AMERICAN ACADEMY™
OF OPHTHALMOLOGY

Telemedical Diagnosis of Stage 4 and Stage 5 Retinopathy of Prematurity

*Samir N. Patel, MD,[1] Ranjodh Singh, BPhil, BSc,[1] Karyn E. Jonas, RN,[1,2] Susan Ostmo, MS,[4] Mrinali P. Gupta, MD,[1] J. Peter Campbell, MD, MPH,[4] Michael F. Chiang, MD,[3,4] R.V. Paul Chan, MD, FACS,[1,2,5] for the Imaging and Informatics for Retinopathy of Prematurity Research Consortium**

Purpose: To determine the accuracy of image-based diagnosis for stage 4 or worse retinopathy of prematurity (ROP) disease.

Design: Prospective cohort study.

Participants: We prospectively obtained data, from 8 major ROP centers, for 1220 eye examinations from 230 infants.

Methods: An ophthalmologist at each center provided a clinical diagnosis using indirect ophthalmoscopy. Wide-angle retinal images (RetCam; Clarity Medical Systems, Pleasanton, CA) were then obtained, and these were independently read by 2 ROP experts using a web-based system for an image-based diagnosis.

Main Outcome Measures: Sensitivity and specificity of image-based diagnosis from the ROP experts were calculated using the clinical diagnosis as the reference standard.

Results: Of 1220 examinations, 28 (2%) had a clinical diagnosis of stage 4 or worse. Sensitivity and specificity for stage 4 or worse disease were 75% and 99% for expert 1, and 86% and 99% for expert 2. Sensitivity and specificity for the detection of stage 5 disease were 69% and 99% for both experts.

Conclusions: There are inconsistencies in the accuracy of image-based diagnosis of stage 4 and stage 5 ROP when compared with the clinical diagnosis. *Ophthalmology Retina 2017;■:1–6 © 2017 by the American Academy of Ophthalmology*

Retinopathy of prematurity (ROP) is a vasoproliferative disease that affects the retinas of premature infants. The Cryotherapy for Retinopathy of Prematurity [1] and Early Treatment for Retinopathy of Prematurity [2] studies have established evidence-based guidelines for ROP diagnosis and management that have been shown to improve structural and functional outcomes; however, ROP continues to be a leading cause of childhood blindness.[3,4]

Limitations to current ROP management include extensive coordination for indirect ophthalmoscopic examination,[5] a decreasing availability of adequately trained ophthalmologists at the point of care,[6–8] and a growing need for ROP care worldwide.[8,9] Telemedicine programs for image-based diagnosis of ROP have been proposed to address some of these limitations.[9–13] The 2013 joint policy statement of the American Academy of Pediatrics Section on Ophthalmology, the American Academy of Ophthalmology, the American Association for Pediatric Ophthalmology and Strabismus, and the American Association of Certified Orthoptists on screening premature infants for ROP acknowledged the growing role of digital imaging in ROP care but emphasized the need for further studies to elucidate its utility in diagnosing and managing ROP.[10]

Real-world telemedicine programs for ROP have been implemented in the United States and throughout the world.[13–15] These programs have historically focused on prevention of retinal detachment by identifying disease that may soon progress to treatment-requiring ROP or disease that requires immediate treatment with laser photocoagulation or anti–vascular endothelial growth factor therapy. In these scenarios, image-based diagnosis has shown to accurately and reliably identify ROP.[11,13,16]

There is, however, a gap in knowledge in the accuracy of image-based diagnosis for stage 4 and stage 5 ROP. This is concerning particularly for international communities that lack access to ophthalmologists experienced in ROP care and rely solely on telemedicine programs for ROP diagnosis and management. Given that the surgical management of ROP with vitrectomy or scleral buckle, or both, is indicated for disease that has progressed to retinal detachment, the telemedical diagnosis of ROP requiring surgical intervention in these communities is relevant for secondary referrals for expedited tertiary care. Because of the growing global burden of ROP and the potential increased reliance on telemedicine programs for ROP, it is important to develop methods to accurately and reliably identify ROP that may require surgery. The purpose of this study was to determine the accuracy of image-based diagnosis for stage 4 and stage 5 ROP.

Methods

The institutional review boards of all participating ROP centers approved this study. Informed consent was obtained from parents of all study participants.

http://dx.doi.org/10.1016/j.oret.2017.04.001
ISSN 2468-6530/17

Study Population

Data for the current study were acquired from the prospectively collected multicenter Imaging and Informatics in ROP Research Consortium (i-ROP) database containing >19 000 fundus images from 2832 unique examinations of >900 infants screened for ROP at 8 major ROP centers. The participating centers were Oregon Health and Science University (Portland, OR), Weill Cornell Medical College (New York, NY), Bascom Palmer Eye Institute (University of Miami; Miami, FL), Children's Hospital Los Angeles (Los Angeles, CA), William Beaumont Hospital (Royal Oak, MI), Columbia University Medical Center (New York, NY), Cedars-Sinai Hospital (Los Angeles, CA), and Asociación para Evitar la Ceguera en México (APEC; Mexico City, Mexico).

As part of the study protocol, infants received standard dilated ophthalmoscopic examination by a study clinician, followed by wide-angle retinal photography (RetCam; Clarity Medical Systems, Pleasanton, CA) and masked remote interpretation of those photographs by several study experts. Infants were included in the current study if (1) an ROP diagnosis was made by both the study-site ophthalmologist, through indirect ophthalmoscopy, and 2 recognized ROP experts (M.F.C., R.V.P.C.) through image-based diagnosis and (2) a diagnosis of stage 4 or stage 5 ROP was made as part of the clinical diagnosis or the image-based diagnosis from either reader.

Image Acquisition

Infants underwent serial dilated ophthalmoscopic examinations by ROP center ophthalmologists and received a clinical diagnosis. All examinations were performed in accordance with current, evidence-based guidelines.[10] ROP center ophthalmologists were either principal investigators or certified investigators in the Early Treatment for Retinopathy of Prematurity study or had published >2 peer-reviewed articles on ROP. After clinical examination, a trained photographer took wide-angle fundus photographs using a commercially available wide-angle camera (RetCam; Clarity Medical Systems, Pleasanton, CA). A typical image set for each retina included 5 images: posterior pole, temporal retina, nasal retina, superior retina, and inferior retina. De-identified clinical data and images were uploaded to the secure i-ROP database.

Image Interpretation

Two study experts (M.F.C., R.V.P.C.) independently conducted remote, image-based interpretation of images through a secure web-based module designed by the coauthors. The image-based interpretation by the 2 study experts was performed at a future time and separate from the clinical examination with indirect ophthalmoscopy, to reduce bias. Wide-angle retinal images were presented on a per infant basis to simulate a real-world telemedicine examination scenario. The study experts were also provided basic demographic information (birth weight, gestational age, and postmenstrual age at time of examination). For each image set, experts were asked to choose the zone (I, II, III), stage (0, 1, 2, 3, 4, 5), plus (no, preplus, plus), category (mild, type 2 ROP or preplus, treatment-requiring ROP), and presence or absence of aggressive posterior retinopathy of prematurity (yes, no). In the database, stage 0 was used to diagnose cases where ROP was milder than stage 1 or if there was no active ROP seen.

Data Analysis

All data were analyzed using statistical software (Stata/SE 13.0; StataCorp, College Station, TX). Using the clinical diagnosis as the reference standard, we evaluated the performance of individual experts by comparing areas under the receiver operating characteristic curves to determine the sensitivity and specificity of diagnosis. In eye examinations with discrepancies between the clinical diagnosis and image-based diagnosis, reasons for diagnostic discrepancies were assigned by consensus of the authors after review of all study data and were determined to fall into ≥1 of the following categories: (1) hazy media, (2) could not appreciate traction and elevation of retina, or (3) insufficient retinal coverage.

Results

Study Participants

Of the infants screened, 1220 eye examinations from 230 infants met the inclusion criteria, and each infant had a mean of 2.65 imaging sessions (range, 1−13 sessions) that were eligible for the study. In all, 28 eye examinations had a clinical diagnosis of stage 4 or stage 5 disease.

Distribution of Image-Based Diagnosis for Eye Examinations with a Clinical Diagnosis of ROP Stage 4 or Greater

Among 28 eye examinations with a clinical diagnosis of stage 4 or worse disease, expert 1 agreed with the clinical diagnosis in 21 of 28 eye examinations (75%), and for the 7 discrepancies, the expert provided a diagnosis of stage 0 in 5 eye examinations and stage 3 in 2 eye examinations. Expert 2 had agreement in 24 of 28 eye examinations (85%), and for the 4 discrepancies, the expert provided a diagnosis of stage 0 in 4 eye examinations. Therefore, for the detection of stage 4 or worse disease, experts 1 and 2 had sensitivities of 75% and 86%, respectively.

Table 1 summarizes eye examinations with a clinical diagnosis of stage 4 disease and ≥1 image-based diagnosis of less than stage 4 disease. There was no eye examination for which the clinical diagnosis was stage 5 and the image-based diagnosis was less than stage 4. There were 3 eye examinations for which the clinical diagnosis was stage 4 but both experts provided an image-based diagnosis of stage 0. Potential reasons for diagnostic discrepancies for these examinations included hazy media (3 eye examinations, 37.5%), could not appreciate traction and elevation of retina (3 eye examinations, 37.5%), and insufficient retinal coverage (2 eye examinations, 25%). Hazy media was most often secondary to vitreous hemorrhage, other media opacity, or poor image quality. And in the cases where there was insufficient retinal coverage, the image sets provided to the 2 expert graders did not reveal the areas of pathology indicating stage 4 or stage 5 that were noted on the clinical examination by indirect ophthalmoscopy. Furthermore, image quality was rated as "not acceptable for diagnosis" in 5 of 16 (31%) eye examinations. Figure 1 shows examples of images of eyes with discrepancies between the clinical diagnosis and the image-based diagnosis.

Table 2 summarizes the accuracy of ROP diagnosis, using the clinical diagnosis as the reference standard. For the detection of stage 4 or worse disease, experts 1 and 2 had sensitivities of 75% and 86%, respectively. For the detection of stage 5 disease, both experts 1 and 2 had a sensitivity of 69%. In the 13 eye examinations with a clinical diagnosis of stage 5 disease, expert 1 provided an image-based diagnosis of stage 5 in 9 of 13 examinations (69%) and stage 4 in 4 of 13 examinations (31%). Similarly, expert 2 provided an image-based diagnosis of stage 5 in 9 of 13 examinations (69%) and stage 4 in 4 of 13 examinations (31%).