Update on Retinopathy of Prematurity

Advances in retinopathy of prematurity imaging

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Abstract:
Retinopathy of prematurity (ROP) remains the leading cause of childhood blindness worldwide. Recent advances in ROP imaging have significantly improved our understanding of the pathogenesis and pathophysiological course of ROP including the acute phase, regression, reactivation, and late complications, known as adult ROP. Recent progress includes various contact and noncontact wide-field imaging devices for fundus imaging, smartphone-based fundus photography, wide-field fluorescein angiography, handheld optical coherence tomography (OCT) devices for wide-field en face OCT images, and OCT angiography. Images taken by those devices were incorporated in the recently updated guidelines of ROP, the International Classification of Retinopathy of Prematurity, Third Edition (ICROP3). ROP imaging has also allowed the real-world adoption of telemedicine- and artificial intelligence (AI)-based screening. Recent study demonstrated proof of concept that AI has a high diagnostic performance for the detection of ROP in a real-world screening. Here, we summarize the recent advances in ROP imaging and their application for screening, diagnosis, and management of ROP.

Keywords: Angiography, imaging, retinopathy of prematurity

INTRODUCTION
Retinopathy of prematurity (ROP) continues to be a leading cause of blindness in preterm children worldwide. [1] Timely screening examinations are essential in optimizing outcomes. [2] Binocular indirect ophthalmoscopy has long been the gold standard for evaluating ROP. [3] However, advances in various imaging techniques, such as fundus imaging, wide-field fluorescein angiography (FA), optical coherence tomography (OCT), and OCT angiography (OCTA), have provided additional insights into the pathogenesis, disease progression, and response to treatment in patients with ROP. Advances in retinal imaging have also facilitated the emergence of telemedicine- and artificial intelligence (AI)-based evaluations for ROP. [4] In this review, we summarize the recent advances in ROP imaging with a focus on findings that may be difficult to otherwise identify on conventional ophthalmoscopic examinations.

FUNDUS IMAGING
Binocular indirect ophthalmoscopy, performed by an experienced ophthalmologist, remains the gold standard for ROP screening. [3] However, fundus imaging/photography is useful in capturing and recording the fundus findings, including zone (anteroposterior location), extent, and severity (stage and plus disease) [Figure 1a and b]. Abnormal retinal findings are used to classify ROP stage according to the guidelines described by the International Classification of Retinopathy of Prematurity, Third Edition (ICROP3), and these include demarcation line (Stage 1), ridge (Stage 2), extraretinal neovascular proliferation (Stage 3), partial retinal detachment that spares (Stage 4A) or involves (Stage 4B) the fovea, total retinal detachment (Stage 5), and the dilation and tortuosity of retinal vessels (plus disease). [3]
The digital imaging systems for fundus imaging include contact and noncontact cameras. Examples of contact cameras include the RetCam® (Natus Medical Systems, Inc., Pleasanton, CA, USA), RetCam Shuttle® (Natus Medical Systems, Pleasanton, CA, USA), and Eyetech® (Kowa Company, Ltd., Tokyo, Japan). This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

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and favorable data from numerous validation studies have
required before widespread adoption, as accuracy is essential regarding its diagnostic reliabilities. Further studies are indeed
limited, and peripheral views are challenging to obtain. Similar
to other conventional noncontact cameras, there are limited data
regarding its diagnostic reliabilities. Further studies are indeed
required before widespread adoption, as accuracy is essential
in ROP screening.

On the other hand, advances in contact-based fundus imaging
allowed the real-world adoption of telemedicine-based ROP
screening. For example, the Stanford University Network for
Diagnosis of Retinopathy of Prematurity (SUNDROP) is a
telemedicine initiative to screen for ROP that warrants treatment.
In one SUNDROP study, 608 preterm infants who met ROP screening criteria were evaluated via remote fundus imaging taken with the RetCam II/III over a 6-year period. The results showed that sensitivity was 100% and specificity was 99.8% for the detection of ROP that warranted treatment when compared with binocular indirect ophthalmoscopy. Elsewhere, the e-ROP study, a multicenter clinical trial, evaluated the validity of a telemmedicine system that used fundus imaging for ROP screening. The fundus photographs were obtained with the RetCam Shuttle by nonphysicians and interpreted remotely by nonphysicians. Of the 1257 infants screened, 19.4% had the characteristics of ROP that warranted referral, and the remote grading of images had a sensitivity of 81.9% and specificity of 90.1%. These studies indicate the usefulness of fundus imaging in telemedicine-based screening for ROP. Some limitations of fundus imaging with contact cameras include the need for experienced photographers and the high initial cost of the cameras.

Fundus imaging has also been central in developing AI-assisted
ROP screening. In the past few years, deep-learning (DL)
algorithms using convolutional neural networks have shown
great promise in automated diagnosis of ROP from fundus imaging. For example, Wang et al. reported that the algorithm DeepROP achieved a sensitivity of 97% and a specificity of 99% for distinguishing ROP cases from normal cases based on
fundus photographs obtained with the RetCam. Brown and colleagues from the Imaging and Informatics in Retinopathy of Prematurity group, a multicenter ROP imaging consortium, developed an algorithm to automatically distinguish the presence of plus disease on fundus images obtained with the RetCam.
This system achieved high sensitivity (93%) and specificity (94%) for the diagnosis of plus disease. A recent study further showed that the ROP DL system, originally developed for a North American population of premature
infants, had high diagnostic accuracy in a real-world ROP screening in India using fundus photographs obtained with the Retcam Shuttle. Another study also demonstrated proof of concept that AI can have high diagnostic performance for detection of Type 2 or worse ROP in real-world ROP screening with the RetCam. AI using fundus images may benefit ROP management by improving the efficiency, accuracy, and objectivity of ROP diagnosis, and to widen the reach of ROP screening worldwide. The performance of AI algorithms for analyzing fundus images from different cameras and populations with variable image quality should be investigated in further studies.

**WIDE-FIELD FLUORESCEIN ANGIOGRAPHY**

FA has been used for more than 50 years in ROP, since Flynn
et al. introduced it as a method to study retrolental fibroplasia in the late 1960s. FA has been shown to be safe in children.
with minimal adverse effects.\textsuperscript{[19]} Portable wide-angle cameras have increased its utility in pediatric retinal diseases. It is particularly useful for atypical cases.

**The role of wide-field fluorescein angiography in retinopathy of prematurity diagnosis**

Several studies have suggested that wide-field FA (WFA) improves the diagnosis of zones in ROP owing to the high-contrast images of the peripheral retina [Figure 1c and d]. WFA is a useful adjunct for visualizing the borders of avascular zones in the peripheral retina. In 2006, Ng et al. described a case series of 23 patients who underwent WFA and found that clear angiograms could be obtained during ROP screening.\textsuperscript{[20]} Lepore et al. reported an atlas of WFA findings in eyes undergoing laser treatment for ROP and showed that WFA was useful for clearly distinguishing the deceptively featureless Zone I junction between vascularized and nonvascularized retina.\textsuperscript{[21]}

Further studies have established that the combination of FA and color fundus photography improved the accuracy of the classification of ROP stages. Klufas et al. demonstrated that, compared with color fundus imaging alone, the addition of WFA resulted in a significant increase in the sensitivity of the diagnosis of Stage 3 or worse disease, type 2 or worse disease, and preplus or plus disease.\textsuperscript{[22]} The addition of WFA to color fundus photography also led to a significant improvement in intergrader agreement for a diagnosis of ROP that requires treatment.

WFA also has the potential to assist with the diagnosis of aggressive ROP (A-ROP) early on in the course of the disease. Aggressive ROP, a severe, rapidly progressive form of ROP, was added to the ICROP in 2005 as aggressive posterior ROP (AP-ROP).\textsuperscript{[23]} In ICROP3 (the third edition and the most recent update), the term “A-ROP” replaced “AP-ROP.”\textsuperscript{[5]} Eyes with A-ROP often demonstrate so-called flat neovascularization, which can be difficult to visualize using a 28-D lens and ophthalmoscopy; however, the use of FA may allow early diagnosis. Yokoi et al. described the characteristic FA features in A-ROP as capillary nonperfusion throughout the vascularized retina, shunting in the vascularized retina, a circumferential demarcation line, and limited vessel development, which were difficult to identify using ophthalmoscopy.\textsuperscript{[24]}

**The role of wide-field fluorescein angiography in monitoring treatment response**

WFA may also facilitate monitoring the effects of ROP treatment. Kusaka et al. reported a reduction in neovascular activity on FA in 14 (93%) of 15 eyes after intravitreal bevacizumab for Stage 3–4B ROP.\textsuperscript{[25]} Yokoi et al. evaluated the efficacy of scleral buckling for active neovascularization in eyes with Stage 4A ROP.\textsuperscript{[26]} They reported a decrease in fluorescein leakage from the fibrovascular tissue in all eyes, which indicated the efficacy of scleral buckling in reducing both tractional forces and neovascular activity. Nishina et al. assessed the effect of early vitrectomy on A-ROP using FA as well.\textsuperscript{[27]} More recently, Harper et al.\textsuperscript{[28]} found that ranibizumab was effective in the initial cessation of Type 1 ROP, but vascularization to Zone III was only achieved in 50% of eyes; most eyes had evidence of vascular anomalies, such as blunting, dilatation, and/or capillary dropout on FA.\textsuperscript{[29]}

FA has also been used to evaluate the differences in peripheral findings after differing treatments. Several studies have shown more peripheral vascular abnormalities in anti-vascular endothelial growth factor (anti-VEGF)-treated eyes compared to laser-treated eyes. Lepore et al. compared FA findings 9 months and 4 years after either intravitreal bevacizumab or laser treatment.\textsuperscript{[29]} The majority of eyes that received bevacizumab compared to only a few laser-treated eyes had abnormalities, including leakage, tangles, shunts, and decreased foveal avascular zone (FAZ). The impact of these various peripheral findings on long-term anatomical and visual outcomes should be evaluated in future studies.

FA is also effective in highlighting the reactivation of ROP after anti-VEGF treatment [Figure 2].\textsuperscript{[30]} Reactivation is associated with the reappearance of neovascularization or worsening fibrovascular proliferation after a period of regression. The reappearance of neovascularization is subtle, but it can be detected clearly on FA.

**Optical Coherence Tomography**

OCT is widely used to diagnose and monitor vitreoretinal diseases in adult patients. Its use in ROP patients has been...
relatively limited due to several challenges, including the difficulty in positioning NICU patients, poor fixation, small eyes, various refractive errors, and other logistical and medical limitations. However, many of these difficulties have been minimized with the development of handheld OCT devices that enable OCT images to be taken during the bedside examinations or under anesthesia. A recent study indicated that the OCT imaging of ROP was less stressful for infants than binocular indirect ophthalmoscopy examinations by trained ophthalmologists. Handheld spectral-domain OCT (SD-OCT) has allowed the detection of subclinical findings (i.e., vitreous opacities, vitreous bands, preterinal neovascularization, epiretinal membrane, macular edema, photoreceptor immaturity, retinoschisis, retinal detachment, and choroidal thinning) that may not be obvious using conventional indirect binocular ophthalmoscopy. Some of these findings are potentially associated with ROP severity and may have prognostic value.

**Optical coherence tomography cross-sectional images**

**Macular edema**

Macular edema has been reported in approximately 50% of ROP cases (range, 38%–60%). The detailed etiologies of the edema are unknown, but increased VEGF and mechanical traction have been proposed as causes. In a prospective case series, Dubis et al. reported that 54% (25/46) of patients had edema. It was found in every stage of ROP, including Stages 0, 1, 2, 3, and 4A; thus, they concluded that the disease stage was not associated with the finding. By contrast, Vinikar et al. reported that edema was not detected in Stage 1 ROP; however, it was observed in 29% (23/79) of patients with Stage 2 ROP. Macular edema peaked at 37 weeks postmenstrual age (PMA) and self-resolved without treatment by 52 weeks PMA or by the 3rd month. Maldonado et al. also sought to determine the association between edema severity in ROP and other systemic health conditions in neonates aged 31–36 weeks PMA. Macular edema was found in 50% (21/42) of the infants. The severity of edema, measured by retinal thickness or using the foveal/parafoveal thickness ratio, was shown to correlate with ROP stage, the presence of plus disease, and subsequent laser treatment, as well as systemic factors, including Apgar score, surgery for patent ductus arteriosus, and the presence of intraventricular hemorrhage.

In addition, Erol et al. reported that the prevalence of edema increased with an increase in ROP stage (i.e., 46%, 57%, and 88% in Stage 1, Stage 2, and Stage 3, respectively). Recently, Mangalesh et al. found that OCT identified macular edema in 60% of infants (50/85) at 36 ± 1 week PMA. Bilateral edema was identified in 82% of the infants (41/50), and severity was associated with higher ROP stages.

It is important to determine whether this edema of prematurity influences visual outcomes. Vinikar et al. reported that visual acuity was lower in infants with ROP with macular edema than in those without edema, or in infants without ROP. Rothman et al. also reported that eyes without edema had better vision than those with edema. Taken together, the edema or prematurity seems to correlate with ROP severity and vision, but further studies are needed to confirm long-term outcomes.

**Vascular abnormality score by optical coherence tomography**

A vascular abnormality score, determined using OCT (i.e., VASO), was proposed by Maldonado et al. to identify vascular and perivascular abnormalities on SD-OCT images associated with plus disease. The score was based on the following features: retinal vessel elevation (1 point or 2 points if severe), scalloped retinal layers (1 point or 2 points if severe), hyporeflective vessels (2 points), and retinal spaces (2 points). The VASO was higher in eyes with plus disease than in those without (4.1 vs. 1.4). Further studies are required to validate the findings, but this is an interesting and objective approach to assessing plus disease.

**Retinoschisis and retinal detachment**

In advanced ROP, both retinoschisis and retinal detachment have been described in the posterior pole by handheld OCT. Clinically, retinoschisis may sometimes be difficult to distinguish from retinal detachment on indirect ophthalmoscopy; however, OCT is effective in differentiating between these two pathologies. Chen et al. reported that all 12 infants diagnosed with Stage 4A ROP had retinoschisis of some degree on handheld OCT, and OCT imaging was effective in determining Stages 4A versus 4B, which is critical for visual prognosis. SD-OCT is also useful for monitoring reattachment of the posterior pole after surgery for Stage 4 and 5 ROP.

**Photoreceptor immaturity**

Compared with full-term infants, premature infants have shallower foveal depressions, attenuated external limiting membrane and photoreceptor ellipsoid zones (EZ), and thinner retinal layers, indicative of photoreceptor immaturity. Vajzovic et al. described the delay in the photoreceptor development of very preterm infants (<32 weeks gestational age), compared with term infants. EZ development was lower in very preterm infants (14%, 9/64 eyes) than in term infants (47%, 22/47 eyes) ($P < 0.001$). There was also a greater mean distance between the EZ and the foveal center in very preterm versus term infants, which further signified a delay in photoreceptor migration.

**Choroidal thinning**

Recent studies have described choroidal thinning in ROP infants with lower gestational age and lower birth weight using handheld SD-OCT. In one study, subfoveal choroidal thickness in premature infants was seen to decrease in relation to ROP severity. Macular edema did not correlate with choroidal thickness in premature infants.

**En Face Optical Coherence Tomography Imaging**

With the advance of high-speed, high-density, volumetric scanning techniques, recently developed handheld OCT devices can provide wide-field en face OCT images of nearly...
the entire retina [Figure 3].

Similarly, Viehland et al. visualized the vascular structure of a preretinal neovascular membrane using a handheld OCT device with a 200 kHz swept-source probe, and Song et al. also reported on the use of an OCTA with a 200 kHz swept-source probe in infants.

However, these prototype handheld OCTA instruments did not have the wide-field imaging needed for the peripheral visualization required to identify most ROP pathologies.

Recent advances in laser light sources and high-performance computing systems have further improved the ability to capture a wide field of view. Ni et al. recently reported wide-field (55°) OCT/OCTA retinal imaging in infants with ROP using a 400-kHz handheld swept-source probe. They successfully visualized the retinal vasculature and neovascularization in the peripheral retina via high-resolution en face OCT/OCTA images. High-speed, high-resolution, and wide-field handheld OCT/OCTA systems have potential as a screening tool in the future.

**Optical Coherence Tomography Angiography**

OCTA allows noninvasive visualization of retinal blood flow without the use of exogenous dyes. The recent development of prototype handheld OCTA by several groups revealed the potential of using OCTA to assess ROP. Campbell et al. first described a handheld OCTA system using a 100-kHz tunable laser to visualize retinal blood flow in ROP. Similarly, Viehland et al. visualized the vascular structure of a preretinal neovascular membrane using a handheld OCTA device with a 200 kHz swept-source probe, and Song et al. also reported on the use of an OCTA with a 200 kHz swept-source probe in infants.

**B-Scan Ultrasoundography in Traction Retinal Detachment in Retinopathy of Prematurity**

B-scan ultrasonography is effective for diagnosis, preoperative evaluation, and surgical planning in cases of tractional retinal detachment in ROP. B-scans are particularly helpful in the setting of media opacity (i.e., corneal scars, poorly dilated pupils, cataracts, hyphema, and vitreous hemorrhage) in patients with Stage 5 ROP. In ICROP3, Stage 5 ROP was subclassified into Stage 5A, in which the optic disc is visible by ophthalmoscopy; Stage 5B, in which the optic disc is not visible because of retrolental fibrovascular tissue or closed-funnel detachment; and Stage 5C, in which Stage 5B is accompanied by anterior segment changes. In Stage 5B and C, the extent of detachment must be examined by B-scan ultrasonography.

Jabour et al. described a series of 368 eyes of 184 patients with Stage 5 ROP. Of ultrasonography, indirect ophthalmoscopy, and biomicroscopy, ultrasonography was the most valuable tool for assessing the configuration of retinal detachment. Similarly, Muslubas et al. reported on a series of 300 eyes of 150 patients with Stage 5 ROP, and they determined that ultrasonography was effective in visualizing the following retinal detachment configurations: closed–closed (82%), open–closed (11%), open–open (6%), and closed–open (2%) retinal detachment configuration, as well as subretinal hemorrhage (26%), anterior loop traction (24%), retinal cyst (2%), and calcification (1%). Preoperative assessment of the retinal detachment configuration with B-scan ultrasonography is not only beneficial in surgical planning but also for predicting prognosis and therefore allows appropriate counseling for the family.

Ultrasound color Doppler imaging has been utilized to investigate the association between flow velocity and ROP. Hartenstein et al. reported an increase in the central retinal artery and central retinal vein velocity in Stage 2 ROP, compared with those without ROP. Likewise, Silverman et al. recently reported that the use of plane-wave ultrasonic imaging, which provides improved spatial resolution, demonstrated that central retinal artery and central retinal vein velocities were higher in infants with ROP, compared to infants without ROP, and this correlated with ROP stage as well. Ultrasonic color Doppler imaging is not currently routinely used to screen for ROP, but such ancillary testing may potentially allow reduction of the frequency of dilated examinations in neonates with normal blood flow velocity, and, conversely, watching neonates with high blood flow velocity more closely. Another benefit of ultrasonography is that it is a nonmydriatic test that can be performed through closed lids.

**Figure 3**: En face optical coherence tomography in retinopathy of prematurity. (a and b) Wide-field en face optical coherence tomography images in an infant with Stage 3 retinopathy of prematurity. Tortuous retinal vessels and the vascular-avascular border demarcated by the ridge are clearly observed. (c and d) Wide-field en face optical coherence tomography and corresponding cross-sectional images. The arrowhead indicates the persistent inner retinal layers at the fovea.
MULTIMODAL IMAGING IN OLDER CHILDREN AND ADULTS WITH HISTORY OF RETINOPATHY OF PREMATURE

In addition to being a neonatal disease, long-term effects of ROP extend into adulthood, making it a lifelong disease. Secondary ROP complications that may develop later in life include cataract, glaucoma, high myopia, corneal decompensation, persistent avascular retina (PAR), vitreous hemorrhage, retinal tears, and retinal detachment. Of these, increasing attention is being paid to the development of PAR. Imaging using wide-field fundus imaging and WFA is particularly useful in evaluating for PAR and associated complications. Optos FA can visualize areas of peripheral nonperfusion associated with PAR, as well as the location and extent of ridge and vascular abnormalities. In a recent multicenter study by Hamad et al., ultra-WFA was shown to effectively identify subtle peripheral vascular abnormalities, including arteriovenous loops, microaneurysms, capillary avascularity, and neovascularization in adult patients with PAR and history of ROP. In their study, adult patients with PAR were reported to experience lattice degeneration (54%), retinal tears (31%), atrophic holes (35%), retinal detachment (39%), and tractional retinoschisis (12%). Atrophic holes and lattice-like changes were commonly found either along or just anterior to the vascular–avascular junction. Such findings are well-documented when a combination of optos fundus imaging and FA was used.

In eyes with late reactivation or neovascular activity associated with PAR, laser treatment in areas affected by PAR can be considered. WFA is helpful in identifying residual vascular activity after such treatment. In eyes with rhegmatogenous retinal detachment, often from atrophic holes, scleral buckling-based surgery is recommended, and wide-field fundus imaging can be a useful tool (Figure 4).

Macular abnormality, such as a decrease in the size of the FAZ, is a common imaging finding in adults with ROP. Using FA, a smaller FAZ was first reported more than 20 years ago, but recent OCTA studies have quantitatively shown a significantly smaller FAZ in patients with a history of ROP compared to other individuals. Several studies have also demonstrated an association between a smaller FAZ and decreased visual acuity and lower gestational age and birth weight. The reason for a smaller FAZ is not fully understood, but an increase in the intraocular VEGF level during the FAZ formation period in ROP may contribute to excessive vasculature, leading to smaller FAZ. One study reported that laser-treated patients had significantly larger FAZs than patients with spontaneously regressed ROP. The impact of treatment (i.e. laser and anti-VEGF) on FAZ is not well elucidated, and further investigations using OCTA are warranted.

CONCLUSION

Recent advances in ROP imaging have improved our understanding of the pathogenesis and pathophysiological course of ROP including the acute phase, regression, and reactivation. Future imaging advances will hopefully further improve ROP care and treatment outcomes. The recently published ICROP3 indicated the areas that require additional research as follows: “methods for quantifying vascular changes, including the rate of disease progression; characterizing clinical findings using other imaging methods (e.g., FA, OCT); understanding long-term risks of PAR; and elucidating signs and timing of ROP reactivation.” Progress in these research areas will likely advance with further improvements in imaging technology, such as in the resolution (higher) and field (wider) of fundus imaging, FA, and OCT/OCTA, via the use of compact, handheld devices that are designed for pediatric eyes. ROP imaging in telemedicine-based screening with the potential for computer-based image analysis paradigms may also lead to improvements in diagnosis and management of ROP, and most importantly, to provide wider access to ROP care.

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Conflicts of interest

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REFERENCES

1. Gilbert C. Retinopathy of prematurity: A global perspective of the epidemics, population of babies at risk and implications for control. Early Hum Dev 2008;84:77-82.

2. Early Treatment for Retinopathy of Prematurity Cooperative Group;
Good WV, Hardy RJ, Dobson V, Palmer EA, Phelps DL, et al. Final visual acuity results in the early treatment for retinopathy of prematurity study. Arch Ophthalmol 2010;128:663-71.

3. Fierson WM; AMERICAN ACADEMY OF PEDIATRICS Section on Ophthalmology; AMERICAN ACADEMY OF OPHTHALMOLOGY; AMERICAN ASSOCIATION FOR PEDIATRIC OPHTHALMOLOGY AND STRABISMUS; AMERICAN ASSOCIATION OF CERTIFIED ORTHOPTISTS. Screening examination of premature infants for retinopathy of prematurity. Pediatrics 2018;142:e20183061.

4. Quinn GE, Ying GS, Daniel E, Hildebrandt PL, Ellis A, Baumritter A, et al. Validity of a telemedicine system for the evaluation of acute-phase retinopathy of prematurity: A pilot study. Br J Ophthalmol 2008;92:1490-5.

5. Chiang MF, Quinn GE, Fielder AR, Ostmo SR, Chan RV, Berrocal A, et al. International classification of retinopathy of prematurity, third edition. Ophthalmology 2021;128:e51-68.

6. Fung TH, Muqit MM, Mordant DJ, Smith LM, Patel CK. Noncontact high-resolution ultra-wide-field oral fluorescein angiography in premature infants with retinopathy of prematurity. JAMA Ophthalmol 2014;132:108-10.

7. Fung TH, Abramson J, Ojha S, Holden R. Systemic effects of optos versus indirect ophthalmoscopy for retinopathy of prematurity screening. Ophthalmology 2018;125:1829-32.

8. Vinekar A, Gilbert C, Dogra M, Kurian M, Shainesh G, Shetty B, et al. The KIDROP model of combining strategies for providing retinopathy of prematurity screening in underserved areas in India using wide-field imaging, tele-medicine, non-physician graders and smart phone reporting. Indian J Ophthalmol 2014;62:41-9.

9. Goyal A, Gopalakrishnan M, Anantharaman G, Chandra Shekharapan DR, Thachil T, Sharma A. Smartphone guided wide-field imaging for retinopathy of prematurity in neonatal intensive care unit – A Smart ROP (SROP) initiative. Indian J Ophthalmol 2019;67:840-5.

10. Patel JP, Aberg MT, Paulus YM, Lieu P, Dedania VS, Qian CX, et al. Smartphone-based fundus photography for screening of plus-disease retinopathy of prematurity. Graefes Arch Clin Exp Ophthalmol 2019;257:2579-85.

11. Fierson WM, Capone A; Ophthalmology AA of PS on, Orthoptists AA of O American Association of Certified. Telemedicine for evaluation of retinopathy of prematurity. Pediatrics 2015;135:e238-54.

12. Wang SK, Callaway NF, Wallenstein MB, Henderson MT, Leng T, Moshfeghi DM. SUNDROP: Six years of screening for retinopathy of prematurity with telemedicine. Can J Ophthalmol 2015;50:101-6.

13. Gensure RH, Chiang MF, Campbell JP. Artificial intelligence for retinopathy of prematurity. Curr Opin Ophthalmol 2020;31:312-7.

14. Wang J, Ji R, Chen Y, Zhang L, Hu J, Wu Y, et al. Automated retinopathy of prematurity screening using deep neural networks. EBioMedicine 2018;35:361-8.

15. Brown JM, Campbell JP, Beers A, Chang K, Ostmo S, Chan RV, et al. Automated diagnosis of plus disease in retinopathy of prematurity using deep convolutional neural networks. JAMA Ophthalmol 2018;136:803.

16. Campbell JP, Singh P, Redd TK, Brown JM, Shah PK, Subramanian P, et al. Applications of artificial intelligence for retinopathy of prematurity screening. Pediatrics 2020;147:e202001618.

17. Greenwald MF, Danford ID, Shahrawat M, Ostmo S, Brown J, Kalpathy-Cramer J, et al. Evaluation of artificial intelligence-based telemedicine screening for retinopathy of prematurity. J Am Assoc Pediatr Ophthalmol Strabismus 2020;24:160-2.

18. Flynn JT, Cassidy J, Essner D, Zuskind J, Merritt J, Flynn R, et al. Fluorescein angiography in retrolental fibroplasia: Experience from 1969-1977. Ophthalmology 1979;86:1700-23.

19. Chee RI, Gupta MP, Valikkadath NG, Cole E, Orlin A, Al-Khaled T, et al. Evaluation of potential systemic adverse events related to fluorescein angiography in pediatric patients. Ophthalmol Retin 2020;4:595-601.

20. Ng EY, Lanigan B, O’Keefe M. Fundus fluorescein angiography in the screening for and management of retinopathy of prematurity. J Pediatr Ophthalmol Strabismus 2006;43:85-90.

21. Lepore D, Molle F, Pagliara MM, Baldascino A, Angora C, Sammartino M, et al. Atlas of fluorescein angiographic findings in eyes undergoing laser for retinopathy of prematurity. Ophthalmology 2011;118:168-75.

22. Klufas MA, Patel SN, Ryan MC, Patel Gupta M, Jonas KE, Ostmo S, et al. Influence of fluorescein angiography on the diagnosis and management of retinopathy of prematurity. Ophthalmology 2015;122:1601-8.

23. International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. Arch Ophthalmol 2005;123:991-9.

24. Yokoi T, Hiraoka M, Miyamoto M, Yokoi T, Kobayashi Y, Nishina S, et al. Vascular abnormalities in aggressive posterior retinopathy of prematurity detected by fluorescein angiography. Ophthalmology 2009;116:1377-82.

25. Kasaka S, Shima C, Wada K, Arahori H, Shimoyoi H, Sato T, et al. Efficacy of intravitreal injection of bevacizumab for severe retinopathy of prematurity. JAMA Ophthalmol 2014;132:1178-84.

26. Yokoi T, Yokoi T, Kobayashi Y, Hiraoka M, Nishina S, Azuma N. Evaluation of scleral buckling for stage 4A retinopathy of prematurity by fluorescein angiography. Am J Ophthalmol 2009;148:544-50.e1.

27. Nishina S, Yokoi T, Yokoi T, Kobayashi Y, Hiraoka M, Azuma N. Effect of early vitreous surgery for aggressive posterior retinopathy of prematurity detected by fundus fluorescein angiography. Ophthalmology 2009;116:2442-7.

28. Harper CA 3rd, Wright LM, Young RC, Read SP, Chang EY. Fluorescein angiographic evaluation of peripheral retinal vasculature after primary intravitreal ranibizumab for retinopathy of prematurity. Retina 2019;39:700-5.

29. Lepore D, Quinn GE, Molle F, Orazi L, Baldascino A, Ji MH, et al. Follow-up to age 4 years of treatment of type 1 retinopathy of prematurity intravitreal bevacizumab injection versus laser: Fluorescein angiographic findings. Ophthalmology 2018;125:218-26.

30. Hamad AE, Moinuddin O, Blair MP, Schecket SA, Shapiro MJ, Quiram PA, et al. Late-onset retinal findings and complications in untreated retinopathy of prematurity. Ophthalmol Retina 2020;4:602-12.

31. Mangalesh S, Sarin N, McGeehan B, Prakashapokorn SG, Tran-Viet D, Costen CI, et al. Preterm infant stress during handheld optical coherence tomography vs. binocular indirect ophthalmoscopy examination for retinopathy of prematurity. JAMA Ophthalmol 2021;139:567-74.

32. Legocki AT, Zepeda EM, Gillette TB, Grant LE, Shariff A, Touch P, et al. Vitreous findings by handheld spectral-domain OCT correlate with retinopathy of prematurity severity. Ophthalmol Retina 2020;4:1008-15.

33. Zepeda EM, Shariff A, Gillette TB, Grant L, Ding L, Tarcy-Hornoch K, et al. Vitreous bands identified by handheld spectral-domain optical coherence tomography among premature infants. JAMA Ophthalmol 2018;136:753-8.

34. Durup AM, Subramaniam CD, Godara P, Carroll J, Costakos DM. Subclinical macular findings in infants screened for retinopathy of prematurity with spectral-domain optical coherence tomography. Ophthalmology 2013;120:1665-71.

35. Maldonado RS, O’Connell R, Ascher SB, Sarin N, Freedman SF, Wallace DK, et al. Spectral-domain optical coherence tomographic assessment of severity of cystoid macular edema in retinopathy of prematurity. Arch Ophthalmol 2012;130:569-78.

36. Erol MK, Ozdemir O, Coban DT, Bilgin AB, Dogan B, Sari ES, et al. Macular findings obtained by spectral domain optical coherence tomography in retinopathy of prematurity. J Ophthalmol 2014;2014:468653.

37. Mangalesh S, McGeehan B, Tai V, Chen X, Tran-Viet D, Vazovic L, et al. Macular OCT characteristics at 36 weeks’ postmenstrual age in infants examined for retinopathy of prematurity. Ophthalmol Retin 2021;5:580-92.

38. Vinekar A, Avadhani K, Sivakumar M, Mahendradas P, Kurian M, Braganza S, et al. Understanding clinically undetected macular changes in early retinopathy of prematurity on spectral domain optical coherence tomography. Invest Ophthalmol Vis Sci 2011;52:5183-8.

39. Vinekar A, Mangalesh S, Jayadev C, Bauer N, Munusamy S, Kemmanu V, et al. Macular edema in Asian Indian premature infants with retinopathy of prematurity: Impact on visual acuity and refractive status after 1-year. Indian J Ophthalmol 2015;63:432-7.

40. Rothman AL, Tran-Viet D, Vazovic L, Tai V, Sarin N, Holgado S, et al. Functional outcomes of young infants with and without macular edema. Retina 2015;35:2018-27.

41. Maldonado RS, Yuan E, Tran-Viet D, Rothman AL, Tong AY, Wallace DK, et al. Three-dimensional assessment of vascular and macular structures in premature infants by spectral-domain optical coherence tomography. Ophthalmology 2017;124:1678-89.
perivascular characteristics in subjects with retinopathy of prematurity. Ophthalmology 2014;121:1289-96.

42. Chen X, Prakalapakorn SG, Freedman SF, Vajzovic L, Toth CA. Differentiating retinal detachment and retinoschisis using handheld optical coherence tomography in stage 4 retinopathy of prematurity. JAMA Ophthalmol 2020;138:81-5.

43. Vajzovic L, Rothman AL, Tran-Viet D, Cabrera MT, Freedman SF, Toth CA. Delay in retinal photoreceptor development in very preterm compared to term infants. Invest Ophthalmol Vis Sci 2015;56:908-13.

44. Erol MK, Coban DT, Ozdemir O, Dogan B, Tunay ZO, Bulut M. Choroidal thickness in infants with retinopathy of prematurity. Retin 2016;36:1191-8.

45. Ni S, Nguyen TP, Ng R, Khan S, Ostmo S, Jia Y, et al. 105° field of view non-contact handheld swept-source optical coherence tomography. Opt Lett 2021;46:5878-81.

46. Campbell JP, Nudleman E, Yang J, Tan O, Chan RV, Chiang MF, et al. Handheld optical coherence tomography angiography and ultra-wide-field optical coherence tomography in retinopathy of prematurity. JAMA Ophthalmol 2017;135:977.

47. Viehland C, Chen X, Tran-Viet D, Jackson-Atogi M, Ortiz P, Waterman G, et al. Ergonomic handheld OCT angiography probe optimized for pediatric and supine imaging. Biomed Opt Express 2019;10:2623-38.

48. Song S, Zhou K, Xu JJ, Zhang Q, Lyu S, Wang R. Development of a clinical prototype of a miniature hand-held optical coherence tomography probe for prematurity and pediatric ophthalmic imaging. Biomed Opt Express 2019;10:2383-98.

49. Ni S, Wei X, Ng R, Ostmo S, Chiang MF, Huang D, et al. High-speed and widefield handheld swept-source OCT angiography with a VCSEL light source. Biomed Opt Express 2021;12:3553-70.

50. Muslubas IS, Karacorlu M, Hocaoglu M, Yamancl C, Arf S, Ozdemir H, et al. Ultrasoundography findings in eyes with stage 5 retinopathy of prematurity. Ophthalmic Surg Lasers Imaging Retina 2015;46:1035-40.

51. Hartenstein S, Müller B, Metze B, Czernik C, Bühler C. Blood flow assessed by color Doppler imaging in retinopathy of prematurity. J Perinatol 2015;35:745-7.

52. Silverman RH, Urs R, Jokl DH, Pinto L, Coki O, Sahni R, et al. Ocular blood flow in preterm neonates: A preliminary report. Transl Vis Sci Technol 2021;10:22.

53. Kaiser RS, Trese MT, Williams GA, Cox MS Jr. Adult retinopathy of prematurity: Outcomes of rhegmatogenous retinal detachments and retinal tears. Ophthalmology 2001;108:1647-53.

54. Mintz-Hittner HA, Knight-Nanan DM, Satriano DR, Kretzer FL. A small foveal avascular zone may be an historic mark of prematurity. Ophthalmology 1999;106:1409-13.

55. Bowl W, Bowl M, Schweinfurth S, Holve K, Knobloch R, Stieger K, et al. OCT angiography in young children with a history of retinopathy of prematurity. Ophthalmol Retina 2018;2:972-8.

56. Rezar-Dreindl S, Eibenberger K, Told R, Neumayer T, Steiner I, Sacu S, et al. Retinal vessel architecture in retinopathy of prematurity and healthy controls using swept-source optical coherence tomography angiography. Acta Ophthalmol 2021;99:e232-9.

57. Takagi M, Maruko I, Yamagushi A, Kakehashi M, Hasegawa T, Iida T. Foveal abnormalities determined by optical coherence tomography angiography in children with history of retinopathy of prematurity. Eye (Lond) 2019;33:1890-6.

58. Nonobe N, Kaneko H, Ito Y, Takayama K, Kataoka K, Tsunekawa T, et al. Optical coherence tomography angiography of the foveal avascular zone in children with a history of treatment-requiring retinopathy of prematurity. Retina 2019;39:111-7.

59. Vural A, Gunay M, Celik G, Demirayak B, Kizilay O. Comparison of foveal optical coherence tomography angiography findings between premature children with ROP and non-premature healthy children. Eye (Lond) 2021;35:1721-9.

60. Miki A, Yamada Y, Nakamura M. The size of the foveal avascular zone is associated with foveal thickness and structure in premature children. J Ophthalmol 2019;2019:8340729.

61. Periti F, Toma C, Platiano C, Guagliano R, Bertone C, Barillà D, et al. Microvascular parameters evaluated with optical coherence tomography-angiography in children: Comparison between preterm and full-term patients. Acta Ophthalmol 2019;97:e1032-4.