

Methodological landscape of clinical trials for diabetic retinopathy: A scoping review of design, implementation, and reporting

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Abstract

Background

Diabetic Retinopathy (DR) is a prevalent and sight-threatening ocular complication of diabetes, and one of the leading causes of vision loss and blindness among the working-age population worldwide. Driven by a growing understanding of the pathophysiological mechanisms underlying DR, treatment strategies have evolved from a sole focus on glycaemic control to comprehensive, multi-targeted, and multimodal therapies. This study systematically summarises the characteristics of current clinical trials focused on DR treatment and evaluates the employed research methodologies. The aim of this review is to optimise trial design and improve trial quality to elucidate treatment efficacy.

Methods

This study followed the PRISMA-ScR reporting guidelines. Clinical trials registered on ClinicalTrials.gov and the China Clinical Trials Registry (ChiCTR) were retrieved (from July 23, 2016 to July 23, 2026). In addition, clinical trials indexed in PubMed from July 23, 2016 to July 23, 2026 were retrieved. Data from the included studies were extracted and presented in tabular form.

Results

Clinical research targeting DR has expanded rapidly, reflecting a shift toward diverse interventions like anti-Vascular endothelial growth factor(anti-VEGF) drugs, laser treatments, and combined therapies. However, these studies are often limited by poor methodology, insufficient data from primary care environments, and low patient follow-up rates.

Conclusion

This review represents the first comprehensive assessment of current DR clinical research, exposing key design weaknesses in existing trials. Future meta-analyses and systematic evaluations are urgently needed to generate robust evidence that can guide optimal treatment strategies.

1. Introduction

Diabetic Retinopathy (DR), a predominant microvascular complication of diabetes, stands as a leading cause of preventable blindness among the global working-age population (1). Epidemiological data indicate that the global prevalence of DR among individuals with diabetes ranges from 21.95% to 31.60%, with Vision-threatening Diabetic Retinopathy (VTDR) accounting for 5.06% of these cases. A 2021 analysis of United States data revealed a DR prevalence of 26.43% (2). Notably, significant geographical heterogeneity exists; the highest prevalence rates are observed in Africa and the Middle

East, contrasting with lower rates in East Asia and Northern Europe. These disparities correlate strongly with regional variances in diabetes management standards and healthcare accessibility (3).

Regarding incidence, the cumulative risk of developing DR within five years of a type 2 diabetes diagnosis is approximately 10–15%, a rate that escalates exponentially with disease duration. In type 1 diabetes, a Saudi Arabian study reported an incidence density of 92.66 per 1,000 person-years (4). Moreover, a 20-year retrospective cohort study in the United States documented a steady annual increase in DR prevalence post-2007, reaching 26.43% by 2021 (5). Collectively, these statistics underscore a substantial and unevenly distributed global burden. Pathophysiologically, DR typically evolves from asymptomatic early Non-proliferative Diabetic Retinopathy (NPDR) to advanced Proliferative Diabetic Retinopathy (PDR), characterized by pathological neovascularization and sight-threatening sequelae such as vitreous hemorrhage and tractional retinal detachment. Concomitantly, Diabetic Macular Edema (DME)—driven by increased vascular permeability and retinal thickening—can manifest at any disease stage, posing a distinct threat to visual acuity (6).

Historically, DR management prioritized systemic optimization of glycemic, blood pressure, and lipid profiles. While these interventions are proven to mitigate risk and decelerate progression(7,8), they offer incomplete protection, implicating auxiliary pathogenic mechanisms such as genetic susceptibility and local ocular factors. Ophthalmic intervention has traditionally relied on laser photocoagulation—specifically Panretinal Photocoagulation (PRP) for PDR and focal/grid laser for DME—to ablate ischemic retina and stabilize edema. Although laser therapy remains effective in preventing severe vision loss, it is not without potential adverse sequelae (9, 10).

The advent of intravitreal pharmacotherapy, particularly anti-vascular anti-VEGF agents, has fundamentally transformed the DR treatment landscape(9). By inhibiting neovascularization and resolving macular edema, anti-VEGF therapy significantly improves visual prognosis(10). Recent randomized clinical trials demonstrate that early intervention with intravitreal anti-VEGF injections in moderate-to-severe NPDR reduces the incidence of vision-threatening complications and improves DR severity scores. This evidence marks a paradigm shift from the traditional "watch-and-wait" approach to proactive pharmacological management (11, 12). However, consensus regarding the optimal timing, dosing frequency, and treatment duration remains elusive. Furthermore, the necessity for repeated intravitreal injections presents significant challenges regarding patient adherence and economic burden (13, 14).

Emerging pathophysiological insights highlight the critical roles of inflammation and neurodegeneration in DR. Elevated levels of systemic and intraocular inflammatory mediators—including interleukins (IL-6, IL-8), interferon-gamma, and tumor necrosis factor-alpha—correlate closely with disease severity and DME presence, underscoring the inflammatory component of DR progression (15). Concurrently, diminished levels of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), have been identified in NPDR and DME patients. This suggests that neurodegenerative processes not only contribute to retinal dysfunction but may also represent viable therapeutic targets (16).

The scientific validity and clinical applicability of research findings are inextricably linked to the rigor of clinical trial design (17). Transparent trial registration is pivotal for mitigating research waste, preventing duplication, and optimizing resource allocation, thereby elevating the overall quality of clinical evidence (18).

This review synthesizes data from ClinicalTrials.gov, the Chinese Clinical Trial Registry (ChiCTR), and PubMed. ClinicalTrials.gov, managed by the U.S. National Library of Medicine and the National Institutes of Health, serves as the world's most comprehensive repository for ongoing and completed clinical trials. Similarly, since its inception in 2007, ChiCTR has served as a primary registry within the World Health Organization International Clinical Trials Registry Platform. Complementing these registries, PubMed provides an extensive archive of biomedical literature essential for systematic reviews. While existing literature reviews address DR treatment and diagnosis, there is a paucity of systematic analyses focusing specifically on the design and outcomes of interventional clinical trials. Consequently, this study aims to comprehensively evaluate the current landscape of DR clinical trial designs. By leveraging data from these premier databases, we seek to identify opportunities for optimizing experimental design, thereby enhancing the level of evidence in DR clinical research.

2. Methods

2.1 Search Strategy

This study adhered to the PRISMA-ScR reporting guidelines. In this study, the researchers (Zixuan Wang, Xuwei Liu) searched the ClinicalTrials, ChiCTR, and PubMed databases using the search terms "diabetic retinopathy," "diabetic retinopathies," "Retinopathies, Diabetic," and "Retinopathy, Diabetic." The search covered the period from the inception of these databases to July 23, 2026. Additionally, through PubMed's article type filtering function, relevant clinical trials and randomized controlled trials were selected to preliminarily identify clinical studies related to diabetic retinopathy. The specific search strategy is detailed in Supplementary Table 1.

2.2 Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 1) Study subjects: Patients with diabetic retinopathy (DR); 2) Interventions: Evaluation of any intervention primarily aimed at treatment, including anti-VEGF, laser, surgery, hormones, and ethnomedicine treatments; 3) Study types: Interventional clinical trials, including randomized controlled trials (RCTs), non-randomized controlled trials (non-RCTs), and single-arm trials; 4) Time frame: Studies published in ClinicalTrials, ChiCTR databases, and PubMed from July 23, 2016 to July 23, 2026.

Exclusion criteria are as follows: 1) Studies unrelated to diabetic retinopathy; 2) Non-clinical trials (basic research, reviews); 3) Studies for which the full text was inaccessible or data could not be extracted.

2.3 Data Extraction

We designed a standardized data extraction form using Microsoft Excel. Before formal data extraction, two reviewers (Zixuan Wang and Xuwei Liu) performed a pilot data extraction on the selected studies using this form. Based on the preliminary results, we adjusted and optimized the data extraction form and rules to ensure inter-reviewer consistency and the feasibility of the extraction protocol. The data extraction form covered the following core variables: number of registrations or published papers, country, type of intervention, characteristics of the study population, primary and secondary outcome measures, and study design. Items not classified under the above variables were uniformly marked as "Other." Data extraction was independently performed by two reviewers (Zixuan Wang and Xuwei Liu). All extracted results were entered into a unified data extraction form. After extraction, the results from the two reviewers were cross-checked. For discrepant items, the reviewers re-examined the original sources and discussed the findings to reach a consensus; if disagreements could not be resolved through discussion, a third senior researcher (Xi Chen) was consulted to adjudicate, and their decision was considered final.

2.4 Statistical Analysis

Data analysis and processing were conducted in Excel. As this study is a comprehensive review of clinical research on diabetic retinopathy, descriptive statistical methods were used to summarize the study characteristics extracted from the included literature using frequencies and percentages.

3. Results

3.1 Study Selection and Inclusion Criteria

A total of 709 clinical trials were included in this study. A total of 1,540 records were retrieved from the ClinicalTrials.gov, ChiCTR, and PubMed databases. First, 113 duplicate records were removed. Next, the remaining records were screened, resulting in the exclusion of 636 irrelevant studies. Finally, full-text reviews were conducted on the remaining records, leading to the exclusion of 82 studies that did not meet the inclusion criteria. Thus, this study ultimately included 709 clinical trials. The literature screening process was conducted in accordance with the PRISMA guidelines, as illustrated in Fig. 1 (24). Detailed search results are provided in Supplementary Table 2.

3.2 Number of registrations and publications, country

The temporal trend of clinical research shows that studies on DR commenced an upward trend in 2005, maintained steady growth, and then experienced a substantial surge from 2018, ultimately attaining its peak. Research activity sustained a high level from 2019 to 2025 and is projected to remain robust through 2026. The annual evolutionary trends of DR are illustrated in Fig. 2.

Geographically, the United States leads in the absolute number of trials (179 studies, 25.25%), with a significant portion of high-quality data originating from the DRCR.net, which has been pivotal in shaping clinical guidelines. China ranks second (147 trials, 20.73%), with a notable focus on traditional Chinese

medicine and plant extracts. European nations also made substantial contributions, including the UK (41 trials, 5.78%), Germany (38, 5.36%), France (27, 3.81%), Spain (27, 3.81%), Italy (26, 3.67%), and Hungary (22, 3.10%). Other key contributors include Japan (32 trials, 4.51%), Brazil (30 trials, 4.23%), Mexico (29 trials, 4.09%), Canada (26 trials, 3.67%), Australia (23 trials, 3.24%), and Iran (20 trials, 2.82%). The global distribution of these trials is illustrated in Fig. 3.

3.3 Classification of Intervention Measures Characteristics

Anti-VEGF therapy was the most prevalent intervention, featured in 174 studies (24.54%)—nearly one-quarter of the total—solidifying its status as the cornerstone of treatment for DR and DME. Perioperative interventions (105 studies, 14.81%) and combination therapies (93 studies, 13.12%) followed in frequency. Together, these three categories accounted for over half (52.47%) of all studies, highlighting the dominance of anti-VEGF-centric pharmacotherapy.

The second tier of interventions included laser therapy (48 studies, 6.77%), comparative effectiveness studies (47 studies, 6.63%), and corticosteroid-based pharmacotherapy (44 studies, 6.21%). The remaining categories were more fragmented, each representing less than 5% of studies. These included traditional Chinese medicine (4.37%), lifestyle interventions (4.23%), ophthalmic surgery (3.39%), systemic metabolic control (3.39%), eye drops (2.40%), nutritional supplements (2.40%), anti-inflammatory agents (2.26%), and targeted therapies (1.69%). Detailed characteristics of interventions are shown in Fig. 4.

Among the 93 studies on combination therapy, regimens were heavily skewed toward anti-VEGF agents. The combination of anti-VEGF therapy and laser photocoagulation was the most common (42 studies, 45.16%), reflecting its role as the standard combined strategy for DME/PDR. The combination of anti-VEGF therapy and corticosteroids ranked second (17 studies, 18.28%). Together, these two regimens constituted the primary tier of combination approaches, accounting for 63.44% of such studies. Detailed characteristics of combination therapy are shown in Fig. 5.

3.4 Study Population and Basic Characteristics of Diabetic Retinopathy

3.4.1 Characteristics of intervention population

Among the 709 studies, over half (365 studies, 51.48%) did not specify the type of diabetes, referring to it only in general terms. Of those that did, 245 studies (34.56%) distinguished between type 1 and type 2 diabetes; of these, 89 (12.55%) focused exclusively on type 2 diabetes, while only 10 (1.41%) were limited to type 1 diabetes.

Regarding DR classification, PDR was the most frequently studied stage (198 studies, 27.93%), followed by NPDR (136 studies, 19.18%). Macular edema was a key feature in 51.48% of studies (365 studies),

with Center-involved Diabetic Macular Edema (CI-DME) being the most specified subtype (208 studies, 29.34%).

Most studies (89.84%) established clear ophthalmic examination criteria. However, fewer specified glycemic control criteria (25.39%) or ancillary examinations (27.50%). In terms of visual impairment, most enrolled patients had early-to-moderate disease, with mild (BCVA < 20/25; 10.72%) and moderate (BCVA < 20/40; 10.30%) decreases being the most common. Central retinal thickness (CRT) was assessed in 21.44% of DME studies, with > 300µm being the most common inclusion threshold (10.86%). Table 1 details the characteristics of the study populations.

Table 1
Characteristics of intervention population

Characteristics	Category	Included literature	Record percentage(%)
Types of Diabetes	Only diabetes	365	51.48%
	Type 1 or 2 diabetes	245	34.56%
	Type 2 diabetes	89	12.55%
	Type 1 diabetes	10	1.41%
Retinopathy Type	NPDR	136	19.18%
	PDR	198	27.93%
	Only DR	80	11.28%
Macular Edema Type	All Types Of Macular Edema	365	51.48%
	CI-DME	208	29.34%
	NCI-DME	3	0.42%
	Only DME	154	21.72%
Specific Inspection Requirements Classification	Ophthalmic examination	637	89.84%
	Glycogen and lipid metabolism indicators	180	25.39%
	Other laboratory indicators	195	27.50%
Assessment Of Vision	Total Number Of Vision Tests	295	41.61%
	Total Decline In Vision	153	21.58%
	Mild decrease in visual acuity (best corrected visual acuity on Snellen test < 20/25)	76	10.72%
	Moderate visual impairment (best corrected visual acuity on Snellen test < 20/40)	73	10.30%
	Significantly decreased visual acuity (best	1	0.14%

DR:Diabetic Retinopathy. NPDR:Non-Proliferative Diabetic Retinopathy. PDR: Proliferative Diabetic Retinopathy. CI-DME:Center-involved Diabetic Macular Edema. DME:Diabetic Macular Edema. NCI-DME:Non-Center-involved Diabetic. Dynamic parameters: Zeiss Cirrus – 275 µm for females, 290 µm for males; Heidelberg Spectralis – 290 µm for females, 305 µm for males.

Characteristics	Category	Included literature	Record percentage(%)
	corrected visual acuity on Snellen test < 20/80)		
	Legal blindness (best corrected visual acuity per Snellen test < 20/200)	3	0.42%
Assessment of central retinal thickness in patients with macular edema	Total number of evaluations for diabetic macular edema	152	21.44%
	>300µm	77	10.86%
	>250µm	25	3.53%
	Dynamic parameters	15	2.12%
	>320µm	12	1.69%
	>275µm	7	0.99%
	>350µm	5	0.71%
	>400µm	4	0.56%
	>325µm	3	0.42%
	>200µm	1	0.14%
	>225µm	1	0.14%
	>260µm	1	0.14%
	>310µm	1	0.14%
Ophthalmic Features	Cataract	19	2.68%
	Hard Exudates	6	0.85%
	Tractional Retinal Detachment	25	3.53%
	Vitreous Hemorrhage	27	3.81%
DR:Diabetic Retinopathy. NPDR:Non-Proliferative Diabetic Retinopathy. PDR: Proliferative Diabetic Retinopathy. CI-DME:Center-involved Diabetic Macular Edema. DME:Diabetic Macular Edema. NCI-DME:Non-Center-involved Diabetic. Dynamic parameters: Zeiss Cirrus – 275 µm for females, 290 µm for males; Heidelberg Spectralis – 290 µm for females, 305 µm for males.			

3.5 Basic characteristics of clinical trials

The included studies were predominantly small, with 61.78% enrolling fewer than 100 participants. Studies with 1–50 participants were the most common (39.21%), followed by those with 51–100 participants (22.57%). Large-scale trials with over 300 participants accounted for only 13.12%.

Adults constituted the primary study population (63.75%), and nearly all studies (99.86%) included both sexes. Reporting on intervention duration was inconsistent, with 37.38% of studies failing to specify it. Among those that did, a single intervention session was most common (23.70%), consistent with the paradigm for procedures like intravitreal injections. Follow-up duration was reported more consistently, with medium-term follow-up (181–365 days) being the most frequent (26.52%). Overall, most studies (64.89%) had follow-up periods between three months and one year, aligning with the conventional window for efficacy assessment. Table 3 details the basic characteristics of the included trials. The basic characteristics of the Clinical trials included in the study are detailed in Table 2.

Table 2
Basic characteristics of clinical trials

Characteristics	Category	Included literature	Record percentage(%)
sample size	Cases 1 to 50	278	39.21%
	Cases 51 to 100	160	22.57%
	Cases 101 to 200	110	15.51%
	Cases 201 to 100	40	5.64%
	Cases over 300	93	13.12%
	Case size not specified/Case size is 0	28	3.95%
Age	Adults (lower age limit: 17–21 years, varying by study)	452	63.75%
	Over 25 years	7	0.99%
	Over 30 years	16	2.26%
	Over 35 years	6	0.85%
	Over 40 years	24	3.39%
	Over 45 years	7	0.99%
	Over 50 years	12	1.69%
	Over 55 years and older(Older Adult)	6	0.85%
Sex	No gender restrictions	708	99.86%
	Only men	1	0.14%
Intervention Time	No intervention time reported	265	37.38%
	Once	168	23.70%
	1 to 15 days	21	2.96%
	16 to 30 days	18	2.54%
	31 to 90 days	89	12.55%
	91 to 180 days	48	6.77%
	181 to 356 days	63	8.89%
	Over 356 days	37	5.22%
Follow-up Time	No intervention time reported	82	11.57%
	1 to 30 days	52	7.33%

Characteristics	Category	Included literature	Record percentage(%)
	31 to 90 days	115	16.22%
	91 to 180 days	152	21.44%
	181 to 356 days	188	26.52%
	Over 356 days	120	16.93%

Table 3
Outcome indicator characteristics

Characteristics	Category	Included literature	Record percentage (%)
Main efficacy indicators	Retinal function indicators	326	45.98%
	Retinal anatomical features	181	25.53%
	Safety indicators	122	17.21%
	Outcome indicators of diabetic retinopathy progression	98	13.82%
	Retinal vascular and circulatory characteristics	70	9.87%
	Laboratory indicators	63	8.89%
	Treatment-related indicators such as number of treatments, treatment duration, and treatment frequency	56	7.90%
	Questionnaire	38	5.36%
	Ophthalmic characteristics	36	5.08%
	Difficult to classify	20	2.82%
	Physical examination	10	1.41%
	Cost-effectiveness	4	0.56%
Secondary efficacy endpoints	Retinal functional indicators	277	39.07%
	Retinal anatomical characteristics	241	33.99%
	Safety indicators	172	24.26%
	Outcome indicators of diabetic retinopathy progression	114	16.08%
	Treatment-related indicators such as number of treatments, treatment duration, and treatment frequency	109	15.37%
	Retinal vascular and circulatory characteristics	88	12.41%
	Laboratory indicators	78	11.00%
	Questionnaire	69	9.73%
	Ophthalmic characteristics	58	8.18%
	Difficult to classify	47	6.63%

Characteristics	Category	Included literature	Record percentage (%)
	Physical examination	24	3.39%
	Cost-effectiveness	12	1.69%
	Adverse reactions/Adverse events	240	33.85%
	Physical examination	58	8.18%
	Laboratory Parameters	7	0.99%
	Mark only "Safety Indicator"	19	2.68%

3.6 Outcome indicator characteristics

Retinal functional outcomes (e.g., visual acuity) were the most common primary endpoint (326 studies, 45.98%), followed by retinal anatomical parameters (e.g., CRT, CMT) (181 studies, 25.53%). Together, these "function plus structure" endpoints accounted for over 70% of primary outcomes. Safety outcomes (17.21%) and DR progression (13.82%) were the next most frequent. The distribution of secondary endpoints was similar but more diverse. Retinal functional outcomes remained the most prevalent (39.07%), while the proportion of studies reporting anatomical parameters Table 3 summarizes the distribution of primary, secondary, and safety outcome measures across the included studies.

3.7 Characteristics of Clinical Trial Design

RCTs were the predominant design (70.52%). Parallel-group designs were most common (76.02%), reflecting the focus on comparing therapeutic efficacy between groups. Blinding implementation varied significantly; open-label or partially blinded studies were the most frequent (30.47%), largely due to the practical challenges of blinding ophthalmic procedures. Single-center studies constituted the majority (51.34%), indicating that research remains largely institution-based. Active treatment controls were the most common comparator (59.38%), followed by placebo controls (22.99%), which were typically used in exploratory or add-on studies. Two-arm designs were the standard configuration (62.34%). The methodological features of the included studies are summarized in Table 4.

Table 4
Characteristics of Clinical Trial Design

Characteristics	Category	Included literature	Record percentage (%)
Allocation	Randomized	500	70.52%
	Non-randomised	56	7.90%
	Queue/Case-Control/Case-Only	46	6.49%
	Unknown	107	15.09%
Intervention Model	Parallel	539	76.02%
	Single Component	138	19.46%
	Cross-over Design	15	2.12%
	Grouped Sequencing Design	10	1.41%
	Factorial Design	3	0.42%
	Unknown	4	0.56%
Blind method: Implementing blindness	Open-label (no blinding)/partially open	216	30.47%
	Single blind	97	13.68%
	double blind	100	14.10%
	Triple Blind	63	8.89%
	Quadruple blind	49	6.91%
	Unknown/Unmarked	184	25.95%
Research Center	Single-center study	364	51.34%
	Multicenter (2–15 centers)	102	14.39%
	Multicenter (16–30 centers)	30	4.23%
	Multicenter (≥ 31 centers)	60	8.46%
	Multicenter(Unknown specific quantity)	40	5.64%
	Unknown	113	15.94%
Treatment regimen for the control group	Placebo Control	163	22.99%

Characteristics	Category	Included literature	Record percentage (%)
	Conventional Treatment Control	421	59.38%
Number of experimental groups	Single-arm design	135	19.04%
	Double-arm design	442	62.34%
	Three-arm design	93	13.12%
	Four-arm design	21	2.96%
	Design with more than five arms	14	1.97%
	Unknown	4	0.56%

4. Discussion

This study provides a comprehensive overview of the current landscape of clinical trials investigating diabetic retinopathy, thereby providing researchers with a structured reference to better inform future trial design. Prior research in this domain has predominantly centered on screening strategies and outcome prediction (22, 23). To date, however, no systematic review has specifically examined the methodological and design characteristics of interventional clinical trials for diabetic retinopathy. The present study therefore constitutes the first comprehensive assessment of diabetic retinopathy clinical trial features.

This study found that clinical research on diabetic retinopathy (DR) began to show an upward trend around 2005. This temporal inflection point closely coincides with the emergence of the anti-VEGF therapeutic era. In 2004, the U.S. Food and Drug Administration (FDA) approved bevacizumab for oncological indications, and the ophthalmology community rapidly initiated exploratory off-label intravitreal injection studies. In 2006, ranibizumab received FDA approval for neovascular age-related macular degeneration and was soon incorporated into clinical trials for DME. The emergence of this paradigm-shifting therapeutic approach fundamentally transformed the DR/DME treatment landscape, where laser photocoagulation had previously been the sole standard of care (24). This shift stimulated a substantial volume of clinical investigations addressing the efficacy, safety, and dosing regimens of anti-VEGF agents. Concurrently, the progressive adoption of optical coherence tomography (OCT) during this period provided a standardized tool for objective quantitative assessment of retinal thickness and lowered the imaging threshold for conducting clinical trials, further contributing to the growth in research output (25).

Between 2005 and 2017, DR clinical research maintained a steady growth trajectory. The principal drivers during this phase included the sequential publication of landmark multicenter randomized controlled

trials by the Diabetic Retinopathy Clinical Research Network (DRCR.net), such as Protocol I (2010, establishing ranibizumab combined with laser as the standard regimen for DME) and Protocol T (2015, a head-to-head comparison of ranibizumab, aflibercept, and bevacizumab). These studies generated high-quality evidence that directly catalyzed subsequent comparative and extension research. Additionally, the FDA approval of aflibercept for DME in 2011 expanded the therapeutic armamentarium and generated numerous studies comparing efficacy among different anti-VEGF agents. Furthermore, the sustained global rise in diabetes prevalence—with the International Diabetes Federation reporting an increase in the global diabetic population from approximately 151 million in 2000 to 425 million in 2017—progressively intensified the disease burden of DR/DME, objectively expanding both the eligible participant pool and the public health imperative for clinical research(26).

This study also revealed that research activity remained at a high level from 2019 through 2025 and is projected to sustain this trajectory into 2026. The maintenance of this high-level plateau reflects the synergistic effects of multiple converging factors. On one hand, post-marketing Phase IV studies, real-world evidence accumulation, and indication-expansion trials for newly approved agents (e.g., faricimab, brolucizumab, and high-dose aflibercept) continue to advance. On the other hand, next-generation therapeutic strategies—including gene therapy, complement pathway inhibitors, sustained-release tyrosine kinase inhibitor formulations, VEGF/FGF dual-target fusion proteins, and neurovascular unit protection strategies—are transitioning from preclinical investigation to clinical translation, thereby providing sustained momentum to the research pipeline. Furthermore, the rapid advancement of artificial intelligence-assisted DR screening and diagnostic technologies, coupled with the proliferation of telemedicine models, has opened new methodological dimensions for DR clinical research (27, 28).

Anti-VEGF combined with retinal laser photocoagulation accounted for 45.16% of the main combination regimens, a finding highly consistent with clinical practice. On one hand, anti-VEGF drugs (e.g., ranibizumab, aflibercept, bevacizumab) rapidly reduce macular edema and inhibit neovascular activity by neutralizing VEGF, with a fast onset but limited duration of action. Laser photocoagulation, by destroying high oxygen-consuming photoreceptor cells, fundamentally reduces retinal ischemia and hypoxia, thereby decreasing the sustained production of VEGF, offering durable efficacy but a slower onset. The combination achieves a synergistic effect of "short-term control and long-term consolidation." Seminal trials, including the Early Treatment Diabetic Retinopathy Study (ETDRS) and DRCR.net Protocol I, have collectively established the evidence base for current management strategies. Specifically, while ETDRS defined the diagnostic criteria and laser standards, Protocol I validated the efficacy of combination therapy, making it a standard treatment pathway for DME and PDR. This makes intravitreal injection combined with laser technically mature and highly reproducible, suitable for promotion across various levels of medical institutions. Anti-VEGF combined with glucocorticoids can treat patients who respond poorly to anti-VEGF therapy alone, but the adverse effects of hormones, such as increased intraocular pressure and accelerated cataract progression, limit their widespread use. The current main treatment regimen for CI-DME/PDR is centered on anti-VEGF therapy, with individualized plans optimized based on the patient's specific condition, suggesting that future research may further focus on the optimal timing

of combination regimens, the most suitable patient populations, and the exploration of novel combination strategies(29).

Regarding the characteristics of the study population in diabetic retinopathy research, 51.48% of studies only labeled "diabetes" without specifying the type. Since type 1 diabetes and type 2 diabetes have fundamental differences—type 1 diabetes is primarily characterized by absolute insulin deficiency, with DR progression often highly linearly correlated with disease duration; while type 2 diabetes is often associated with metabolic syndrome, insulin resistance, and chronic low-grade inflammation, and its DR may be occultly present before diagnosis—aggregating these distinct populations may introduce significant heterogeneity, weakening the external validity of the study conclusions(30). The predominance of CI-DME (29.34%) is consistent with current clinical practice, as center-involving DME is the core indication for anti-VEGF therapy and the main inclusion criterion for most RCTs.

89.84% of studies set clear ophthalmic examination standards. Although most studies established inclusion criteria, a relatively small number specified clear blood glucose control requirements (180 studies, 25.39%) and other examination standards (195 studies, 27.50%). In particular, the number of studies with blood glucose control standards and other laboratory indicator control standards was insufficient; most studies defined the target population based on diabetes history and ophthalmic examination indicators. A large number of experiments focused on populations with mild to moderate vision loss, with most using $> 300\mu\text{m}$ as the evaluation standard for central retinal thickness assessment in patients with macular edema (77 studies, 10.86%), and some studies targeted specific ophthalmic specialty populations(31, 32).

The sample sizes of diabetic retinopathy studies are generally small, which is related to the fact that PDR patients themselves are fewer, and it is difficult for a single center to produce clinical studies exceeding 100 cases(33). The establishment of multicenter collaborative networks, such as the DRCR.net series studies (Protocol I/T/V, etc.), RESTORE, RESOLVE, VISTA/VIVID, is needed to help reduce publication bias. Age standards are primarily focused on adults, consistent with normal research patterns. Gender standards did not impose restrictions, reflecting good awareness of external validity. Only one study was limited to males. Overall, reporting on the gender dimension is relatively standardized, but subsequent analyses should still pay attention to efficacy differences in gender subgroups. Baseline CRT values in women are usually lower than in men, which may affect the diagnostic threshold for DME and the assessment of treatment response.

Intervention timing is mostly individualized, often without fixed treatment numbers and frequencies. Follow-up time designs are predominantly medium to long-term, with studies of 91–365 days accounting for 47.96%. The conventional window for efficacy assessment after anti-VEGF therapy typically uses 6-month or 12-month primary endpoints, which is the main observation period design for most registered clinical trials(34).

Among the 709 studies analyzed herein, retinal functional indicators (represented by best-corrected visual acuity and visual field) constituted the largest proportion of primary efficacy endpoints (326

studies, 45.98%), followed by retinal anatomical parameters (represented by central retinal thickness and macular thickness, 181 studies, 25.53%), with the two combined accounting for over 70%. This distribution pattern fully reflects the dominant position of the "function and structure" dual-dimensional paradigm in current DR/DME efficacy evaluation. From a pathophysiological perspective, visual acuity reflects the patient's subjective visual benefit and is the recognized "gold standard" endpoint for anti-VEGF drug registration and approval by major international regulatory agencies (FDA, European Medicines Agency, National Medical Products Administration), while anatomical indicators such as CRT objectively quantify the extent of resolution of retinal edema via OCT, providing reproducible structural evidence for efficacy determination. The two are moderately correlated but not entirely consistent in DME treatment; some patients may exhibit a "function-structure dissociation" phenomenon with a significant decrease in CRT but limited improvement in visual acuity, suggesting the irreversibility of photoreceptor layer damage or the persistent impact of non-edematous factors (e.g., cataracts, ischemic maculopathy) on visual function. Therefore, the widespread adoption of the dual-dimensional evaluation system is supported by strong clinical rationale and methodological necessity.

DR progression indicators (98 studies, 13.82%) and retinal vascular/circulatory parameters (70 studies, 9.87%) constitute the second tier of the endpoint system. The former, centered on neovascular regression and DR stage improvement, reflects a fundamental modification of the disease's natural course rather than mere symptom control, possessing irreplaceable disease-modifying evaluation value in intervention studies for PDR and severe NPDR. The latter encompasses FFA non-perfusion area and hemodynamic indicators, which can reveal improvements in the core pathological mechanism of DR—microvascular ischemia—but their application is limited by the invasiveness of FFA, the lack of standardized Optical Coherence Tomography Angiography (OCTA) quantification, and high technical thresholds. With the increasing maturity of OCTA technology and the promotion of AI-assisted quantitative analysis, vascular/circulatory parameters are expected to play a more important role as endpoints in future research.

The distribution of secondary endpoints largely mirrors that of primary endpoints, but the reporting rates for all categories are generally higher (anatomical parameters from 25.53% to 33.99%, safety from 17.21% to 24.26%, questionnaires from 5.36% to 9.73%), indicating that researchers are attempting to incorporate more dimensional supplementary assessments beyond core efficacy evaluation, reflecting a trend towards diversification of the outcome evaluation system. However, an increase in the number of secondary endpoints without prior hierarchical design and multiple comparison correction may increase the risk of false-positive findings. Some studies may exhibit a tendency towards "endpoint selection bias," i.e., turning to secondary endpoints for positive results when the primary endpoint does not reach statistical significance, compromising the reliability of the study conclusions. Future studies should clearly prespecify the hierarchical structure of primary, key secondary, and exploratory endpoints, along with the statistical analysis plan, during the protocol registration phase to avoid post-hoc selective reporting.

In terms of safety assessment, adverse drug reactions/adverse events are the most commonly reported component (240 studies, 33.85%), forming the core of safety evaluation. Physical examinations (intraocular pressure measurement, blood pressure, etc.) were reported in 58 studies (8.18%). For anti-VEGF intravitreal injections, although the incidence of endophthalmitis, retinal detachment, and arterial thromboembolic events is low, their consequences are severe, requiring sufficient sample sizes and long-term follow-up for reliable assessment. Furthermore, anti-VEGF drugs can still enter the systemic circulation after intravitreal injection, posing a potential threat to diabetic patients with high cardiovascular risk factors.

Among the 709 studies included in this analysis, 70.52% (500 studies) used random allocation methods, indicating that RCTs constitute the main design type for DR/DME intervention studies. Parallel group designs accounted for 76.02% (539 studies), a high proportion highly consistent with the disciplinary characteristic of DR/DME research focusing on inter-group efficacy comparison. Parallel group designs achieve baseline balance between groups through concurrent randomization, effectively controlling for time-related confounding factors (e.g., natural disease progression, seasonal fluctuations), making them the optimal design choice for evaluating the relative efficacy of interventions.

The implementation of blinding showed significant heterogeneity. Open-label or partially blinded studies had the highest proportion (30.47%, 216 studies), followed by double-blind (14.10%), single-blind (13.68%), triple-blind (8.89%), and quadruple-blind (6.91%). This distribution clearly illustrates the inherent challenges in implementing blinding in ophthalmic intervention studies. Due to the operational process of intravitreal injection (needle penetration, injection sensation), the visibility of laser photocoagulation spots and post-operative reactions, and the surgeon's perception of surgical procedures, achieving complete blinding for both the operator and the patient is technically challenging.

Single-center studies accounted for 51.34% (364 studies), revealing the current decentralized, institution-based landscape of DR/DME research. Single-center designs offer advantages in implementation convenience, ethical review efficiency, and accumulation of researcher experience. However, the patient population drawn from a single institution is limited by geography, referral patterns, and population composition, constraining the external validity and generalizability of the study conclusions.

Placebo controls (22.99%) were mainly seen in two scenarios: first, exploratory studies (e.g., early proof-of-concept for novel target drugs), where no established effective comparator is available; second, add-on designs for evaluating the additional efficacy of combination therapies, where an experimental intervention is added to standard treatment, and a placebo simulates the additional procedure to isolate the independent contribution of the experimental intervention. The latter is methodologically sound but requires that the background treatment is consistent across all groups, and ethical review should fully assess the risk of delayed effective treatment for patients in the placebo group. This landscape reflects both the significant progress made in the methodological standardization of DR/DME intervention studies and exposes structural shortcomings such as difficulties in implementing blinding, insufficient multicenter collaboration, and limited application of complex designs.

5. Conclusion

This study systematically identifies the current landscape and shortcomings of DR intervention trials regarding study design, outcome evaluation, and safety assessment, offering guidance for the standardized conduct of future research.

Declarations

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The authors declare that no Generative AI was used in the creation of this manuscript.

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Authors' contributions

ZW: Conceptualization, Data curation, Methodology, Writing-original draft, Writing-review & editing. XL: Conceptualization, Writing-original draft, Writing-review & editing. MY: Conceptualization, Data curation, Methodology, Writing-original draft. GY: Conceptualization, Data curation, Methodology, Writing-original draft. XF: Conceptualization, Data curation, Methodology, Writing-original draft. JY: Conceptualization, Data curation, Methodology, Writing-original draft. JZ: Conceptualization, Data curation, Methodology, Supervision, Writing-original draft, Writing-review & editing. SY: Conceptualization, Data curation, Methodology, Writing-original draft, Writing-review & editing. CX: Conceptualization, Data curation, Methodology, Supervision, Writing-original draft, Writing-review & editing. Zixuan Wang contributed to this article. Correspondence should be addressed to Chen Xi and Yingjing Shi. All authors contributed to the article and approved the submitted version.

Availability of data and materials

All data related to the research are included in the article and Supplementary Material. The included trials were published on open access websites and databases. If necessary, contact the first author for information. The review did not require prior ethical approval and consent from the participants because it only involved previously published RCT studies.

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Figures

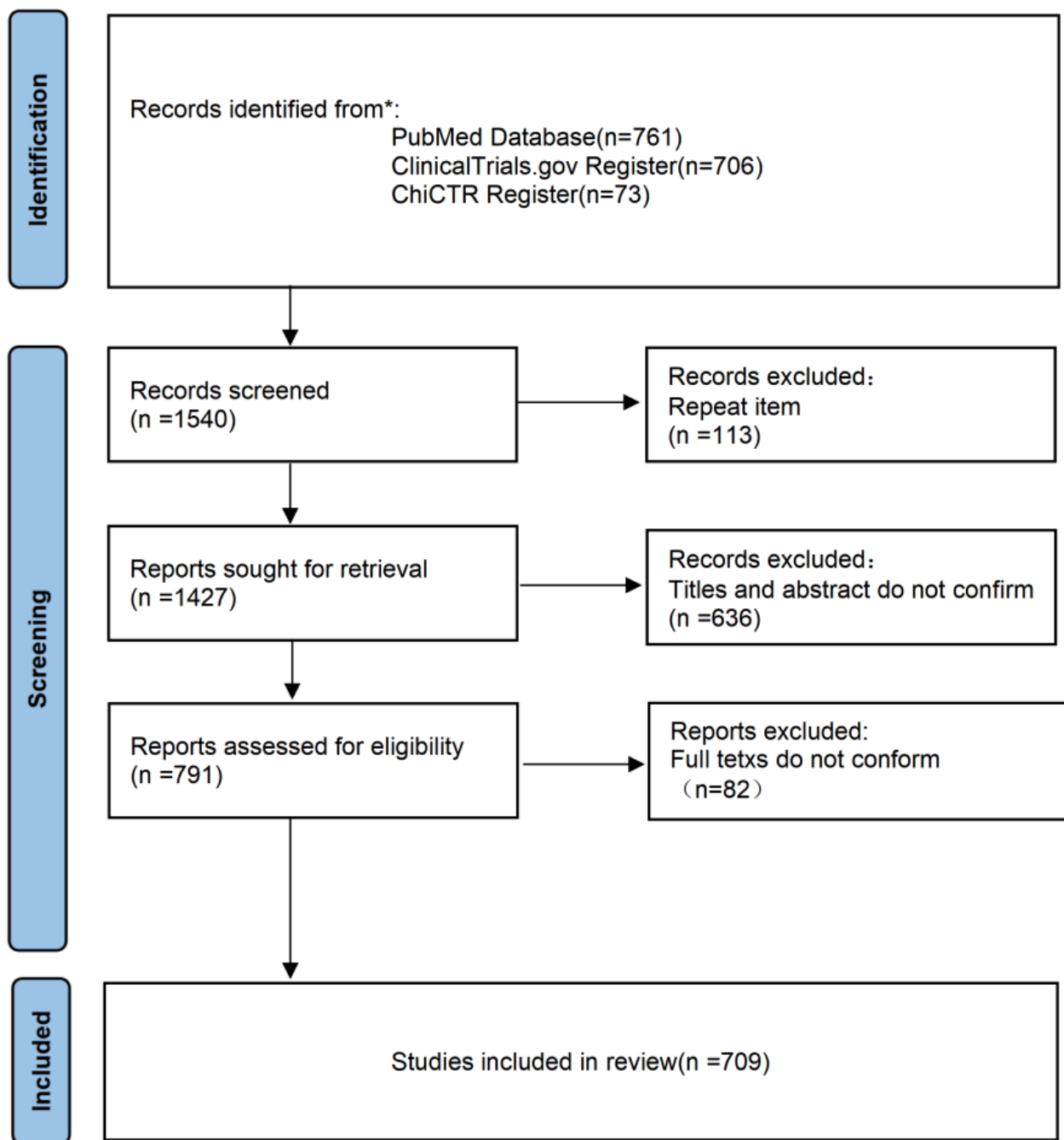


Figure 1

PRISMA Search Flowchart

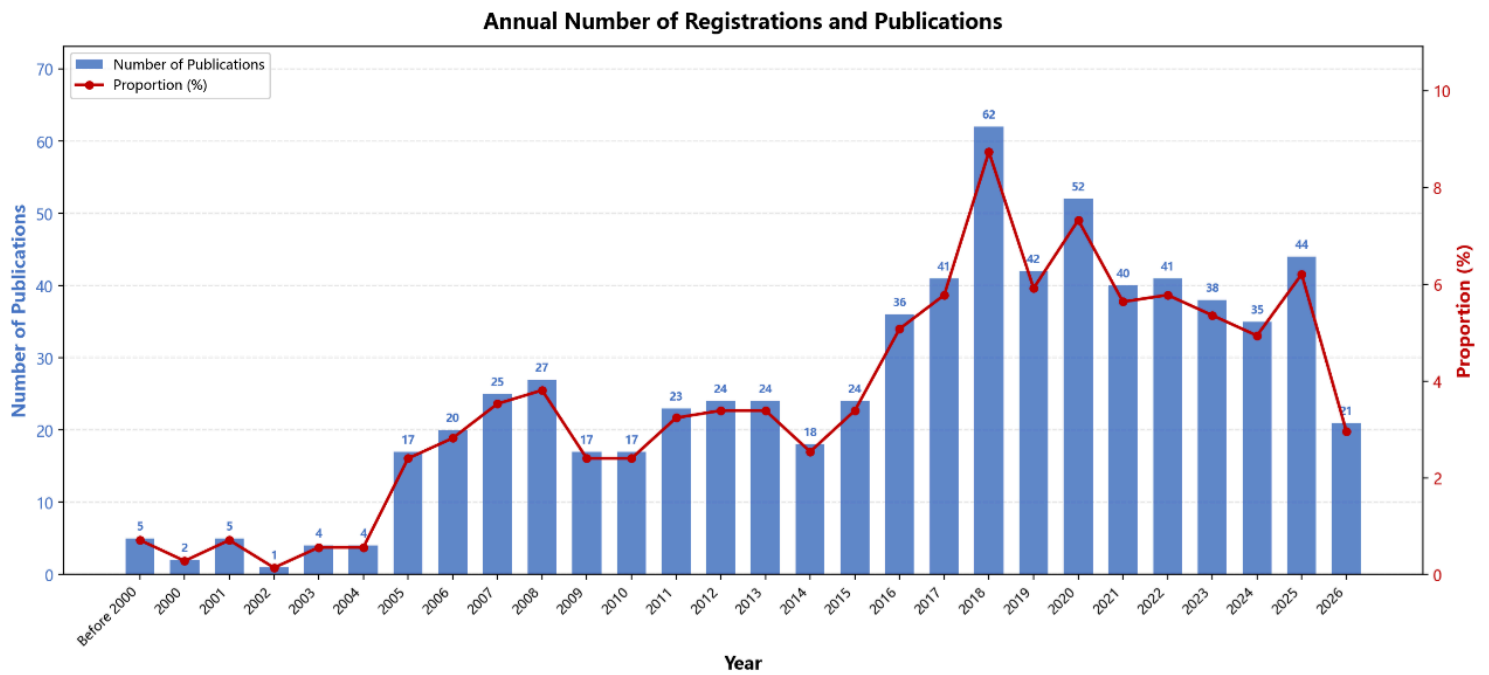


Figure 2

Annual number of registrations and publications: abscissa represents the year, left ordinate represents the proportion, and right ordinate represents the number.

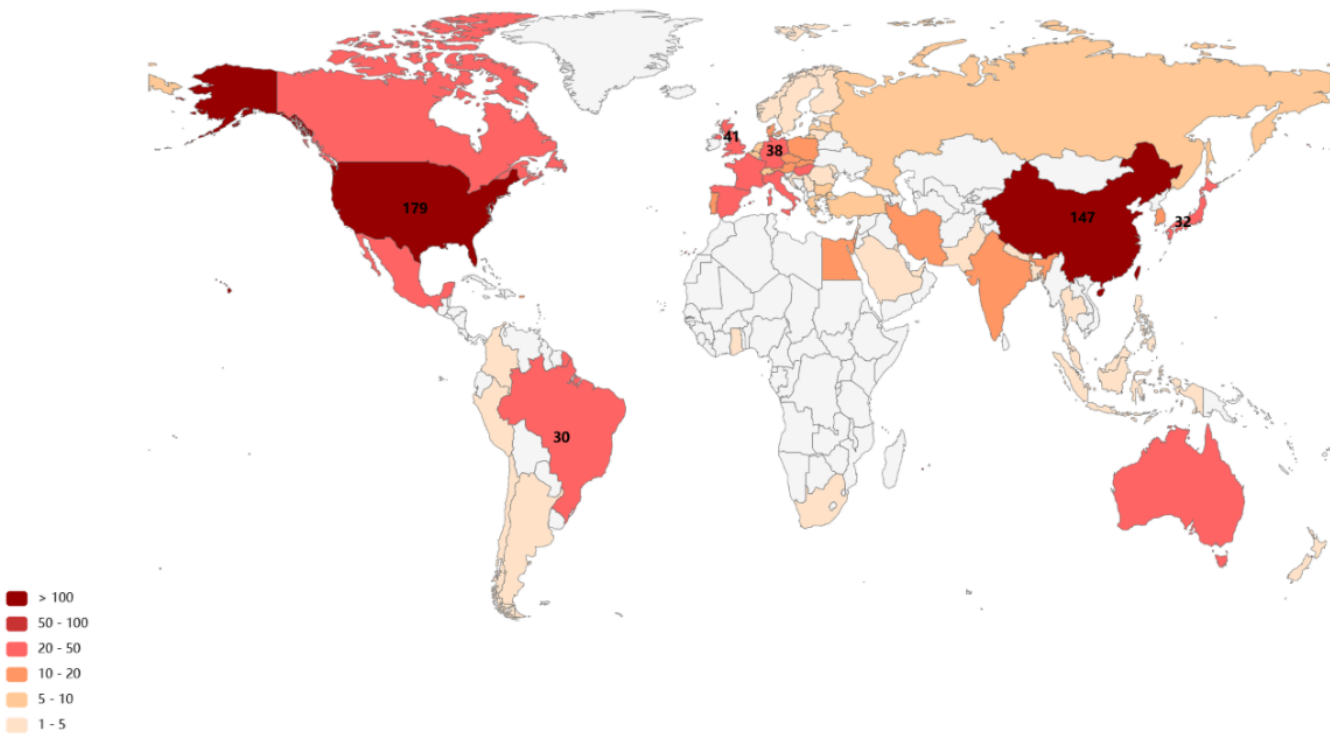


Figure 3

Published or registered country.

Combination Therapy - Percentage Ranking (Ascending)

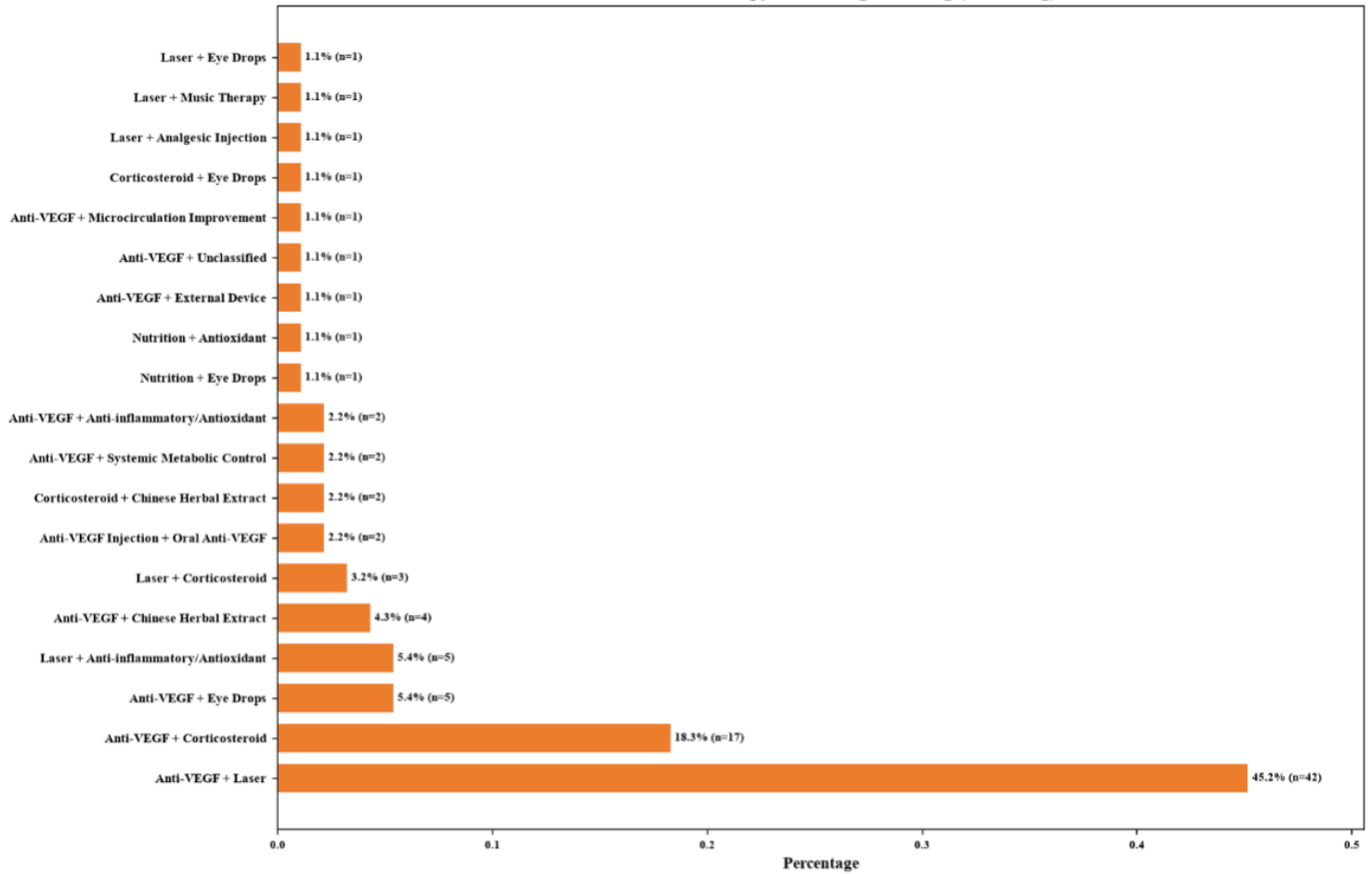


Figure 4

Classification of combination therapy

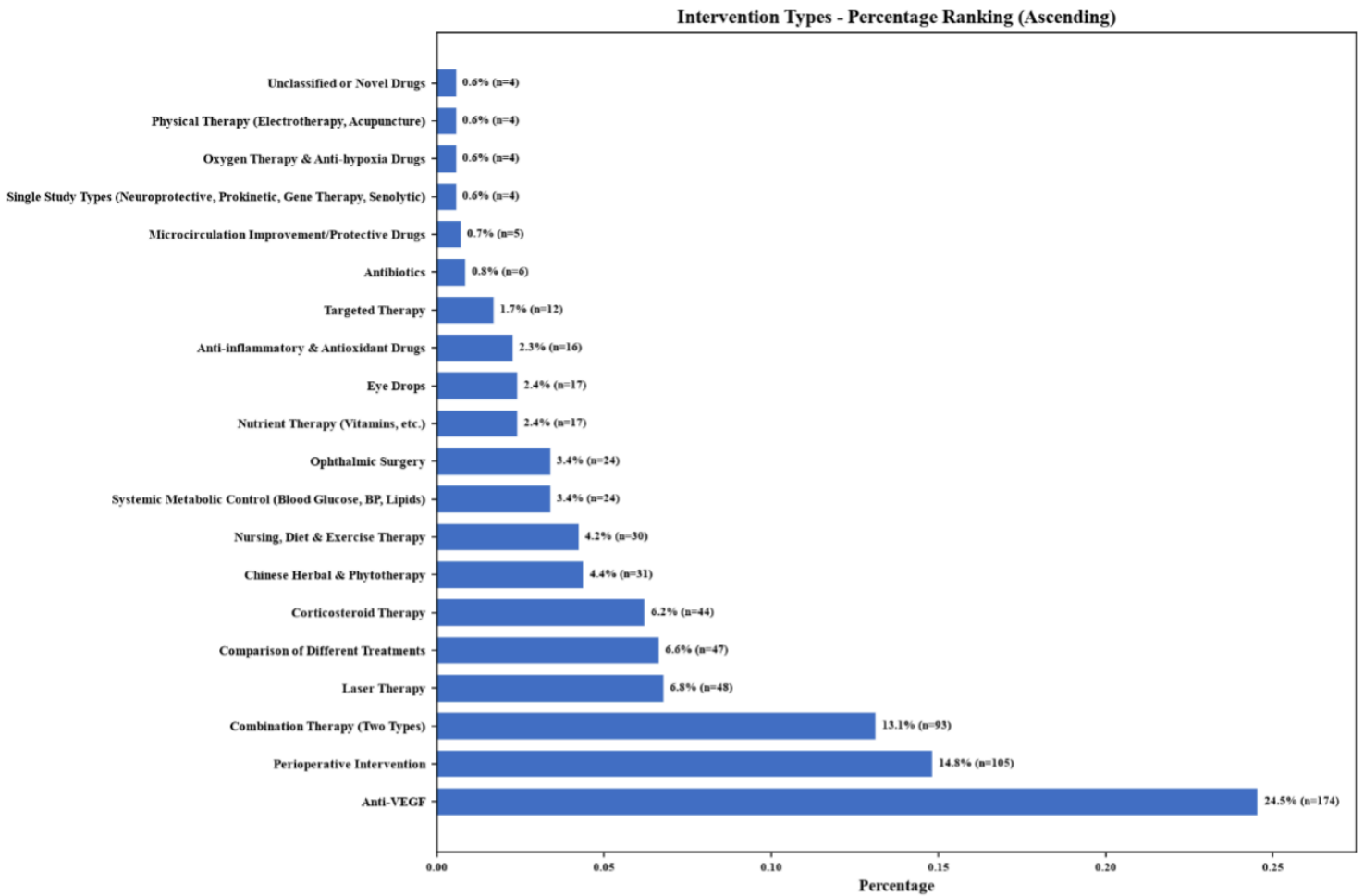


Figure 5

Classification of interventions.

Supplementary Files

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