

REVIEW PAPER

Advances in the management of retinopathy of prematurity: novel therapeutic approaches and evolving protocols for diagnosis and monitoring

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ABSTRACT

Retinopathy of prematurity (ROP) is a leading, largely preventable cause of childhood blindness in preterm infants, arising from disturbed retinal vascular development and multiple perinatal risk factors. The purpose of this narrative review is to synthesize current evidence on ROP epidemiology, pathophysiology, and modifiable risks, and to outline recent advances in diagnosis and management. We summarize the evolution from laser photocoagulation to intravitreal anti-vascular endothelial growth factor (VEGF) therapy, discussing benefits, limitations, and safety concerns, including persistent avascular retina and late reactivation. Emerging strategies such as dual VEGF/angiopoietin-2 blockade, insulin-like growth factor-1-targeted interventions and ultra-low-dose anti-VEGF regimens are briefly reviewed. We also highlight evolving screening paradigms – including wide-field imaging, optical coherence tomography, optical coherence tomography angiography, fluorescein angiography, teleophthalmology, and artificial-intelligence-supported tools – that may enable more individualized, risk-adapted ROP care and help reduce avoidable blindness worldwide.

KEY WORDS:

retinopathy of prematurity, anti-VEGF, neonatal ophthalmology, monitoring protocols.

INTRODUCTION

Retinopathy of prematurity (ROP) is a serious neonatal retinal disorder that can cause vision loss, characterized by an initial halt in vessel growth followed by abnormal neovascularization, driven by developmental immaturity and factors like oxygen exposure [1].

this process is interrupted at birth [1]. Postnatal hyperoxia suppresses HIF-1 α and key angiogenic factors such as vascular endothelial growth factor (VEGF) and IGF-1, halting vessel growth and sometimes causing regression [1, 2]. Additional oxygen-related stresses, including fluctuating saturations and developmental immaturity, further impair angiogenesis and leave large avascular retinal areas that predispose to the second phase of the disease [1].

PHASE I – SUPPRESSION OR REGRESSION OF PHYSIOLOGICAL VASCULARIZATION

Retinal vascular development normally progresses from the optic disc to the periphery, but in preterm infants,

PHASE II – PATHOLOGICAL NEOVASCULARIZATION

As the avascular retina's metabolic demand rises, hypoxia triggers excess VEGF and other proangiogenic fac-

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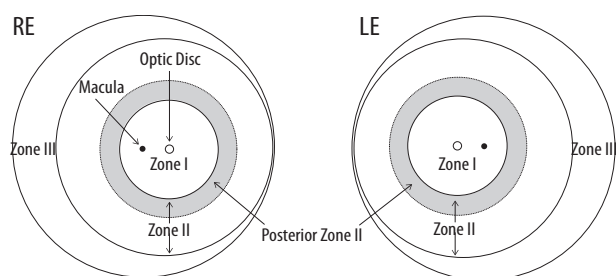


FIGURE 1. Zone borders in the right eye and left eye used to describe the localization of retinopathy of prematurity

LE – left eye, RE – right eye

tors. This reactivates vessel growth, but in a disorganized way: endothelial cells proliferate irregularly, forming abnormal neovascular tufts extending into the vitreous [2].

ZONES AND STAGES OF RETINOPATHY OF PREMATURITY

The International Classification of Retinopathy of Prematurity, Revisited (ICROP) should be used to classify and describe retinal changes [3]. Lesions are categorized into three zones: Zone I – the smallest and most posterior; Zone II – encircling zone I and Zone III – crescent-shaped, encompassing the most temporal peripheral retina. Figure 1 presents zone borders in ROP. Retinopathy of prematurity is staged according to lesion characteristics:

Stage 1 presents as a faint demarcation line separating vascularized from avascular retina, sometimes with abnormal posterior vessel branching, though peripheral vessel dilation or tortuosity alone does not confirm the diagnosis [3].

Stage 2 is characterized by an elevation of the demarcation line, with variable height and width, and coloration ranging from white to pink. Small, isolated neovascular tufts – often called “popcorn” – may appear posterior to the ridge but do not constitute Stage 3 [3].

Stage 3 is defined by extraretinal neovascularization growing from the ridge into the vitreous, sometimes appearing flat in Zone I or posterior Zone II, even without a clear ridge, with variable degrees of proliferative tissue [3].

Stage 4 ROP is a partial retinal detachment – either sparing the fovea (4A) or involving it (4B) – characterized by peripheral traction, loss of choroidal detail, and possible exudative or tractional components; optical coherence tomography (OCT) aids in detecting subtle foveal involvement [3].

Stage 5 represents total retinal detachment, classified as open-funnel (5A), closed-funnel (5B), or closed-funnel with anterior segment abnormalities such as lens displacement or corneal opacification (5C) [3].

In addition to staging and zonal classification, ICROP also recognizes the presence of plus disease. In the most recent revision, plus disease was defined as a spectrum of vascular abnormalities determined by the appearance of vessels within Zone I. Alongside these definitional re-

finements, representative reference images of plus disease have been published with each ICROP edition to support standardized clinical assessment [4].

RISK FACTORS

Low birth weight and gestational age (GA): these are key determinants of ROP severity. A lower birth weight and earlier GA increase the risk, as they are associated with greater retinal immaturity [2]. Oxygen exposure: excessive oxygen, insufficient oxygen, and fluctuations between them drive ROP by suppressing and then overstimulating VEGF, causing vessel regression followed by abnormal neovascularization. These shifts increase oxidative stress in preterm infants with limited antioxidant capacity. Lower oxygen saturation targets reduce severe ROP but raise mortality, highlighting the need for careful oxygen management [5]. Maternal factors: maternal contributors to ROP include chorioamnionitis [5], hypertensive disorders of pregnancy, and diabetes [6]. Chorioamnionitis may increase ROP risk through antenatal inflammation, yet findings vary, with some studies showing no association or even potential protective effects [5]. Hypertensive disorders show similarly conflicting results, ranging from increased risk to no effect or possible protection [6], and no clear consensus has been reached regarding the association between hypertensive disorders of pregnancy and ROP in preterm infants [7]. Maternal diabetes is more consistently linked to severe ROP, likely through fetal hyperglycemia, with gestational diabetes carrying a higher risk than hypertensive disorders of pregnancy [6].

Additionally, fetal hemoglobin (HbF) may serve as a potential biomarker for ROP because its proportion in early postnatal life influences oxygen delivery to the developing retina. Higher HbF levels, due to their greater oxygen affinity compared with adult hemoglobin, may limit excessive oxygen release and thereby reduce hyperoxia-related retinal injury. Conversely, reductions in HbF – particularly following adult red blood cell transfusions – may increase retinal oxygen exposure and contribute to ROP development. Therefore, monitoring HbF percentages during the first weeks of life could help identify preterm infants at higher risk of ROP and support strategies aimed at preserving HbF levels [8].

EPIDEMIOLOGY

Retinopathy of prematurity shows wide global variation in incidence and severity due to differences in neonatal care, screening, and survival of premature infants [9]. Between 1990 and 2021, an estimated 8.79 million cases of ROP-related visual loss were recorded globally (4.57 million males and 4.22 million females), with overall case numbers remaining relatively stable. Higher prevalence of visual loss was significantly associated with lower primary education completion, limited prenatal screening coverage, lower so-

cial insurance coverage, reduced nursing staff density, and higher out-of-pocket health expenditure. In 2021, the burden was concentrated in countries with a low and low-middle sociodemographic index, accounting for the majority of cases [10]. In the United States, around 14,000 infants are diagnosed annually. Across Europe, prevalence varies, with Sweden reporting ROP in 73% of infants born before 27 weeks (35% severe), compared with 26% of severe ROP in Belgium and 16% in Austria [9]. African countries show similarly broad variability: Egypt reports 19.2–69.4% incidence, Kenya 16.7%, and Nigeria 15–47.2% [11]. Asia accounts for about half of global preterm births and ROP-related blindness. Major contributors include India, China, Bangladesh, Pakistan, and Indonesia. Reported ROP incidence range is 20–51.9% in India (4.7–13.2% severe), 14–33% in the Philippines, 11.9–30.5% in Indonesia, and about 40.7% in Thailand [12].

In Poland, ROP screening covers infants ≤ 33 weeks or ≤ 1800 g, and those with complications suggesting elevated risk. Between 2012 and 2021, ROP incidence showed an overall rise, with diagnosis rates averaging 15.6% (2012–2019) and 18.3% (2016–2021). Screening reached about one-third of preterm infants, and diagnosis of ROP increased from 4.99% in 2016 to 9.34% in 2020, then fell to 6.12% in 2021. Overall, Poland's ROP prevalence and treatment rates remain lower than in many other European countries [13].

IMPORTANCE OF EARLY DIAGNOSIS AND TREATMENT

SIGNIFICANCE OF SCREENING

Early detection of ROP allows for close monitoring and timely intervention if the disease advances to a stage requiring treatment [14]. Stages 1, 2, or 3 ROP may regress spontaneously as the retinal vessels continue to develop naturally in some infants. However, when ROP progresses to Stage 3 accompanied by plus disease, treatment is essential to preserve vision. Without intervention, the condition may advance to Stages 4 and 5, characterized by retinal detachment and a high risk of blindness [15]. Additionally, children born prematurely may also develop chronic eye conditions such as strabismus, refractive errors, amblyopia and glaucoma due to impaired further development of vision and ROP-related retinal changes [16, 17]. Therefore, it is crucial to conduct timely ophthalmologic examinations for all at-risk preterm infants, even though not every child will require treatment [12].

SCREENING CRITERIA

Table 1 presents the recommended timing for the first ROP screening based on the infant's GA at birth [14]. The earliest cases of ROP occur within the current recommended screening windows [18]. Additionally, it should be

TABLE 1. Timing of the first screening based on gestational age at birth

Gestational age	Age at first examination (weeks)	
	Postmenstrual age	Postnatal age
22	31	9
23	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
31	35	4
32 (BW < 1501 g)	36	4
33 (BW < 1501 g)	36	3
34 (BW < 1501 g)	36	2
35 (BW < 1501 g)	36	1

BW – birth weight

emphasized that all infants who undergo ROP screening, regardless of whether treatment was required, should be evaluated by a pediatric ophthalmologist within 4–6 months after completion of ROP-related care. These visits focus not on monitoring retinal vascularization but on identifying ocular conditions that may affect visual development [17].

CAUSES OF DELAYED DIAGNOSIS

Retinopathy of prematurity diagnosis requires multiple follow-ups; missing these visits can result in delayed detection [19]. In a 2016 study by Azad *et al.* [19], among 115 infants diagnosed with Stage 5 ROP, 109 had never undergone prior screening. Due to the limited efficacy of surgical intervention at this stage, most patients suffered complete, irreversible vision loss [20]. Proper diagnosis is equally critical. Some clinicians face challenges in correctly identifying ROP [21]. Moreover, indirect ophthalmoscopy relies on subjective assessment, which can be influenced by previous observations, increasing diagnostic variability. In a 12-year longitudinal study by Zhao *et al.* [22] including 1860 preterm infants, weekly examinations conducted by the same ophthalmologist prevented retinal detachment and vision loss, highlighting the importance of consistent, regular follow-ups. Standardizing screening protocols may improve diagnostic consistency and ensure timely intervention.

IMPACT OF TIMING ON TREATMENT EFFICACY AND COMPLICATIONS

In a 2025 study by Yuan *et al.* [23], extreme micro- and nano-preterm infants were analyzed. Retinopathy

of prematurity was diagnosed in 524 infants (80.6%), with 180 (34.4%) detected at the first examination. Stage 3 ROP was present in 142 infants (22%), and type 1 treatment-requiring ROP (TR-ROP) was identified in 9 infants (1.4%) at the first or second neonatal unit examination. Timely screening allowed effective treatment, with only one infant progressing to bilateral Stage 4 ROP. These findings underscore the clinical significance of early, regular screening in high-risk populations. Stages 4 and 5 ROP require surgical intervention. Retinal reattachment is challenging, and functional recovery is restricted; even with successful reattachment (achieved in ~20–50% of patients), only ~20% achieve meaningful visual function, such as shape recognition or light perception. However, reattachment improves visual prognosis compared with the natural course of advanced ROP, and slight visual improvement may occur over time. Recurrence of detachment is observed in ~22% of Stage 5 cases vs. 5% in Stage 4, highlighting the need for long-term follow-up [24].

In a 2022 study by Moin *et al.* [20], infants who had not undergone prior ROP screening or treatment developed Stage 4 or 5 ROP. None retained normal visual function, and over 75% were bilaterally blind. These findings confirm the critical importance of screening at-risk preterm infants and preventing progression to Stage 5, as changes at this stage are largely irreversible.

EMERGING THERAPIES

TREATMENT MODALITIES BASED ON RETINOPATHY OF PREMATURITY TYPE AND STAGE

The retinopathy of prematurity is determined by the anatomical zone involved, the presence of active neovascular disease, and the overall clinical status of the infant. Type 1 ROP in Zone I generally requires prompt intervention with intravitreal anti-VEGF agents, either as monotherapy or in combination with adjunctive laser photocoagulation [25]. Type 1 ROP in Zone II is classified into two subtypes. In anterior Zone II disease, laser photocoagulation alone is considered effective due to the peripheral location of neovascularization relative to the fovea [3]. In posterior Zone II, intravitreal anti-VEGF monotherapy is preferred, as the disease occurs in close proximity to the macula and optic nerve head, where the retina is highly immature, exhibits increased angiogenic activity, and is more susceptible to laser-induced damage [3]. In Zone III, laser photocoagulation remains the treatment of choice for Type 1 ROP [26]. Type 2 ROP is typically managed with close observation every 1–3 days due to the high likelihood of spontaneous regression [3]. The stage of disease also plays a critical role in guiding treatment decisions. In conjunction with disease location (zone) and the presence or absence of plus disease, it determines whether ROP is classified as Type 1

or Type 2, and thus the recommended intervention [3]. Stages 1 and 2 without plus disease are managed with observation due to the mild or moderate degree of retinal neovascularization and high probability of spontaneous regression [27]. In contrast, Stages 2 and 3 with plus disease are classified as Type 1 ROP and require anti-VEGF therapy, particularly in Zone I and posterior Zone II, where neovascular proliferation forms tissue mass in close proximity to the fovea [27]. Advanced stages (Stage 4 and Stage 5) pose significant surgical challenges and require invasive intervention [28].

In a study by Bahrani *et al.* [29], 31 eyes of 19 infants underwent surgical intervention. All eyes received preoperative anti-VEGF therapy to facilitate retinal reattachment. Lens-sparing vitrectomy (LSV) was performed in 28 eyes, lens removal with vitrectomy in 3 eyes, and a scleral buckle was applied in one case. According to ICROP classification, 35.5% of eyes were Stage 4A, 45.2% were Stage 4B, and 19.4% were Stage 5A. The highest anatomical success rate was observed in Stage 4A (90.9%), reflecting partial retinal detachment, whereas lower success rates in Stage 4B and Stage 5 (57.1% and 33.3%, respectively) were attributed to foveal involvement or total retinal detachment. Lens vitrectomy was associated with a 100% recurrence or redetachment rate, emphasizing that advanced stages of ROP require aggressive interventions with a higher risk of complications.

Moreover, a systematic review and meta-analysis including 12 randomized controlled trials (RCTs) and 58 observational studies (10,516 infants) compared anti-VEGF therapy with laser photocoagulation. Anti-VEGF therapy was associated with lower risks of retinal detachment (RR 0.36), need for surgical intervention (RR 0.38), and myopia (RR 0.67). However, the pooled analysis suggested higher mortality mainly in observational studies, while RCTs showed no significant difference, highlighting the need for well-powered trials and long-term safety monitoring [30].

ANTI-VEGF THERAPY

Currently used anti-VEGF agents include bevacizumab (IVB), a full-length recombinant humanized monoclonal antibody targeting VEGF-A [31]; ranibizumab (IVR), a recombinant humanized monoclonal antibody fragment selectively binding VEGF-A [31]; and aflibercept (IVA), a recombinant fusion protein composed of extracellular domains from human VEGF receptors 1 and 2 fused to the Fc region of human IgG1, capable of binding VEGF-A, VEGF-B and placental growth factor (PlGF) [32]. Novel agents include conbercept (IVC), another recombinant fusion protein targeting VEGF-A, VEGF-B, and PlGF with broader anti-angiogenic activity [33], and faricimab (IVF), a bispecific antibody designed to inhibit both VEGF-A and angiopoietin-2 (Ang-2) [34]. These agents are administered intravitreally in low doses to achieve lo-

TABLE 2. Comparative overview of established and investigational therapies for retinopathy of prematurity, focusing on mechanisms, clinical development stage, and therapeutic potential

Category	Therapy	Mechanism/target	Stage of development	Advantages	Limitation
First generation anti-VEGF	IVB (bevacizumab)	VEGF-A inhibition [24]	Clinical practice [20]	Strong efficacy in Zone I [19]	Systemic suppression [28]
Next generation anti-VEGF	IVC (conbercept)	VEGF-A/B + PlGF [26]	Phase II/III [26]	Broader target profile [26]	Limited pediatric data
	IVF (faricimab)	VEGF-A + Ang-2 [27]	Phase II [27]	Dual pathway modulation [27]	No completed clinical trials in ROP
Future dosing strategy	Ultra-low-dose anti-VEGF	Reduced VEGF blockade [28]	Clinical investigation [30]	Minimizes systemic exposure [28]	Optimal dose not established [30]
Molecular/gene pathway therapies	IGF-1/IGFBP-3 supplementation	Physiological vascular maturation [32]	Phase II [32]	Mechanistic relevance [32]	No significant clinical outcomes yet
	Scutellarin	Ang-1 $\uparrow$ /Ang-2 $\downarrow$ /Tie2 $\uparrow$ [33]	Preclinical (<i>in vitro</i> /in silico) [32]	Dual angiogenic modulation [32]	No <i>in vivo</i> or human data [32]

Ang – angiopoietin, ROP – retinopathy of prematurity, VEGF – vascular endothelial growth factor

calized ocular effects with minimal systemic VEGF suppression [35]. IVB is commonly administered at a dose of 0.625 mg [20], whereas in the RAINBOW RCTs, IVR at a dose of 0.2 mg demonstrated superior efficacy compared with 0.1 mg [26]. In the FIREFLEYE trial, IVA at a dose of 0.4 mg resulted in clinically meaningful regression of active ROP [32]. Pharmacokinetic analysis from the RAINBOW study showed that IVR has minimal systemic exposure (plasma elimination half-life of approximately 0.3 days) and does not significantly reduce circulating VEGF levels, which are essential for neurodevelopment and pulmonary maturation [35]. In contrast, IVB exhibits prolonged systemic persistence (plasma elimination half-life of approximately 21 days), associated with sustained systemic VEGF suppression lasting up to eight weeks [31]. IVA demonstrates an intermediate plasma half-life of approximately 5–6 days [31]. Clinical data further support the efficacy of anti-VEGF therapy.

In a retrospective cohort study by Süren *et al.* [36] involving 2018 premature infants, 111 were diagnosed with ROP and treated with intravitreal anti-VEGF agents. Although regression was achieved across all treatment groups, IVB and IVA demonstrated lower retreatment rates (14.2% and 14.8%, respectively) compared with IVR (24.6%; $p < 0.05$), and time to recurrence was significantly longer in the IVB (12 ± 2.47 weeks) and IVA (13 ± 2.37 weeks) groups vs. the IVR group (8 ± 1.72 weeks; $p < 0.01$). Although anti-VEGF therapy has demonstrated superior efficacy in Zone I and posterior Zone II ROP, concerns remain regarding systemic VEGF suppression and potential long-term neurodevelopmental effects [35]. Additionally, anti-VEGF therapy provides temporary VEGF suppression; therefore, ROP may recur or reactivate after an initial period of quiescence, particularly when peripheral retinal vascularization remains incomplete (persistent avascular retina). This necessitates prolonged follow-up after anti-VEGF monotherapy until

vascularization is complete or laser has been applied to the persistent peripheral avascular retina [37].

EMERGING THERAPEUTIC STRATEGIES

Given the limitations of anti-VEGF monotherapy in fully promoting physiological retinal vascularization and preventing late reactivation, several novel therapeutic strategies are under investigation. Table 2 provides an overview of current and investigational therapies for ROP. Current research in the management of ROP focuses on multi-receptor agents such as faricimab and conbercept, modulation of non-VEGF angiogenic pathways, gene and cell-based therapies, and the use of ultra-low-dose anti-VEGF regimens [33, 34, 38, 39]. Gene therapy and cell-based approaches have gained considerable interest due to their potential to promote vascular maturation rather than solely inhibit pathological angiogenesis [39]. Current studies are evaluating microRNA inhibitors that bind target mRNA transcripts and prevent their degradation; however, this approach requires further assessment to determine the optimal gene delivery vector.

In recent years, there has also been a growing interest in targeting non-VEGF angiogenic pathways. According to a meta-analysis conducted by Almutairi *et al.* [40], IGF-1/IGF binding protein-3 axis demonstrates the strongest and most consistent correlation with severe ROP development, as premature birth abruptly disrupts placental IGF-1 transfer, resulting in postnatal IGF-1 deficiency [40]. These data support the mechanistic relevance of IGF-1, suggesting that restoration of physiological IGF-1 levels may hold therapeutic potential and warrants continued investigation.

Another promising area of investigation lies in therapies targeting the Ang-2/Tie2 signaling pathway. In a preclinical *in vitro* study by Ding *et al.* [41], scutellarin – a compound that restores the balance between Ang-1 and Ang-2 and

enhances Tie2 activation – was shown to significantly inhibit retinal neovascularization at concentrations of 5 μ M and 50 μ M under hypoxic conditions. Furthermore, *in silico* molecular docking analysis demonstrated a favorable theoretical binding affinity of scutellarin to angiogenic targets ($p < 0.01$); however, these findings are limited to *in vitro* and *in silico* models, and no *in vivo* or clinical efficacy has yet been established [41]. Dual inhibition of VEGF and Ang-2 has been shown to be more effective than VEGF inhibition alone, due to the complementary regulation of angiogenic pathways that influence both vascular permeability and pathological neovascularization [42].

SHIFTS IN MONITORING PROTOCOLS AND DIAGNOSTIC APPROACHES

TRADITIONAL AND MODERN DIAGNOSTIC METHODS IN THE ASSESSMENT OF RETINOPATHY OF PREMATURITY

Binocular indirect ophthalmoscopy (BIO) remains the clinical gold standard for the diagnosis and monitoring of ROP, enabling high-resolution, dynamic assessment of vascularization, disease zone, and stage after pharmacologic pupil dilation [43, 44]. Although BIO allows real-time evaluation of the retina, its applicability is limited by physiological and organizational constraints. The examination is associated with stress and cardiovascular and respiratory burden, often necessitating pain mitigation (e.g., sucrose solution) [43, 45]. Moreover, it is time-consuming, requires the ophthalmologist's physical presence at the incubator, and is difficult to scale for large patient volumes [44]. Substantial inter-observer variability, especially in the assessment of plus disease, reflects the intrinsic subjectivity of the method [46]. Despite these limitations, BIO remains the reference standard in clinical practice and is essential in cases of incomplete or suboptimal digital imaging [46].

Recent efforts to reduce subjectivity in the assessment of disease plus have focused on quantitative analysis of retinal vessels. In the third edition of the ICROP3, indices of tortuosity (TI) of major vessels in the temporal quadrant demonstrated a gradual increase from Stages 1–6 for both arteries and veins, as well as for the combined TI values. Arterial tortuosity increased more prominently than venous tortuosity in the early stages, whereas Stage 6 showed a marked increase in venous tortuosity. The arterial-to-venous TI ratio (A/V) rose from Stages 1–3, remained stable at Stages 3–5, and reached its highest value at Stage 6. Analysis of data from real-world clinical cases confirmed increases in both arterial and venous TI in eyes without plus disease, with pre-plus, and with plus disease, although without a consistent rise in the A/V ratio. These findings support the concept that plus disease represents a continuum rather than a discrete, separate category, and demonstrate that quantitative vascular met-

rics may reduce interobserver variability and improve diagnostic objectivity [47]. Digital wide-field retinal documentation, such as the RetCam system, enables acquisition and archiving of high-quality fundus images and their remote evaluation within tele-screening programs for ROP [48]. This technology allows partial standardization of image acquisition, although significant inter-center variability persists due to differences in protocols and operator experience. The field of view may be insufficient for peripheral pathology, often necessitating complementary BIO evaluation [48, 49]. Image quality depends on patient stability and operator skill, and motion artifacts can limit the evaluation of vascular abnormalities such as plus disease [48, 49]. Emerging technologies, including artificial intelligence (AI) algorithms and ultrawide-field OCT, show promise in improving diagnostic consistency but still require rigorous clinical validation [48].

Optical coherence tomography and OCT angiography (OCTA) provide non-invasive, high-resolution assessment of retinal morphology and microcirculation [50, 51]. Portable systems allow imaging in unsedated preterm infants, though limitations include a relatively small field of view, motion artifacts, and the absence of unified interpretation norms [51, 52]. High costs and the need for trained personnel restrict their widespread adoption, although advances in automated analysis increase their future potential [52, 53]. Fluorescein angiography (FA) enables precise visualization of the vascularization boundary and retinal perfusion, supporting early detection of abnormalities and potentially informing decisions regarding laser or anti-VEGF therapy, though it is not routinely required for treatment qualification [54]. Fluorescein angiography is time-consuming, requires specialized expertise, and carries risks such as transient bradycardia or oxygen desaturation [54, 55]. B-scan ultrasonography remains useful when optical media are opaque, allowing assessment of complications such as tractional membranes or retinal detachment, though its low resolution and inability to visualize vascular flow limit its role to an adjunctive modality [55]. Overall, BIO remains the foundational diagnostic tool and reference point for newer imaging technologies, while digital imaging, OCT/OCTA, and FA enhance the analytical capabilities of ROP assessment but require further standardization and cost reduction [48, 50, 56]. The main limitations of these imaging modalities are summarized in Table 3.

TELEMEDICINE AND ARTIFICIAL INTELLIGENCE IN RETINOPATHY OF PREMATURITY DIAGNOSTICS

Telemedicine in ROP screening is built on four pillars: standardized image acquisition, the use of trained technicians, secure data transmission, and clearly defined referral and triage criteria [56]. Wide-field digital fundus imaging serves as the reference standard for image acquisition in tele-ROP (tROP) programs and as the benchmark

TABLE 3. Key limitations of imaging modalities used in screening and management of retinopathy of prematurity

Limitation	BIO	Wide-field digital imaging	OCT/OCTA	FA	B-scan
Subjective, dependent on the examiner experience	+	+	+	+	+
Physiological stress/discomfort for the infant	+	–	+/–	+	–
Time-consuming/difficult to scale	+	+	+	+	–
Limited peripheral field of view	–	+	+	+/–	–
Motion artifacts	–	+	+	+	+
Operator-dependent acquisition/interpretation	+	+	+	+	+
High equipment/infrastructure cost	–	+	+	+	+
Lack of standardization/normative datasets	–	+/–	+	+	+
Low resolution of fine anatomical structures	–	+	–	–	+

BIO – binocular indirect ophthalmoscopy, FA – fluorescein angiography, OCT – optical coherence tomography, OCTA – optical coherence tomography angiography

for validating new imaging technologies, though not as the clinical gold standard of diagnosis, which remains BIO [57]. Due to the global shortage of pediatric ophthalmologists, image acquisition is increasingly delegated to trained technicians and nurse imagers. Programs such as Vision on Wheels, Karnataka Internet-Assisted Diagnosis of Retinopathy of Prematurity (KIDROP), Stanford University Network for Diagnosis of Retinopathy of Prematurity (SUNDROP), and the Danish tROP have demonstrated high agreement between local personnel and remote experts ($\kappa \approx 0.82$) [58, 59]. Teleophthalmology systems must comply with strict data-security regulations (e.g., GDPR – General Data Protection Regulation, HIPAA – Health Insurance Portability and Accountability Act), while privacy-preserving approaches such as federated learning mitigate data-exposure risks [57]. Lower-cost smartphone-based fundus imaging (SBFI) systems show high sensitivity for TR-ROP (as defined by early treatment for retinopathy of prematurity criteria) and referral-war-ranted ROP (a telemedicine classification indicating disease that requires ophthalmic evaluation), with some studies reporting sensitivity approaching 100% for both expert graders and AI algorithms in selected protocols [60]. Hybrid models, technician acquisition, AI-based preliminary analysis, and expert verification represent the most scalable and equitable implementation pathway, provided that acquisition standards and operator training are maintained [56, 57]. Substantial clinical evidence supports the effectiveness of telemedicine in ROP screening. In the SUNDROP cohort, sensitivity reached 100%, specificity 99.8%, positive predictive value 95.5%, and negative predictive value 100% [56]. In a study of 267 infants (median GA 32 weeks, birth weight 1,780 g), telemedicine identified an identical incidence of ROP (6.7%) compared with bedside BIO [60]. Other analyses (156 infants, 312 eyes) demonstrated 100% sensitivity and 83.5% specificity for human graders, and AUROC values of 0.95–0.96 for AI systems [57]. The Danish tROP program reported interobserver agreement of $\kappa = 0.82$ [59]. Collectively, these findings indicate that telemedicine maintains diagnostic performance comparable to indirect

ophthalmoscopy while improving screening access and equity [56, 57, 59].

Artificial intelligence plays a central role in tROP workflows through automated image analysis and standardized evaluation of retinal findings [61]. Multicenter validations show high performance of deep-learning models and improved reproducibility in plus disease assessment using quantitative metrics such as the vascular severity score (VSS) [48, 49]. Algorithm performance depends strongly on training data quality (e.g., SUNDROP, KIDROP, AECS – Aravind Eye Care System) and image preprocessing (illumination normalization, color harmonization) [62, 63].

Recent studies emphasize that the development of reliable AI-based ROP systems requires access to well-annotated, publicly available datasets, as many earlier models were trained on single-center data with limited generalizability. The recently introduced Macretina dataset, comprising 1,432 wide-field retinal images of 112 premature infants, addresses several limitations of prior public resources by providing expert-verified, multi-task annotations for ridge detection, optic disc localization, and retinal vessel segmentation within a single framework. Importantly, the dataset includes severe aggressive ROP cases and reflects real-world neonatal screening conditions in low- and middle-income settings. Experimental validation using deep convolutional neural networks demonstrated consistent performance across classification, detection, and segmentation tasks, supporting its suitability for clinically relevant and generalizable AI model development [64].

Artificial intelligence facilitates prioritization of high-risk cases, reduces clinician workload, and can be deployed even on low-cost SBFI systems [61–63]. Studies have further advanced automated ROP classification through hybrid deep learning architectures that combine convolutional feature extraction with sequential modeling. A decision-explainable screening system, developed using the HVDROPDB-STAGE and HVDROPDB-PLUS datasets, employs a MultiCNN_LSTM framework, integrating features extracted from pretrained networks. This approach enables Stages 1–3 classification based on ridge

segmentation, as well as detection of pre-plus/plus disease on RetCam and Neo images [65].

The MultiCNN_LSTM and MultiCNN_DNN models achieved state-of-the-art performance, with accuracy, F1-score, and receiver operating characteristic (ROC) values reaching up to 93% for stage classification, and the highest metrics reported for pre-plus/plus/normal classification. Although the datasets are derived from a single regional population and require further expansion for broader generalization, the findings demonstrate that multi-feature fusion strategies substantially improve stage and plus disease detection, while potentially reducing interobserver variability and screening workload [65].

From a health-economic perspective, simulation models suggest potential improvements in cost-efficiency, particularly in resource-limited settings, although unified imaging standards and regulatory validation remain essential [59, 63]. Predictive models (WINROP-like systems, VSS-based thresholds, telemedicine retinopathy of prematurity severity score [tROP-SS]) and retrospective analyses indicate that integrating clinical and imaging data can safely extend follow-up intervals for low-risk infants, reducing visit numbers by 25–75% while maintaining high sensitivity for detecting TR-ROP [58, 63].

Recently, tROP-SS underwent extensive multicenter validation within the tROP network, encompassing 14 neonatal intensive care units and 2,037 infants over a seven-year period. Across 11,368 ROP examinations (192,704 images), tROP-SS generated severity assessments in all cases (100%), significantly outperforming the modified ROP activity score (mROP-ActS), which provided valid results in 92.3% of examinations and only 40.0% of treated cases [66].

Among high-risk and treatment-eligible infants, tROP-SS maintained full assessment availability, whereas mROP-ActS showed substantial rates of invalid results. Increments in tROP-SS were more strongly associated with disease progression (OR 3.37 vs. 1.57, $p < 0.0001$), and ROC curve analysis demonstrated superior discriminative ability (AUC 0.991 vs. 0.825). These findings confirm the robustness, granularity, and multicenter generalizability of tROP-SS as a telemedicine-based severity metric, enabling accurate monitoring of disease progression and treatment risk across diverse clinical settings [66].

Continuous quality assurance, periodic revalidation, and close integration with local care pathways are crucial for timely referral of high-risk cases and seamless documentation in electronic medical records [61, 63].

The future of ROP diagnostics lies in deeper integration of AI with telemedical platforms, real-time image analysis, and automated data synchronization. The human-in-the-loop model, combining algorithmic automation with expert oversight, increases safety and transparency in clinical decision-making [60, 62]. Key development priorities include standardization of acquisition protocols, interoperable data formats, multicenter validation, and

robust methods for automated image-quality assessment and color harmonization, elements crucial for AI stability [54]. As miniaturized and mobile imaging systems expand access, responsible implementation requires addressing ethical and regulatory concerns to ensure that AI augments, rather than replaces, clinical judgment. Equally important is the need for interpretable outputs and continuous validation across diverse populations [62, 63].

CONCLUSIONS

Retinopathy of prematurity remains a preventable cause of childhood blindness. Its biphasic pathophysiology, driven by retinal immaturity, oxygen dysregulation, and angiogenic and inflammatory pathways, interacts with maternal, perinatal, and neonatal risk factors. Geographic variation in incidence, screening access, and treatment availability shows that ROP is also a health-system challenge. Management has evolved from cryotherapy through laser photocoagulation to intravitreal anti-VEGF therapy, with zone-adapted algorithms balancing rapid disease regression and preservation of peripheral retina against the risks of persistent avascular retina, late reactivation, and possible systemic VEGF suppression. Surgery for advanced stages remains technically demanding with guarded visual outcomes. Emerging approaches, including dual-pathway angiogenic modulation, ultra-low-dose anti-VEGF regimens, and early gene- or cell-based strategies, together with biomarkers of vascular activity, may support more individualized, mechanism-based treatment. In parallel, advances in wide-field imaging, optical coherence tomography, teleophthalmology, digital surveillance, and AI-assisted grading enable more objective, risk-adapted screening and may extend access in under-resourced settings, provided that image quality, validation, and data security are assured. Future priorities include long-term safety studies of novel therapies, multicenter evaluation of digital tools, and close collaboration between neonatology, ophthalmology, and health-system stakeholders to implement equitable, evidence-based ROP care and prevent avoidable blindness in preterm infants.

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REFERENCES

1. Dammann O, Hartnett ME, Stahl A. Retinopathy of prematurity. *Dev Med Child Neurol* 2023; 655: 625–631.
2. Kaur K, Mikes BA. Retinopathy of prematurity. In: StatPearls. Treasure Island (FL): StatPearls 2025. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK562319/>.

3. Chiang MF, Quinn GE, Fielder AR, Ostmo SR, Chan RVP, Berrocal A, et al. International Classification of Retinopathy of Prematurity, 3rd ed. *Ophthalmology* 2021; 128: e51-e68.
4. Wang W, Freedman SF, Wallace DK, Pralapakorn SG. Quantitative comparison of vascular characteristics of plus disease images published over time: International Classification of Retinopathy of Prematurity. *J AAPOS* 2025; 29: 104101.
5. Prasad M, Ingolfssland EC, Christiansen SP. Modifiable risk factors and preventative strategies for severe retinopathy of prematurity. *Life (Basel)* 2023; 13: 1075.
6. Kim SJ, Port AD, Swan R, Campbell JP, Chan RVP, Chiang MF. Retinopathy of prematurity: a review of risk factors and their clinical significance. *Surv Ophthalmol* 2018; 63: 618-637.
7. Katsuki S, Ushida T, Nakatochi M, Kobayashi Y, Tano S, Matsuo S, et al. Hypertensive disorders of pregnancy and retinopathy of prematurity in extremely preterm infants: a causal mediation analysis. *Pregnancy Hypertens* 2026; 43: 101410.
8. Fevereiro-Martins M, Aguiar L, Inácio Â, Cardoso C, Santos AC, Marques-Neves C, et al. Fetal Hemoglobin as a predictive biomarker for retinopathy of prematurity: a prospective multicenter cohort study in Portugal. *Biomedicines* 2025; 13: 110.
9. Nair A, El Ballushi R, Anklesaria BZ, Kamali M, Talat M, Watts T. A review on the incidence and related risk factors of retinopathy of prematurity across various countries. *Cureus* 2022; 14: e32007.
10. Wong ES, Choy RW, Zhang Y, Chan HY, Chen LJ, Pang CP, et al. Global and regional trends in retinopathy of prematurity. *JAMA Ophthalmol* 2026; 144: 139-147.
11. Wang D, Duke R, Chan RP, Campbell JP. Retinopathy of prematurity in Africa: a systematic review. *Ophthalmic Epidemiol* 2019; 26: 223-230.
12. Azad R, Gilbert C, Gangwe AB, Zhao P, Wu WC, Sarbajna P, et al. Retinopathy of prematurity: how to prevent the third epidemics in developing countries. *Asia Pac J Ophthalmol (Phila)* 2020; 9: 440-448.
13. Modrzejewska M, Bosy W. Nine-year epidemiological data on the incidence of retinopathy of prematurity in Poland—a literature review for the 2012–2021 period. *Int J Environ Res Public Health* 2022; 19: 15694.
14. Fierson WM. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2018; 142: e20183061.
15. Agrawal R, Kulkarni S, Walambe R, Kotecha K. Assistive framework for automatic detection of all the zones in retinopathy of prematurity using deep learning. *J Digit Imaging* 2021; 34: 932-947.
16. Luse EM. Ophthalmic outcomes in preterm infants. *Neoreviews* 2025; 26: e411-e418.
17. Xing SX, Hyman N, Kim DK, Horowitz JD, Hark LA, Rosenberg SE, et al. Adherence to pediatric ophthalmology follow-up after completion of retinopathy of prematurity: a retrospective review. *Patient Prefer Adherence* 2026; 20: 582716.
18. Vinekar A, Jayadev C, Dogra M, Shetty B. Improving follow-up of infants during retinopathy of prematurity screening in rural areas. *Indian Pediatr* 2016; 53: S151-S154.
19. Azad R, Chandra P, Gangwe A, Kumar V. Lack of screening underlies most stage-5 retinopathy of prematurity among cases presenting to a tertiary eye center in India. *Indian Pediatr* 2016; 53: S103-S106.
20. Moin M, Mian LS, Gilbert C, Irfan A, Mian UK. Blindness in infants presenting with advanced and untreated ROP: a single-centre study in Pakistan. *BMJ Open Ophthalmol* 2022; 7: e000911.
21. Norman M, Hellström A, Hallberg B, Wallin A, Gustafson P, Tornqvist K, et al. Prevalence of severe visual disability among preterm children with retinopathy of prematurity and association with adherence to best practice guidelines. *JAMA Netw Open* 2019; 2: e186801.
22. Zhao CS, Brant AR, Shah SV, Wood EH, Koo E, Antonini RE, et al. Long-term retinopathy of prematurity outcomes with mandated screening interval and grader continuity at a high-volume quaternary center. *Am J Ophthalmol* 2025; 279: 147-155.
23. Yuan M, Altamirano F, Hu D, Hoyek S, Chaaya C, Abidi M, et al. Timing of retinopathy of prematurity diagnosis and treatment in micro-premature and nano-premature infants during inpatient screening. *Ophthalmol Retina* 2025; S2468-6530(25)00252-0.
24. Sen P, Jain S, Bhende P. Stage 5 retinopathy of prematurity: an update. *Taiwan J Ophthalmol* 2018; 8: 205-215.
25. Nowroozzadeh MH, Sadeghi E, Shahriari-Garaee H, Badie MR, Banihashemi J, Garg SJ. An update on anti-vascular endothelial growth factor treatment for retinopathy of prematurity. *J Curr Ophthalmol* 2023; 35: 125-134.
26. Wang AT, Dai S. Preferred treatment patterns of retinopathy of prematurity: an international survey. *Pediatr Rep* 2024; 16: 816-822.
27. Bishnoi K, Prasad R, Upadhyay T, Mathurkar S. A narrative review on managing retinopathy of prematurity: insights into pathogenesis, screening, and treatment strategies. *Cureus* 2024; 16: e56168.
28. Sen P, Bhende P, Maitra P. Surgical outcomes in aggressive retinopathy of prematurity (AROP)-related retinal detachments. *Indian J Ophthalmol* 2023; 71: 3454-3459.
29. Bahrani HM, Alhasseny KF. Vitrectomy results for stages 4 and 5 retinopathy of prematurity in Iraq. *Clin Ophthalmol* 2023; 17: 4033-4041.
30. Wang WD, Yao YH, Lan CH, Hung SH, Tsung TH, Chen YG, et al. Impact of anti-VEGF therapy versus laser therapy on mortality and treatment outcomes in retinopathy of prematurity: a systematic review and meta-analysis. *Acta Ophthalmol* 2026; 104: e1-e17.
31. Dogra MR, Vinekar A. Role of anti-vascular endothelial growth factor (anti-VEGF) in the treatment of retinopathy of prematurity: a narrative review in the context of middle-income countries. *Pediatric Health Med Ther* 2023; 14: 59-69.
32. Stahl A, Azuma N, Wu WC, Lepore D, Sukgen E, Nakanishi H, et al. Correction: Systemic exposure to aflibercept after intravitreal injection in premature neonates with retinopathy of prematurity: results from the FIREFLYE randomized phase 3 study. *Eye (Lond)* 2024; 38: 1599-1600.
33. Wu Z, Zhao J, Lam W, Yang M, Chen L, Huang X, et al. Comparison of clinical outcomes of conbercept versus ranibizumab treatment for retinopathy of prematurity: a multicenter prospective randomised controlled trial. *Br J Ophthalmol* 2022; 106: 975-979.
34. Chaudhary V, Mar F, Amador MJ, Chang A, Gibson K, Jousen AM, et al. Emerging clinical evidence of a dual role for Ang-2 and VEGF-A blockade with faricimab in retinal diseases. *Graefes Arch Clin Exp Ophthalmol* 2025; 263: 1239-1247.
35. Fidler M, Fleck BW, Stahl A, Marlow N, Chastain JE, Li J, et al. Ranibizumab population pharmacokinetics and free VEGF pharmacodynamics in preterm infants with retinopathy of prematurity in the RAINBOW trial. *Transl Vis Sci Technol* 2020; 9: 43.
36. Sören E, Özkaya D, Çetinkaya E, Kalaycı M, Yiğit K, Küçük MF, et al. Comparison of bevacizumab, ranibizumab and aflibercept in retinopathy of prematurity treatment. *Int Ophthalmol* 2022; 42: 1905-1913.
37. Kumawat D, Kandasamy S, Chandra P. Reactivation of retinopathy of prematurity after anti-VEGF treatment: a review. *Br J Ophthalmol* 2026; 110: 117-124.
38. Freedman SF, Hercinovic A, Wallace DK, Kraker RT, Li Z, Bhatt AR, et al. Low- and very low-dose bevacizumab for retinopathy of prematurity: reactivations, additional treatments, and 12-month outcomes. *Ophthalmology* 2022; 129: 1120-1128.
39. Ryu J. New aspects on the treatment of retinopathy of prematurity: currently available therapies and emerging novel therapeutics. *Int J Mol Sci* 2022; 23: 8529.
40. Almutairi M, Chechalk K, Deane E, Fox R, Jones A, Maguire-Henry T, et al. Biomarkers in retinopathy of prematurity: a systematic review and meta-analysis. *Front Pediatr* 2024; 12: 1371776.

41. Ding S, Wang W, Liu C, Zhang W, Wang J, Zhang F. Scutellarin attenuates hypoxia-induced retinal neovascularization through bidirectional modulation of the VEGF/Ang/Tie2 pathway. *Front Pharmacol* 2025; 16: 1631316.
42. Wu PY, Fu YK, Lien RI, Chiang MC, Lee CC, Chen HC, et al. Systemic cytokines in retinopathy of prematurity. *J Pers Med* 2023; 13: 291.
43. Das U, Cho E, Balasubramanian T, Zhou J, Mansoor S, Kapoor R, et al. Comparing infant pain and stress during retinopathy of prematurity screening using ophthalmoscopy and non-contact imaging. *Sci Rep* 2025; 15: 32771.
44. Tram JS, Golding BM, Lim C, Kuschel CA, Elder JE. Changed ophthalmic workload following introduction of digital retinal photography for retinopathy of prematurity screening. *Clin Exp Ophthalmol* 2021; 49: 368-372.
45. Purohit R, Usman F, Ie A, van der Vaart M, Robinson S, Buckle M, et al. Physiological responses to retinopathy of prematurity screening: indirect ophthalmoscopy versus ultra-widefield retinal imaging. *Pediatr Res* 2025; 98: 1801-1808.
46. Tan Z, Isaacs M, Zhu Z, Simkin S, He M, Dai S. Retinopathy of prematurity screening: a narrative review of current programs, teleophthalmology, and diagnostic support systems. *Saudi J Ophthalmol* 2022; 36: 283-295.
47. Maitra P, Kang EY, Wu WC. Establishing an objective quantitative method for assessing the severity of plus disease in retinopathy of prematurity. *Graefes Arch Clin Exp Ophthalmol* 2025; 263: 985-992.
48. Belenje A, Pandya D, Jalali S, Rani PK. Accuracy of artificial intelligence versus clinicians in real-life case scenarios of retinopathy of prematurity. *Cureus* 2025; 17: e78597.
49. Roti EV, Ni S, Bayhaqi Y, Ostmo SR, Burt SS, Woodward MK, et al. Ultra-widefield optical coherence tomography beyond the ora serrata in retinopathy of prematurity. *JAMA Ophthalmol* 2025; 143: 165-170.
50. Hanif AM, Jian Y, Young BK, Campbell JP. Implementation of optical coherence tomography in retinopathy of prematurity screening. *Curr Opin Ophthalmol* 2024; 35: 252-259.
51. Jabroun MN, AlWattar BK, Fulton AB. Optical coherence tomography angiography in prematurity. *Semin Ophthalmol* 2021; 36: 264-269.
52. Rowe LW, Belamkar A, Antman G, Hajrasouliha AH, Harris A. Vascular imaging findings in retinopathy of prematurity. *Acta Ophthalmol* 2024; 102: e452-e472.
53. Burt SS, Woodward M, Ni S, Jackson J, Coyner AS, Ostmo SR, et al. Isolated retinal neovascularization in retinopathy of prematurity: clinical associations and prognostic implications. *Ophthalmol Retina* 2024; 8: 1021-1028.
54. Klufas MA, Patel SN, Ryan MC, Gupta MP, Jonas KE, Ostmo S, et al. Influence of fluorescein angiography on the diagnosis and management of retinopathy of prematurity. *Ophthalmology* 2015; 122: 1601-1608.
55. Hans A, Narang S, Sindhu M, Jain S, Chawla D. Fundus fluorescein angiography in retinopathy of prematurity. *Eye (Lond)* 2022; 36: 1604-1609.
56. Brady CJ, D'Amico S, Campbell JP. Telemedicine for retinopathy of prematurity. *Telemed J E Health* 2020; 26: 556-564.
57. Young BK, Cole ED, Shah PK, Ostmo S, Subramaniam P, Venkatapathy N, et al. Efficacy of smartphone-based telescreening for retinopathy of prematurity with and without artificial intelligence in India. *JAMA Ophthalmol* 2023; 141: 582-588.
58. Nguyen TAL, Raileanu V, Smith B, Griffin A, Shah S. Excellent accuracy of trained neonatal nurses in the detection of referral-warranted retinopathy of prematurity within an established telemedicine screening programme. *J Paediatr Child Health* 2024; 60: 369-374.
59. Al-Abaiji HA, Bangsgaard R, Kofod M, Faber C, Larsen AC, Brost AG, et al. Evaluating the feasibility of a telescreening program for retinopathy of prematurity (ROP) in Denmark. *J Pers Med* 2024; 14: 1020.
60. Guo Z, Ma N, Wu Y, Yuan H, Luo W, Zeng L, et al. The safety and feasibility of the screening for retinopathy of prematurity assisted by telemedicine network during COVID-19 pandemic in Wuhan, China. *BMC Ophthalmol* 2021; 21: 258.
61. Ortiz A, Patiño S, Torres J, Mármol J, Serafin C, Dodhia R, et al. AI-enabled screening for retinopathy of prematurity in low-resource settings. *JAMA Netw Open* 2025; 8: e257831.
62. Rao DP, Savoy FM, Tan JZE, Fung BPE, Bopitiya CM, Sivaraman A, et al. Development and validation of an artificial intelligence based screening tool for detection of retinopathy of prematurity in a South Indian population. *Front Pediatr* 2023; 11: 1197237.
63. Morrison SL, Dukhovny D, Chan RVP, Chiang MF, Campbell JP. Cost-effectiveness of artificial intelligence-based retinopathy of prematurity screening. *JAMA Ophthalmol* 2022; 140: 401-409.
64. Trivedi U, Srivastava A, Mahajan P. Macretina: a dataset, to support deep learning assisted retinopathy of prematurity diagnosis. *Sci Rep* 2025; 16: 1993.
65. Agrawal R, Kulkarni S, Deshpande M, Gaikwad A, Walambe R, Kotecha KV. Classification of Stages 1, 2, 3 and preplus, plus disease of ROP using MultiCNN_LSTM classifier. *MethodsX* 2025; 14: 103182.
66. Shah SV, Brant AR, Zhao C, Wood EH, Scarboro SD, Kumm J, et al. Multi-site performance of the telemedicine retinopathy of prematurity severity score (tROP-SS). *Acta Ophthalmol* 2026; 104: e590-e595.