our patient further supports these imaging signatures as predictors of a benign course. Importantly, observation is not passive; it requires strict monitoring with predefined conversion criteria (e.g., vision decline ≥ 2 lines, increased subretinal fluid, or CNV enlargement) and reliable patient and family compliance. Future prospective studies using standardized protocols are warranted to validate these clinical criteria and to elucidate the mechanisms underlying spontaneous regression in pediatric CNV.

Our case adds uniquely to the pediatric CNV evidence base in several ways. First, to our knowledge, this is the longest documented follow-up (3 years) of a spontaneously regressed pediatric idiopathic CNV patient with complete multimodal imaging documentation. Second, the bilateral hyperfluorescence on fluorescein angiography and hypofluorescence on FFA observed at the final follow-up raised the possibility of an underlying subclinical choroidal or RPE diathesis, such as a pachychoroid or low-grade inflammatory phenotype, that may predispose the

patient to CNV formation in one eye and subsequent spontaneous resolution. Third, the presence of myopia (− 5.0 D) without pathologic myopic changes further supports classifying this case as truly idiopathic rather than myopic CNV. This further supports the concept that certain idiopathic pediatric CNVs are inherently self-limiting.

However, this study has limitations. We reported only one case, which may not be representative of the broader population. In addition, the studies included in our meta-analysis were of moderate to low quality as assessed by the GRADE system. Except for the BCVA improvement, other outcomes, including the central macular thickness change and number of injections, showed high heterogeneity, which limited the precision of the pooled results.

Overall, this study presents a case report of a child undergoing close observation for CNV that spontaneously regressed. The study then summarizes the etiologies of CNV and demonstrates the efficacy and safety of anti-VEGF therapy in the pediatric population. Future prospective studies are needed to determine whether different CNV etiologies require different treatments and to collect intraocular biomarkers that distinguish idiopathic CNV from an inflammatory origin that may lead to different outcomes.

Declarations

Ethics approval and consent to participate

This study protocol adhered to the ethical principles of the Declaration of Helsinki (2013) and was approved by the Ethics Committee of the Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, China (IIT-O-2025-252). All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Written informed consent for publication of their clinical details and clinical images was obtained from the parent relative of the patient. A copy of the consent form is available for review by the Editor of this journal.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Xinyi Zuo and Yuhan Yu conceptualized and designed the study. Xinyi Zuo collected the clinical data and performed the literature review. Xinyi Zuo and Yuhan Yu performed the statistical analysis and meta-analysis. Xinyi Zuo drafted the initial manuscript. Lin Xie critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Figures

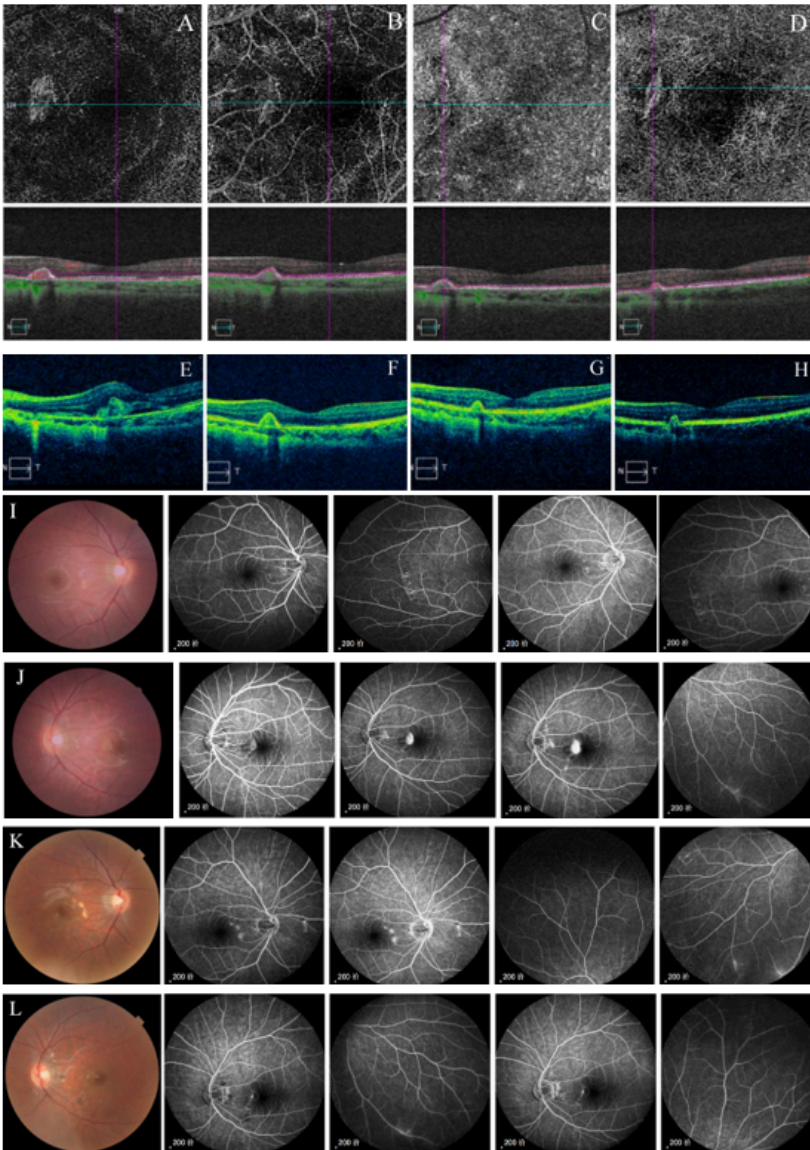
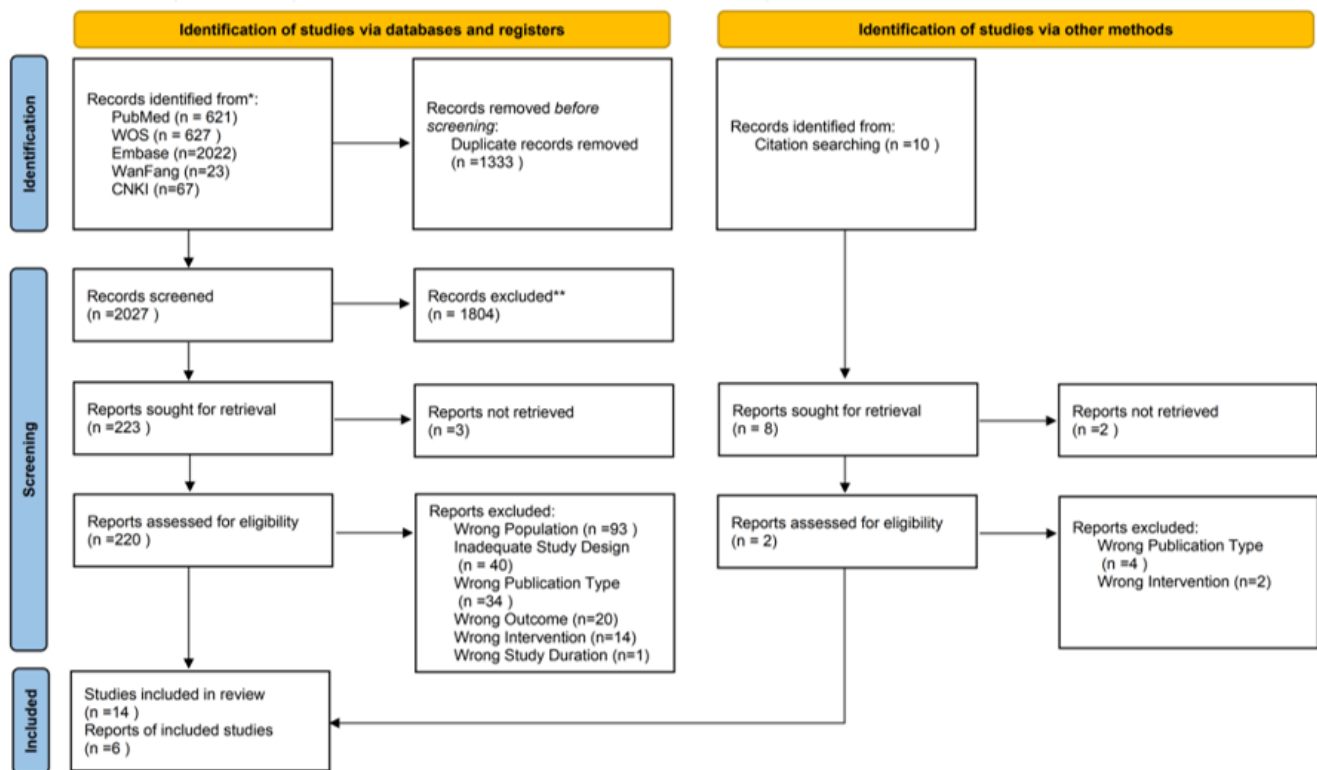


Figure 1

Imaging results of the pediatric patient with CNV over 3 years. (A–C) En face OCTA shows the gradual regression of the CNV vascular network and a decreasing blood flow signal. (D) Final OCTA (2025-08-06) shows the complete absence of a blood flow signal, consistent with fibrotic scar tissue. (E–H) Corresponding structural OCT showing subretinal fluid resolution and CNV regression. (I, J) Initial FFA (2022-01-26). The right eye revealed hyperfluorescence in the temporal mid-peripheral retina without any change in size or extent during the late phase. In the left eye, early arterial phase angiography showed an irregular hyperfluorescent spot nasal to the fovea. Over the course of angiography, the hyperfluorescent spot demonstrated progressive leakage, evolving into intense fluorescence, indicating choroidal neovascularization in the left eye. Additionally, focal mottled fluorescence was noted in the inferior peripheral region of the left eye and in the temporal mid-peripheral region of the right eye. (K, L) Final FFA (2025-08-08). The right eye showed early hypofluorescence of the peripapillary crescent with late marginal staining. Scattered hyperfluorescent patches were observed in the posterior pole retina, with partial staining in the late phase. In the left eye, an irregular hyperfluorescent patch was observed on the nasal side of the macula during the early angiographic phase, which showed no significant changes during the late phase. In addition, focal mottled fluorescence was also noted in the inferior peripheral region of both eyes.



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
 **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

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Figure 2

PRISMA 2020 flow diagram for screening pediatric CNV literature for inclusion in the systematic review. This included searches of databases, registers, and other sources.

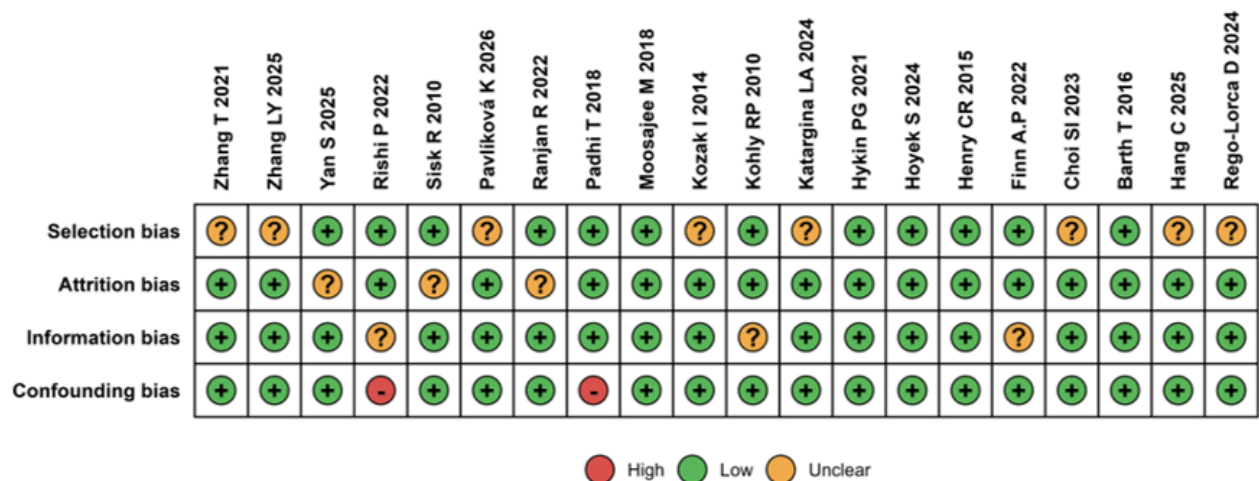


Figure 3

Risk of bias shown as a traffic light plot (JBI and NOS).

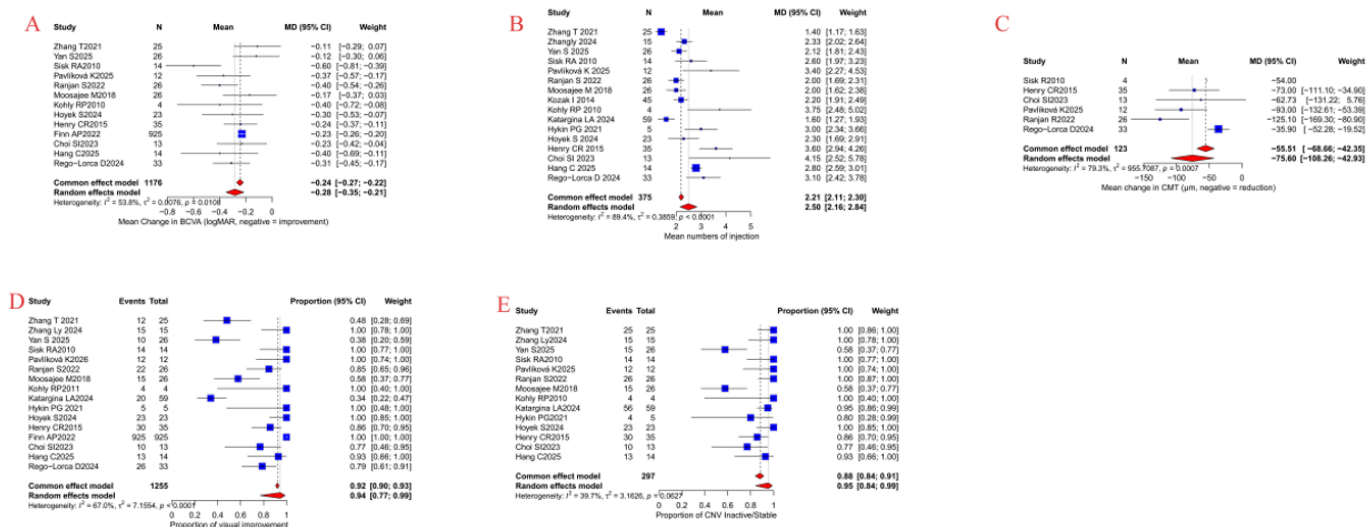


Figure 4

Forest plots of the meta-analysis (random-effects model).

(A) BCVA change from baseline to the last follow-up (logMAR). Negative values indicate improvement. Pooled mean difference: -0.28 (95% CI: -0.35 to -0.22); $I^2 = 53.5\%$, $P = 0.0108$.

(B) Number of anti-VEGF injections. Pooled mean: 2.50 (95% CI: 2.16 to 2.84); $I^2 = 89.4\%$, $p < 0.0001$.

(C) Central macular thickness (CMT) change (μm). Negative values indicate a reduction. Pooled mean difference: -75.6 (95% CI: -108.3 to -42.9); $I^2 = 79.3\%$, $p = 0.0007$.

(D) Proportion of eyes with VA improvement. Pooled proportion: 94% (95% CI: 77% to 99%); $I^2 = 68.2\%$, $p < 0.0001$.

(E) Proportion of eyes with an anatomical response (CMT improvement or CNV regression). Pooled proportion: 95% (95% CI: 84% to 99%); $I^2 = 39.7\%$.

Abbreviations: BCVA, best-corrected visual acuity; CI, confidence interval; MD, mean difference; VEGF, vascular endothelial growth factor; CNV, choroidal neovascularization; CMT, central macular thickness.

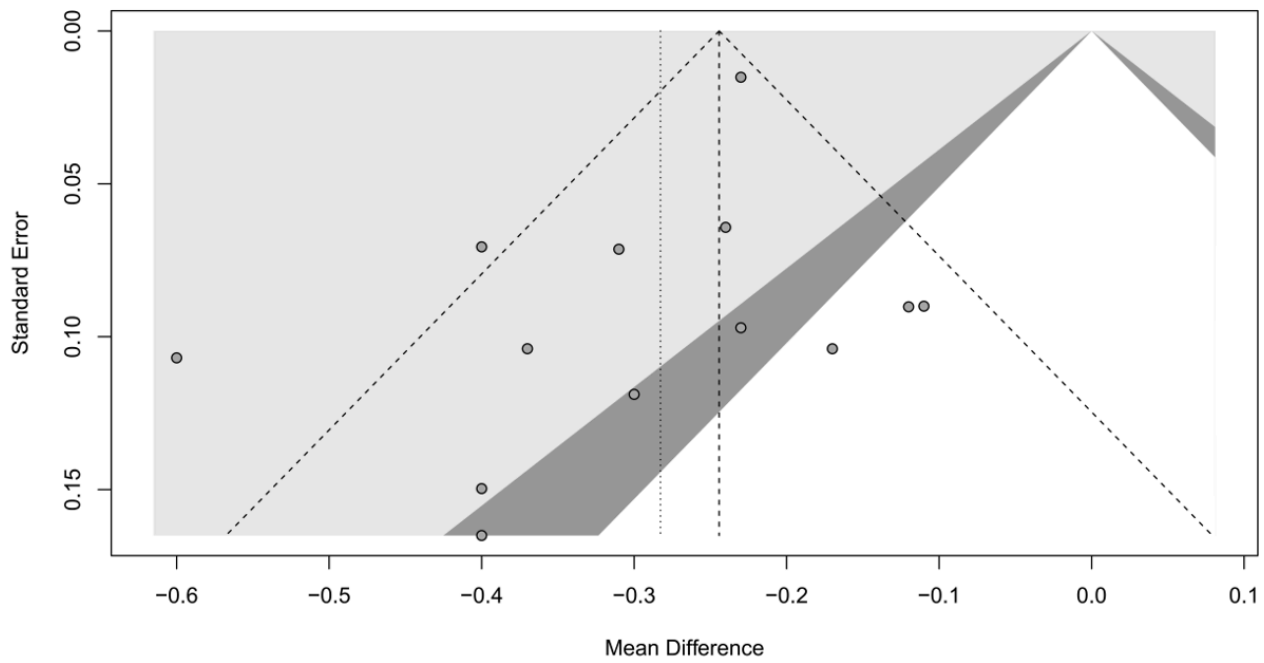


Figure 5

Funnel plot of the BCVA change. Each dot represents an individual study (13 studies, 1176 eyes). The vertical dashed line indicates the pooled effect estimate from the random-effects model (MD = -0.28 logMAR). The diagonal lines represent the pseudo-95% confidence limits around the summary effect. The funnel plot appears roughly symmetrical, and Egger's regression test was not significant ($p = 0.164$), suggesting no strong evidence of publication bias. BCVA, best-corrected visual acuity; MD, mean difference; SE, standard error.

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