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Real-Time, Computer-Assisted Quantification of Plus Disease in Retinopathy of Prematurity at the Bedside

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Abstract

BACKGROUND AND OBJECTIVE—Plus disease is the primary indication for retinopathy of prematurity (ROP) treatment, but ophthalmologists often struggle to judge whether it is present. ROPtool is a semi-automated computer program that objectively assesses plus disease by measuring retinal vascular tortuosity and width. This study determined ROPtool's bedside diagnostic accuracy concurrent with ROP screening.

PATIENTS AND METHODS—ROP screening examinations were recorded using Keeler video indirect ophthalmoscopy. A masked operator traced images in ROPtool at the bedside, comparing ROPtool's plus diagnosis to the examiner's clinical judgment.

RESULTS—Four hundred sixty-four examinations (129 eyes of 65 infants) were performed. ROPtool's sensitivity, specificity, and area under the receiver operating characteristic curve for plus diagnosis was 71% (CI: 38%–100%), 93% (CI: 89%–98%) and 0.87, and for pre-plus or worse was 68% (CI: 51%–85%), 82% (CI: 77%–86%) and 0.81, respectively.

CONCLUSION—ROPtool can provide a real-time second opinion of plus disease at the bedside. Image enhancement technologies may further improve ROPtool's diagnostic accuracy.

INTRODUCTION

Retinopathy of prematurity (ROP) remains an important cause of treatable childhood blindness.[1] Optimal timing of treatment for severe ROP relies in part on accurate diagnosis of plus[2–4] and pre-plus[5] disease, defined based on the abnormal dilation and tortuosity represented by a standard photograph.[2] Disagreement on plus and pre-plus disease diagnosis is common, even among experienced examiners and experts in the field,[6–8] which may lead

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to inconsistency in diagnosis and treatment among medical centers.[9] It would be ideal to have objective measures of plus disease to assist with appropriate management of ROP.

ROPtool is a computer program with validated, semi-automated measures of retinal vascular dilation and tortuosity, and it can objectively diagnose plus and pre-plus disease from high-quality RetCam fundus photographs (Clarity Medical Systems, Pleasanton, CA) of infants with ROP.[10–12] ROPtool has the potential to be useful as a "second opinion." However, prior studies have not assessed ROPtool's real-time accuracy at the bedside. Previously validated for identification of clinically important ROP,[13] Keeler wireless digital indirect ophthalmoscopy (Keeler Instruments, Broomall, PA) was selected for this study because, in contrast to RetCam, it is noncontact, more portable, and significantly less expensive, making it more suitable for the developing world, where this technology may be useful. Disadvantages include lower image quality, smaller field of view, and the need for operator skills in indirect ophthalmoscopy. In this study, ROPtool was used at the bedside to quantify plus and pre-plus disease using video indirect ophthalmoscopic still images captured during routine indirect ophthalmoscopy and compared to the examiner's diagnosis as the reference standard.

PATIENTS AND METHODS

Study Participant Recruitment

Sixty-five infants undergoing routine ROP examinations were recruited in the neonatal intensive care unit at Duke Hospital. Parents or legal guardians of all infants undergoing routine ROP examinations were offered enrollment in this institutional review board–approved study, and informed consent was obtained. Infants could begin participation at any time prior to discharge from the hospital.

Reference Standard: Determination of Plus by Clinical Examination

According to standard ROP examination protocol, participants had their pupils dilated using a combination eye drop (cyclopentolate 0.2% and phenylephrine 1%). Each infant had his/her first examination performed 4 to 6 weeks after birth, following routine screening guidelines.[14] As usual, infants at risk for progression based on the clinician's funduscopic examination results were monitored more closely (every week) than others (every 2 weeks) for the next 3 to 4 months.

During each routine ROP examination, one of two ROP-experienced examiners (SFF or DKW) graded each quadrant as plus, pre-plus, or neither, without knowledge of ROPtool's analysis. The overall designation of plus, pre-plus, or neither was based on two or more quadrants meeting criteria, consistent with the clinical definition of plus disease.[15] The infants' treatment and follow-up were based on the examiner's clinical findings, consistent with standard care.

ROPtool Quantification of Vascular Abnormality

Each examination was videotaped using the Keeler wireless digital indirect ophthalmoscope with a 28-diopter condensing lens. Several still fundus images (typically five to 10 per eye)

centered on the optic nerve were taken while obtaining video footage. Masked to the clinical diagnosis, one researcher (MTC) selected two still images for analysis, based on qualitative assessment of best centration and focus. The setting for ROPtool analysis was identical to the setting where bedside examinations occurred but in a separate patient room, so that the examiner was masked to subject identity, health status, and the results of the clinical eye examination. ROPtool software was run by a single operator (MTC) to establish values for tortuosity-weighted plus,[12] a previously validated measure that combines ROPtool-generated tortuosity index and dilation index[10] into an overall measure of plus disease (Figure 1). Tortuosity-weighted plus mathematically accounts for the empiric observation that some examiners give dilation more weight as tortuosity increases.[12] To calculate sensitivity and specificity, ROPtool's values for tortuosity-weighted plus were converted to quadrant-level designations of plus, pre-plus, or neither based on previously chosen thresholds from an expert-validated ROPtool study using a selection of borderline plus disease enriched high-quality RetCam images.[12] Whole-eye designations of plus, pre-plus, or neither were based on two or more quadrants meeting criteria, consistent with the clinical definition of plus disease.[15] The total time required for each image analysis, from opening the image file to saving ROPtool's output, was measured on a stopwatch.

Calculating Image Quality

Image quality determination occurred on a subsequent day, with several days' still fundus images pooled together to minimize recall of ROPtool's individual image performance. Without access to clinical or ROPtool diagnosis, the examiner graded each quadrant on a scale from 1 to 4 for factors noted to interfere with ROPtool's ability to trace images, including fundus pigmentation, decentration, vessel blur, vessel obscuration due to glare, and vessel obscuration due to shadow (Table 1). For each image's composite quality score, the lowest quadrant image quality (based on the sum of quadrant scores, excluding fundus pigmentation) was calculated on a scale from 4 to 16 (25% to 100%) to estimate its impact on ROPtool's functionality.

Statistical Analysis

ROPtool's traceability was defined as at least one vessel traced in all four quadrants for a distance of at least one disc diameter, as described previously.[12,16] Among the best-quality traceable images, ROPtool's sensitivity and specificity for assessment of plus and pre-plus disease were calculated, using the examiner's clinical bedside diagnosis as the reference standard. Predetermined cut points for plus and pre-plus disease were used for this analysis, based on previous ROPtool validation with three-expert consensus analyzing high-quality RetCam photographs.[12] Logistic regression was used to determine the influence of clinical and demographic parameters on ROPtool's diagnostic agreement with the examiner.

Receiver operating characteristic curves were generated at the quadrant level using varying cut points of tortuosity-weighted plus values for both plus and pre-plus or worse diagnosis to generate sensitivity on the y-axis and 1-specificity on the x-axis, with the examiner diagnosis as the reference standard.

For all of the above calculations, generalized estimating equations were used to account for multiple observations per infant. Analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

In total, 464 examinations of 129 eyes of 65 premature infants (33 white, 28 black, and two Hispanic) were performed. Median gestational age was 26 weeks (range: 23 to 34 weeks), and median birth weight was 850 g (range: 473 to 1,660 g). Median number of visits per infant was three (range: 1 to 12). Median postmenstrual age at the time of examination was 36 weeks (range: 30 to 58 weeks). Among those with complete clinical fundus evaluation, plus disease was present in 16 of 462 examinations (3.5%) and six of 65 infants (9.2%), and pre-plus was present in 38 of 462 examinations (8.2%) and 14 of 65 infants (21.5%).

ROPtool's Performance at the Bedside

The median composite image quality score among all best images was 81% (13/16; range: 7/16 to 16/16, or 44% to 100%). Eighty-two percent (380/464, CI: 76% to 88%) of these images were traceable by ROPtool. Of these, two clinical diagnoses were indeterminate because the examiner did not observe any major vessels in one quadrant, although ROPtool was able to trace a thin vessel in that quadrant. Among images with both ROPtool traceability and a clinical diagnosis, 15 of 378 (4.0%) had a clinical diagnosis of plus disease and 36 of 378 (9.5%) had a clinical diagnosis of pre-plus disease. Traceable images had a significantly higher image quality score compared to non-traceable images (median: 13/16 or 81%, compared to 11/16 or 69%, respectively; $P < .001$). Median time to complete each ROPtool analysis of traceable images was 2.2 minutes (range: 1 to 7.25 minutes).

To determine ROPtool's reproducibility at the bedside, quadrants from two different traceable video still images taken from the same imaging session were analyzed; agreement for plus disease diagnosis was 92% (CI: 90% to 93%) and 77% (CI: 75% to 80%) for pre-plus or worse.

Comparing ROPtool and Clinical Examiner's Diagnosis as Reference Standard

When using the examiner's diagnosis as the reference standard, the area under the receiver operating characteristic curve was 0.87 for diagnosing plus disease (Figure 2A) and 0.81 for diagnosing pre-plus or worse disease (Figure 2B). Using predetermined cut points from a previous study,[12] ROPtool's sensitivity and specificity for diagnosing plus disease was 10/14 or 71% (CI: 38% to 100%) and 337/361 or 93% (CI: 89% to 98%), and pre-plus disease was 34/50 or 68% (CI: 51% to 85%) and 265/325 or 82% (CI: 77% to 86%), respectively. Younger infant age at the time of examination ($P = .014$) and lower ROP stage ($P = .006$) were significantly associated with better diagnostic agreement between ROPtool and the examiner (Table 2). Sex, race, gestational age, weight, right or left eye, pupil size, ventilation status, identity of examiner, zone of disease, laser history, image quality, and retinal pigmentation were not associated with diagnostic agreement between ROPtool and the examiner (Table 2).

DISCUSSION

Availability of experienced providers to meet the needs of the community may be inadequate in some regions of the United States and certainly in developing countries.[17] Furthermore, ophthalmologists treating ROP are confronted with the subjective nature of stage, zone, and plus disease diagnosis,[2] which may result in over- or under-treatment.[9] Identification of plus disease in particular often predicts treatment.[2] Objective assistance with ROP diagnosis, including plus disease, would be ideal to address both the shortage of experienced examiners (via a telemedicine approach) and the inaccuracies of the bedside diagnosis.

Advantages of ROPtool include speed (median time to execute was just over 2 minutes) and good reproducibility. However, the diagnostic agreement between Keeler video indirect ophthalmoscopic images and an experienced examiner did not compare favorably to findings of a prior study[12] assessing ROPtool using RetCam images selected for high quality. We observed sensitivity, specificity, and area under the receiver operating characteristic curve of 71%, 93%, and 0.87, respectively, compared to 85%, 85%, and 0.94 in the previous study.[12] Although the magnification of the video indirect images in the present study differed from that of RetCam images used previously, ROPtool software accounts for magnification in its calculations.[10]

The present study has greater relevance to ROPtool's real-world application at the bedside; however, one explanation for our lower sensitivity and area under the receiver operating characteristic curve is the inferior quality of still images taken during video indirect fundus photography (vs selection of only high-quality RetCam photographs in the prior study). Lower-quality video indirect photographs may have resulted in overall changes in ROPtool's measurements; for example, image blurring can make a vessel look wider and cause ROPtool to overestimate retinal vascular thickness. As expected, lower image quality contributed to poor traceability because nontraceable images had lower image quality compared to traceable images. ROPtool was able to successfully trace only 82% of video indirect images (compared to 100% of high quality RetCam images previously[12]). It is possible that a 20- rather than 28-diopter condensing lens would have resulted in higher-quality images. Nonetheless, the 28-diopter lens is preferred by many ROP examiners due to its wider field of view.

Our point estimates of ROPtool's reproducibility and agreement with the examiner were both less favorable for diagnosing pre-plus compared to plus disease. Pre-plus is more subjectively defined (abnormal dilation and tortuosity but less than the standard plus disease photograph).[15] Therefore, the examiner's diagnosis may be less consistent, leading to less agreement with ROPtool. Furthermore, because pre-plus values are lower than plus values, errors of similar magnitude in ROPtool's measurements may have been magnified because they represented larger percentages of the tortuosity-weighted plus value.

One possible limitation of this study is that the examiner's bedside diagnosis may be inaccurate. Previous studies have shown that experts and experienced examiners often disagree on the diagnosis of plus and pre-plus disease.[6–8] We considered using an alternative

reference standard based on three-expert consensus interpretation of ophthalmoscopic videos. However, unlike RetCam images, expert interpretation of Keeler ophthalmoscopic video has not been validated previously and therefore cannot be considered a reliable reference standard. This study's level of agreement in the diagnosis of plus disease between ROPtool and each examiner (SFF vs DKW) was similar (90% vs 95%; $P = .22$) (Table 2). Furthermore, studies that guide current treatment criteria, such as Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP)[18] and Early Treatment for Retinopathy of Prematurity (ETROP),[3] were based on the examiner's clinical diagnosis. Therefore, the examiner's clinical diagnosis remains the gold standard.

This study must be viewed in light of some additional limitations. Plus disease was graded by examiners at the quadrant level, which is not the typical way of diagnosing plus disease in the clinical setting. Nonetheless, quadrant-level diagnosis allowed for construction of more accurate receiver operating characteristic curves, because it increased the number of observations fourfold. Furthermore, quadrant -evel diagnosis is relevant to current diagnostic criteria, which stipulate that at least two quadrants must have sufficient abnormality to diagnose plus disease.[15] Whole-eye diagnoses were extrapolated and used for all other analyses. If ROPtool's thresholds for plus and pre-plus disease were based on video images rather than RetCam images from prior studies,[12] it is possible that ROPtool's performance in this study would have improved. Nonetheless, we decided to use RetCam image interpretation from prior studies[12] for cut point selection because video indirect image interpretation is not a well-established standard. This study was also limited by lack of validation of ROPtool with a second ROPtool operator. However, ROPtool inter-operator validation has been performed previously with 95% concordance.[19]

There are challenges worldwide to delivering care to infants with retinopathy of prematurity, as fewer ophthalmologists are able and willing to evaluate and treat the disease, while a higher proportion of premature infants survive to warrant ROP screening.[20] This study demonstrates that ROPtool's utility as a clinical adjunct for ROP diagnosis with current video indirect imaging shows promise, but it cannot be considered a highly accurate second opinion at the bedside yet. Image enhancement technologies,[21,22] advancements in video indirect image quality, use of RetCam instead of video indirect ophthalmoscopy, and adjustments in ROPtool's pre-plus and plus thresholds may improve ROPtool's future performance at the bedside, and these modifications deserve further study.

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REFERENCES

1. Kong L, Fry M, Al-Samarraie M, Gilbert C, Steinkuller PG. An update on progress and the changing epidemiology of causes of childhood blindness worldwide. J AAPOS. 2012; 16(6):501–507. [PubMed: 23237744]
2. An international classification of retinopathy of prematurity. Br J Ophthalmol. 1984; 68(10):690–697. [PubMed: 6548150]

3. Good WV. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. Trans Am Ophthalmol Soc. 2004; 102:233–248. discussion 248–250. [PubMed: 15747762]
4. Mintz-Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011; 364(7):603–615. [PubMed: 21323540]
5. Wallace DK, Freedman SF, Hartnett ME, Quinn GE. Predictive value of pre-plus disease in retinopathy of prematurity. Arch Ophthalmol. 2011; 129(5):591–596. [PubMed: 21555612]
6. Chiang MF, Jiang L, Gelman R, Du YE, Flynn JT. Interexpert agreement of plus disease diagnosis in retinopathy of prematurity. Arch Ophthalmol. 2007; 125(7):875–880. [PubMed: 17620564]
7. Wallace DK, Quinn GE, Freedman SF, Chiang MF. Agreement among pediatric ophthalmologists in diagnosing plus and pre-plus disease in retinopathy of prematurity. J Aapos. 2008; 12(4):352–356. [PubMed: 18329925]
8. Slidsborg C, Forman JL, Fielder AR, et al. Experts do not agree when to treat retinopathy of prematurity based on plus disease. Br J Ophthalmol. 2012; 96(4):549–553. [PubMed: 22174097]
9. Darlow BA, Elder MJ, Horwood LJ, Donoghue DA, Henderson-Smart DJ. Does observer bias contribute to variations in the rate of retinopathy of prematurity between centres? Clin Exper Ophthalmol. 2008; 36(1):43–46.
10. Kiely AE, Wallace DK, Freedman SF, Zhao Z. Computer-assisted measurement of retinal vascular width and tortuosity in retinopathy of prematurity. Arch Ophthalmol. 2010; 128(7):847–852. [PubMed: 20625044]
11. Wallace DK, Freedman SF, Zhao Z, Jung SH. Accuracy of ROPtool vs individual examiners in assessing retinal vascular tortuosity. Arch Ophthalmol. 2007; 125(11):1523–1530. [PubMed: 17998514]
12. Cabrera MT, Freedman SF, Kiely AE, Chiang MF, Wallace DK. Combining ROPtool measurements of vascular tortuosity and width to quantify plus disease in retinopathy of prematurity. J Aapos. 2011; 15(1):40–44. [PubMed: 21397804]
13. Prakalapakorn SG, Freedman SF, Wallace DK. Evaluation of an indirect ophthalmoscopy digital photographic system as a retinopathy of prematurity screening tool. J AAPOS. 2014; 18(1):36–41. [PubMed: 24568980]
14. Early Treatment For Retinopathy Of Prematurity Cooperative G. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol. 2003; 121(12):1684–1694. [PubMed: 14662586]
15. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005; 123(7):991–999. [PubMed: 16009843]
16. Ahmad S, Wallace DK, Freedman SF, Zhao Z. Computer-assisted assessment of plus disease in retinopathy of prematurity using video indirect ophthalmoscopy images. Retina. 2008; 28(10): 1458–1462. [PubMed: 18664936]
17. Richter GM, Williams SL, Starren J, Flynn JT, Chiang MF. Telemedicine for retinopathy of prematurity diagnosis: evaluation and challenges. Surv Ophthalmol. 2009; 54(6):671–685. [PubMed: 19665742]
18. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. Pediatrics. 2000; 105(2):295–310. [PubMed: 10654946]
19. Wallace DK, Zhao Z, Freedman SF. A pilot study using “ROPtool” to quantify plus disease in retinopathy of prematurity. J Aapos. 2007; 11(4):381–387. [PubMed: 17532238]
20. Quinn GE, Gilbert C, Darlow BA, Zin A. Retinopathy of prematurity: an epidemic in the making. Chin Med J (Engl). 2010; 123(20):2929–2937. [PubMed: 21034609]
21. Estrada R, Tomasi C, Cabrera MT, Wallace DK, Freedman SF, Farsiu S. Enhanced video indirect ophthalmoscopy (VIO) via robust mosaicing. Biomedical optics express. 2011; 2(10):2871–2887. [PubMed: 22091442]
22. Estrada R, Tomasi C, Cabrera MT, Wallace DK, Freedman SF, Farsiu S. Exploratory Dijkstra forest based automatic vessel segmentation: applications in video indirect ophthalmoscopy (VIO). Biomedical optics express. 2012; 3(2):327–339. [PubMed: 22312585]

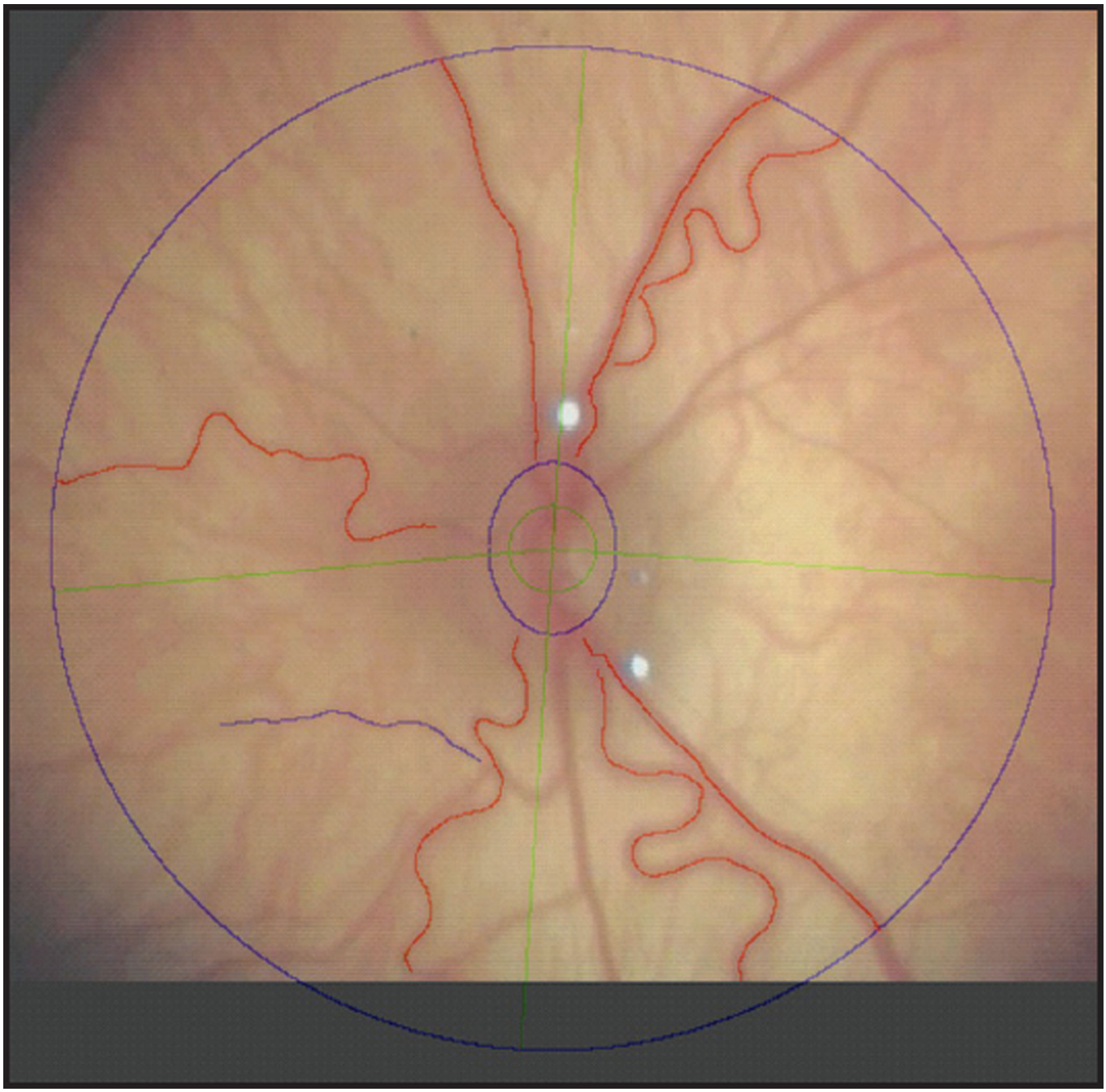

Figure 1.

Example of ROPtool's desktop user interface. ROPtool's computer-assisted tracing of a retinal still image from video indirect ophthalmoscopy of an infant with retinopathy of prematurity is shown, with output of each quadrant's tortuosity index and dilation index. Calculations of plus disease by sum of adjusted indices and tortuosity-weighted plus (TWP) are shown. The current study used TWP for all analyses.

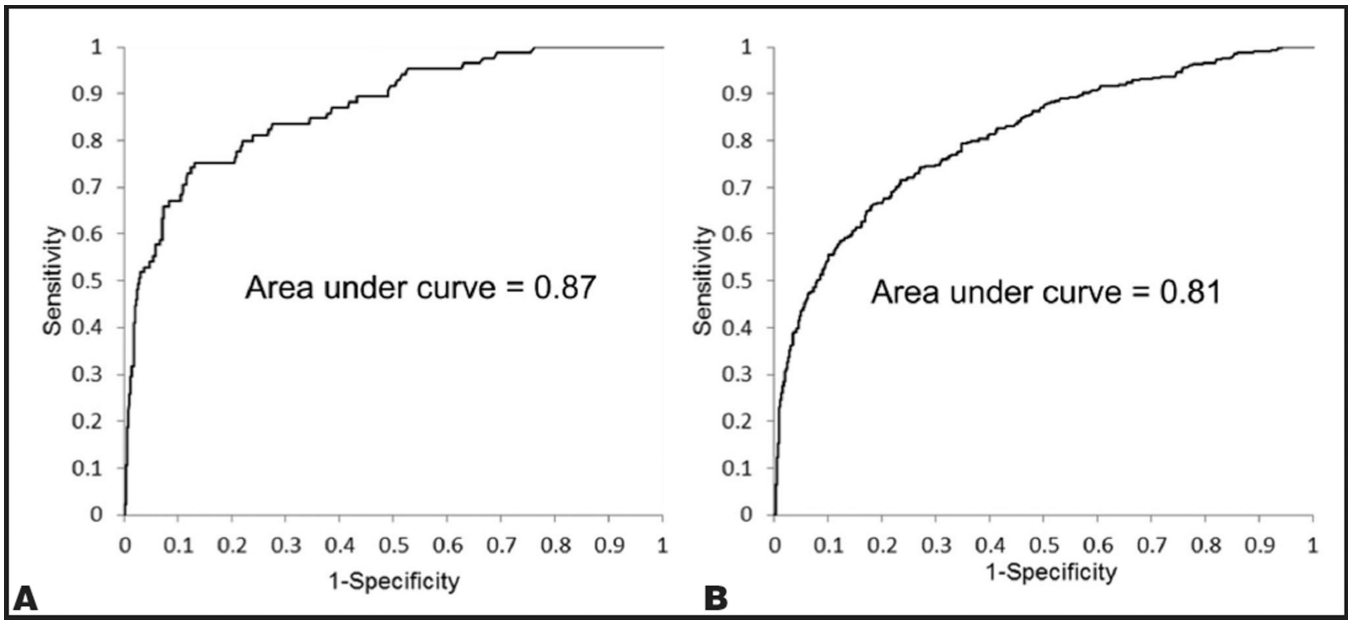

Figure 2.

Receiver operating characteristic curve for ROPtool computer program's diagnosis of plus disease (A) and pre-plus disease (B) or worse, with the examiner's clinical diagnosis as the reference standard.

TABLE 1

Image Quality Measures and Score Definitions

Image Characteristic*	Score 1	Score 2	Score 3	Score 4
Fundus pigmentation	Light	Medium	Dark	
Decentration	Entire quadrant missing or less than or equal to 1 disc diameter of length of major vessels present in quadrant or center of macula missing from whole eye image.	Between 1 and 2 disc diameters of length of major vessel present in quadrant.	Slightly shortened quadrant size.	Normal quadrant size or enlarged quadrant size due to decentration.
Vessel blur	Extremely distorted image quality due to defocus.	Substantial blurring of vessels.	Slight blurring of vessel margins.	Sharp or almost sharp vessel margins.
Vessel obscuration due to glare	Vessels almost completely obscured under diffuse mild to moderate glare or substantial glare takes up greater than half of the quadrant.	Vessels moderately obscured under diffuse mild glare or substantial glare takes up greater than a quarter and less than half of the quadrant.	Mild glare takes up most of the quadrant and vessels not noticeably obscured or substantial glare takes up less than a quarter of the quadrant.	No glare.
Vessel obscuration due to shadow	Vessels almost completely obscured under diffuse mild to moderate shadow or substantial shadow takes up greater than half of the quadrant.	Vessels moderately obscured under diffuse mild shadow or substantial shadow takes up greater than a quarter and less than half of the quadrant.	Mild shadow takes up most of the quadrant but vessels not noticeably obscured or substantial shadow takes up less than a quarter of the quadrant.	No shadow.

*Image quality was graded in each quadrant for these characteristics. A composite image quality score was calculated from the sum of decentration, vessel blur, vessel obscuration due to glare, and vessel obscuration due to shadow scores.

TABLE 2

Influence of Infant, Image, and Examiner Factors on Plus Disease Diagnosis Agreement Between ROPtool and the Examiner

Variable	Statistic	No Agreement for Plus Disease[a] (n = 28)	Agreement for Plus Disease[a] (n = 347)	*P* Value
Gender				
Male	N (%)	9 (7)	129 (93)	717
Female	N (%)	19 (8)	218 (92)	
Race[b]				
White	N (%)	22 (10)	199 (90)	.112
Black	N (%)	5 (4)	137 (96)	
Gestational age in weeks	Median (range)	25 (23–28)	26 (23–34)	.160
Weight in grams	Median (range)	785 (473–1110)	840 (473–1660)	.259
Age in postmenstrual weeks	Median (range)	38.5 (34–53)	36 (30–58)	.014[c]
Eye				
Right	N (%)	19 (10)	177 (90)	.051
Left	N (%)	9 (5)	170 (95)	
Pupil[d]	Median (range)	6 (4–8)	7 (2–9)	.281
Ventilation status				
No oxygen	N (%)	18 (7)	223 (93)	
Nasal cannula	N (%)	5 (6)	72 (94)	.779
CPAP	N (%)	3 (8)	35 (92)	
Intubated	N (%)	1 (1)	8 (89)	
Examiner				
SFF	N (%)	18 (10)	157 (90)	.222
DKW	N (%)	10 (5)	190 (95)	
Stage of retinopathy of prematurity				
0	N (%)	3 (3)	104 (97)	
1	N (%)	2 (3)	61 (97)	.006c
2	N (%)	9 (6)	136 (94)	
3	N (%)	13 (25)	39 (75)	
Zone of retinopathy of prematurity				.134

Variable	Statistic	No Agreement for Plus Disease[a] (n = 28)	Agreement for Plus Disease[a] (n = 347)	*P* Value
1	N (%)	2 (6)	30 (94)	
2	N (%)	22 (8)	242 (92)	
3	N (%)	2 (3)	62 (97)	
Fully vascularized	N (%)	0	6 (100)	
Laser prior to exam				
No	N (%)	18 (5)	316 (95)	.122
Yes	N (%)	10 (24)	31 (76)	
Image quality score[e]	Median (range)	13.5 (9–15)	13 (9–16)	.536
Fundus pigmentation				
Light	N (%)	16 (13)	109 (87)	.308
Medium	N (%)	8 (5)	141 (95)	
Dark	N (%)	4 (4)	97 (96)	

[a] Frequencies in subcategories may not sum to the totals due to missing data.

[b] Hispanics not included here because group was too small.

[c] P value < .05.

[d] Size in mm.

[e] A composite image quality score for the worst quadrant from each fundus image used in ROPtool, which is the sum of scores for decentration, vessel blur, vessel obscuration due to glare, and vessel obscuration due to shadow; lower scores represent lower quality