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Accuracy and Reliability of Telemedicine for Diagnosis of Cytomegalovirus Retinitis

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Keywords

telemedicine; cytomegalovirus retinitis; HIV/AIDS; Thailand

INTRODUCTION

The World Health Organization estimates that there are currently 33.4 million people living with HIV world-wide, with the most severely affected regions being Sub-Saharan Africa, Southeast Asia and India.¹ In many of these countries, intensive national and international efforts have led to the development of programs for HIV diagnosis and treatment. In contrast, most of these programs have no systems in place for screening patients for CMV disease. As a consequence, CMV retinitis is emerging as a leading cause of blindness in regions of the world most severely affected by HIV/AIDS.^{2–7} Nevertheless, it is difficult to fully understand the magnitude of this problem since limited screening for CMV retinitis is taking place in these regions. In Southeast Asia, CMV retinitis may be present in as many as one-third of patients with AIDS.² At Chiang Mai University in northern Thailand, CMV retinitis is the second most common cause of blindness, just behind cataract.⁸

Using indirect ophthalmoscopy, an experienced ophthalmologist can detect CMV retinitis in a highly sensitive and specific manner. Unfortunately, the countries with the highest prevalence of HIV infection often have the fewest ophthalmologists and are therefore unable to meet the existing and growing need for screening examinations. As the number of at-risk patients is large and increasing in regions affected by the current HIV/AIDS pandemic, novel ways of screening for CMV retinitis are needed.

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In the current study we describe the use of a commercially available, non-contact retinal camera to obtain retinal images for remote diagnosis of CMV retinitis by expert graders with extensive experience in diagnosing and treating CMV retinitis. We propose that telemedicine can be an effective strategy to screen for CMV retinitis in under-served areas. We chose to study the application of telemedicine for CMV retinitis in northern Thailand due to the excellent existing ophthalmic care and internet capabilities coupled with the high prevalence of disease and need for increased diagnostic capacity.

METHODS

Study Design.

We conducted a prospective study at the Ocular Infectious Diseases Clinic at the Maharaj Nakorn Chiang Mai Hospital, a university-based tertiary medical center. From August 7, 2008 until April 9 2009, subjects were interviewed and examined according to a pre-specified protocol, with a standardized data form. We enrolled all HIV-positive patients newly referred to the clinic in whom a clinical diagnosis of CMV retinitis was made, as well as those HIV-positive patients diagnosed with CMV retinitis at the clinic in the preceding month. In addition, from August 7, 2008 until January 7, 2009, we also enrolled all newly referred HIV-positive patients without clinical evidence of CMV retinitis.

Study visits took place on only one occasion for each enrolled subject. At this time, an attending ophthalmologist examined each enrolled patient with an indirect ophthalmoscope through a dilated pupil. A detailed retinal drawing was performed for each examined eye, with location of disease categorized by zone, as described previously.⁹ A trained ophthalmic photographer used a Topcon TRC-NW 6S digital fundus camera to capture ten images per eye (1 image of the external segment, and 9 overlapping 45° fundus images). Automated composite images covering an 85° retinal field were created for each photographed eye using software included with the camera, and both individual and composite images were then transferred to a secure online server via a file transfer protocol. Three expert graders (DH, GNH, TPM) evaluated each eye in 3 separate rounds of grading—first, the composite images; second, the single central image including the macula and optic nerve; and third, the set of all individual images. Each expert grader was a uveitis specialist with extensive expertise in diagnosing and treating CMV retinitis. Diagnosis of the presence or absence of CMV retinitis was made according to the clinical experience of each expert grader; zones were assigned using the same guidelines as used by the indirect ophthalmoscopist.⁹ Eyes were analyzed independently, in random order. No clinical information was provided to the remote expert graders. In each round of grading, images were graded for gradability, and the presence or absence of CMV retinitis, vitreous haze, and cotton wool spots. Gradability was defined as good (focused images including the entire 85° retinal field), acceptable (images did not include the entire 85° retinal field, but the presence or absence of CMV retinitis could still be determined; or images moderately out of focus), or poor (images included such a small degree of retinal field that no determination of the presence or absence of CMV retinitis could be made; or images were extremely out of focus). Remote expert grading was then compared to on-site examinations in Thailand, which served as the gold standard. After sensitivity and specificity were calculated, eyes that were incorrectly classified (false

positive or false negative) by all 3 remote expert graders were identified for further analysis. Two authors (AHS, JDK) analyzed the corresponding fundus images and retinal drawings of these eyes to determine reasons for misclassification.

Statistical analysis.

Descriptive data were analyzed as medians with interquartile range (IQR), or as proportions. The sensitivity and specificity of remote diagnosis by expert graders was calculated separately for each grader using the on-site examination as the gold standard. Eyes were excluded if the on-site ophthalmologist could not determine with certainty whether CMV retinitis was, or was not, present. The goal of remote screening by remote expert graders was to identify all possible cases of CMV retinitis for referral. Therefore, for the purposes of our analysis any eyes graded by the remote expert graders as either “CMV retinitis present” or “cannot determine” were classified as a CMV retinitis diagnosis. Negative and positive predictive values were calculated using the prevalence of CMV retinitis observed at the Ocular Infectious Diseases Clinic during the course of the study, including those not enrolled in the study. Exact binomial confidence intervals were calculated. Intra-rater reliability was estimated for each grader with a kappa statistic by comparing grades of 50 duplicate composite images. Inter-reader reliability was estimated for all 3 graders together, using a kappa statistic. Positive and negative predictive values were estimated assuming the prevalence of CMV retinitis seen at the clinic during the study period, and exact binomial confidence intervals for these values were estimated assuming the total number of patients seen during this time. All analyses were conducted with Stata 10 (Statacorp, College Station, TX).

RESULTS

Ninety-four patients were enrolled during the 8-month study period. Characteristics of these patients are summarized in Table 1. Ophthalmologists at Chiang Mai University diagnosed 59 of the 94 patients (62.8%) with CMV retinitis in at least one eye. They were able to definitively determine whether CMV retinitis was present or absent in 182 of the 188 eyes (96.8%). Of these, 89 eyes (48.9%) had CMV retinitis. Indirect ophthalmoscopy could not definitively determine the presence or absence of CMV retinitis in 6 eyes due to *seclusio pupillae* (n=3), dense vitreous haze/hemorrhage (n=2), or cataract (n=1); these 6 eyes were excluded from further analysis. At least one image was captured for each of the 182 eyes in the study. All captured images from these 182 eyes were successfully uploaded to an online server, and accessed by the three remote expert graders (Figure 1).

Remote Expert Grading.

With regard to gradability, remote expert graders determined that 81.9 – 92.9% of the composite images were satisfactory or good quality images. Detection of CMV retinitis by remote expert grading had a sensitivity of 88.8 – 91.0% and specificity of 84.9 – 88.2%, when the composite image was compared against the gold standard of indirect ophthalmoscopy. The sensitivity and specificity was similar when graders scored only a single central image (Table 2). When graders scored a set of individual 45° images for each eye instead of a single composite image, sensitivity decreased, and specificity increased

(Table 2). Intra-rater reliability was high ($\kappa=0.93$ for each grader). Inter-rater reliability among the three graders was also high ($\kappa=0.86$). The prevalence of newly-diagnosed CMV retinitis in eyes examined at the clinic during the study period was estimated as 35.6% (89/250). Assuming this prevalence, the positive predictive value ranged from 76.9 – 80.8% and the negative predictive value ranged from 93.4 – 94.5%.

Discrepancies.

There were 16 eyes for which at least one remote expert grader diagnosed CMV retinitis, but the onsite examiners did not diagnose CMV retinitis by indirect ophthalmoscopy (false positives). In 10 of these 16 eyes, CMV retinitis was diagnosed by all 3 remote expert graders. The images from seven of these ten eyes were rated as poor quality by 2 or more of the remote expert graders. In the remaining three eyes a post hoc analysis revealed either retinal scarring consistent with prior CMV retinitis (2 eyes), or a small patch of CMV retinitis in an eye with multiple cotton wool spots (1 eye). There were 12 eyes for which at least one grader failed to diagnose CMV retinitis, but a diagnosis was made by indirect ophthalmoscopy (false negatives). In 7 of these eyes, none of the remote expert graders made the diagnosis of CMV retinitis. Four of these 7 eyes had CMV retinitis in zone 3 only, and the remaining 3 eyes were scored by the remote expert graders as having cotton wool spots.

Zone 3 Retinitis.

CMV retinitis confined to zone 3 would not be detected by the camera used in this study. Indirect ophthalmoscopy classified 14 of 182 eyes as having CMV retinitis localized to zone 3 only. Nevertheless, remote expert graders failed to diagnose CMV retinitis in only 4 of these eyes. Review of the images of the remaining 10 eyes revealed that 2 had significant vitreous haze, 1 had a small focus of CMV retinitis in zone 1 that had been classified as a cotton wool spot by indirect ophthalmoscopy, 1 had an area of scarring in zone 2, and 6 were misclassified by the on-site ophthalmologist, as evidenced by retinal drawings that clearly show disease in zone 1 or 2.

DISCUSSION

In this study we have shown that remote expert graders can reliably diagnose CMV retinitis from photographs taken with an easy-to-use, commercially available digital retinal camera. When composite images were graded, sensitivity and specificity for CMV retinitis diagnosis approached 90%. Measures of intra- and inter-rater reliability were excellent, with kappas of 0.93 and 0.86, respectively. Our study demonstrates that remote expert graders can detect CMV retinitis with sensitivities and specificities comparable to those demonstrated for remote diagnosis of diabetic retinopathy.^{10, 11} In studies of telemedicine for diabetic retinopathy, sensitivities have ranged from 90–98%, and specificities from 88–100%. This level of sensitivity and specificity has proven sufficient for telemedicine screening of diabetic retinopathy, which is currently in use in some parts of North America.^{12, 13} Remote diagnosis of CMV retinitis also appears to be at least as effective as the use of the more expensive Ret-Cam for remote diagnosis of retinopathy of prematurity, where studies indicate sensitivities ranging from 46–97% and specificities ranging from 49–100%.¹⁴

Remote expert graders were completely masked. They received no clinical information about the patients, and analyzed each eye independently, not as a pair. While conservative, this study design denied diagnostic clues to the remote graders that were available to the on-site ophthalmologist, such as the patient's general appearance, chief complaint, medical history, and CD4 count. We suspect that this may have accounted for some of the differences in diagnosis made by the remote graders and the onsite ophthalmologist. In future applications of telemedicine for CMV retinitis diagnosis, these data, in particular CD4 count, could be provided to remote graders and may increase sensitivity and specificity for CMV retinitis diagnosis.

Although the possibility of using telemedicine for CMV retinitis diagnosis has been raised before,¹⁵ we are unaware of any studies that have examined the validity of telemedicine for CMV retinitis screening. Li and colleagues examined the feasibility of telemedicine for diagnosis of CMV retinitis among inmates using both still and video digital imaging systems. The feasibility of this approach was found to be highly dependent upon the ease of use of the imaging system, with a retinal camera being the easiest and most feasible system studied. For the current study, the Topcon TRC-NW 6S camera selected was chosen for its simplicity and ease of use.

As part of this study we made use of software incorporated into the Topcon imaging system for automatically creating composite retinal images from individual retinal photos taken with the patients' eye in different fields of gaze. During initial training we noted some problems with this software including the introduction of image blur and duplication, and improper image placement and alignment. Out of concern that these problems might reduce a remote expert reader's ability to accurately detect retinal disease, each reader scored not only a composite image but also a set of individual images taken of each eye. In contrast to our hypothesis, when readers graded these images, sensitivity of remote expert grading decreased. It is likely that a more comprehensive view of the fundus in the composite images was advantageous to remote expert readers, although we cannot rule out reader fatigue due to the increased volume of individual images necessary to make a diagnosis.

In this study we demonstrate excellent sensitivity, specificity, and inter- and intra-reader reliability for remote diagnosis of CMV retinitis, as performed by expert readers. We used expert graders because we wished to study the overall strategy of telemedicine diagnosis, not the skills of any specific grader. Now that acceptable diagnostic test properties have been established, a next step would be to train non-expert graders in reading centers, as has been done for other diseases such as diabetic retinopathy and retinopathy of prematurity.¹⁶ With appropriate training, non-expert trained readers can reliably diagnose these conditions with sensitivities and specificities approaching, if not surpassing, those of expert graders. The utility of non-expert graders in evaluating CMV retinitis from non-digital photographs has been previously demonstrated, and should be translatable to the digital era.¹⁷ An alternative to non-expert readers may be the development of pattern-recognition software for automated analysis of digital retinal images. This strategy has great potential and has been explored and found to be promising in the diagnosis of other retinopathies including diabetic retinopathy, age-related macular degeneration, and more recently, retinopathy of prematurity.^{18–22}

In the current study, the Topcon NW6S camera and its software package was used to obtain retinal images and to create automated composite images. Similar cameras are already in use in some primary care centers in Thailand for telemedicine diagnosis of diabetic retinopathy. Assuming that social, cultural and political issues can be overcome, the use of these existing cameras for imaging patients with AIDS could radically change the prevalence of blindness from CMV retinitis in Thailand. However, at a cost of ~\$30,000 the Topcon camera used in our study is simply too expensive to implement in most countries where screening for CMV retinitis is needed. Determining a cost-effective telemedicine approach for diagnosis of CMV retinitis will require a more complete understanding of the prevalence of this blinding disease and will likely depend upon development of reliable low-cost cameras. Developing a low-cost camera to reliably capture peripheral retinal images may prove more difficult than one that captures only central images. It is encouraging that in the current study, remote grading of central images (central 45 degrees) alone had nearly equivalent sensitivity (85.4–91%) and greater specificity (86–91.4%) to remote grading of composite photos covering the central 85 degrees of the fundus. While the excellent reliability of central images may reflect the advanced stage of disease in the patients enrolled, and may not prove generalizable, zone 1 disease is responsible for the majority of blindness from CMV retinitis.^{23, 24}

There were several limitations to the current study. One limitation was that the study was conducted at a tertiary medical center, which may limit the generalizability of our results. We chose this study site because it would readily allow us to conduct a proof-of-concept pilot study in a clinic known to have a high volume of CMV retinitis cases, as well as ophthalmologists experienced in the diagnosis of CMV retinitis. The experienced ophthalmic photographers in this setting may have contributed to the high rate of success. In addition, referral bias likely resulted in a relatively high percentage of study patients with easily photographed disease of the posterior pole. Further study outside of a tertiary medical center is warranted to determine the feasibility and generalizability of this technique in the primary care setting, where it would be most useful.

Another limitation of this study was that the imaging system we used did not capture images of the peripheral retina, specifically zone 3 and outer zone 2. The long-term risk of initially missing CMV retinitis limited to the peripheral retina in a patient population that is being treated with HAART has not been established. However, in the pre-HAART era in the United States only 2% of newly diagnosed CMV retinitis cases were exclusive to zone 3.²⁵ In addition, previous studies have demonstrated that posterior pole disease is responsible for the majority of CMV-related vision loss, rather than retinal detachments caused by peripheral lesions.^{23, 24} Thus, most vision threatening lesions are photographable and most patients initially presenting with isolated peripheral CMV retinitis may be identified during follow-up visits with serial imaging sessions before their disease is a serious visual threat.

The cost-effectiveness of a telemedicine approach to screen for CMV retinitis remains unclear, in part because of a lack of systematic screening in Thailand and elsewhere to determine the incidence of CMV retinitis in the HIV-positive population. The economic feasibility of a telemedicine approach will almost certainly hinge upon use of non-expert photographers and trained lay graders, as well as development of low-cost, easy to use retinal cameras that can be placed in HIV clinics. We are currently conducting studies to

determine the feasibility, accuracy, and reliability of non-expert photographers and trained lay graders in the primary care setting.

This study demonstrates that remote telemedicine diagnosis by remote experienced ophthalmologists can be a sensitive and specific method for diagnosing CMV retinitis among HIV patients. Given the limited availability of ophthalmologists in many regions of the world and the large and consistently growing numbers of patients at risk for CMV retinitis, telemedicine has the potential to significantly decrease blindness in the developing world.

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- D. Statement about conformity with author information: Institutional review board approval was obtained at the University of California, San Francisco, and Chiang Mai University, Chiang Mai, Thailand. The study adhered to the tenets of the Declaration of Helsinki. All study participants gave written informed consent.
- E. Other acknowledgements: None.

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Figure 1. Representative fundus images of CMV retinitis from a tertiary medical center in northern Thailand, captured with the Topcon TRC-NW 6S digital fundus camera. Images captured disease in zone 1 (upper left, upper right, lower left) and zone 2 (upper right, lower left, lower right).

Table 1.

Characteristics of 94 HIV-infected patients from an ocular infectious diseases clinic in Thailand who participated in a study to determine the reliability of telemedicine diagnosis of CMV retinitis

Characteristic	Median (IQR) or Proportion
Age, median years (IQR)	38 (33 – 45)
Female, %	53.2%
Self-reported CD4 count ^a	
Median (IQR)	52 (17.5 – 173.5)
CD4 < 50, %	48.4%
CD4 <100, %	62.5%
On antiretroviral therapy, %	76.6%
1 eye with CMV retinitis, %	62.8%
1 eye with visual symptoms, %	77.7%

IQR=interquartile range; CMV=cytomegalovirus

^aOnly 64 patients had available CD4 data

Table 2.

Sensitivity and specificity of remote CMV retinitis diagnosis, as compared to a gold standard of indirect ophthalmoscopy, in a study of 182 eyes examined at an ocular infectious diseases clinic in Thailand

	Grader 1	Grader 2	Grader 3
Gradability	87.9% (82.2 – 92.3)	92.9% (88.1 – 96.1)	81.9% (75.5 – 87.2)
Sensitivity			
Composite photograph	88.8% (80.3 – 94.5)	89.9% (81.7 – 95.3)	91.0% (83.1 – 96.0)
Central photograph	85.4% (76.3 – 92.0)	91.0% (83.1 – 96.0)	91.0% (83.1 – 96.0)
Individual photographs	79.8% (69.9 – 87.6)	82.0% (72.5 – 89.4)	84.3% (75.0 – 91.1)
Specificity			
Composite photograph	88.2% (79.8 – 93.9)	88.2% (79.8 – 93.9)	84.9% (76.0 – 91.5)
Central photograph	91.4% (83.8 – 96.2)	90.3% (82.4 – 95.5)	86.0% (77.3 – 92.3)
Individual photographs	91.4% (83.8 – 96.2)	91.4% (83.8 – 96.2)	88.2% (79.8 – 93.9)
Intra-rater reliability ^a	0.93 (0.80 – 1.00)	0.93 (0.80 – 1.00)	0.93 (0.79 – 1.00)
Positive Predictive Value	80.6% (71.4 – 87.9)	80.8% (71.6 – 88.0)	76.9% (67.3 – 84.5)
Negative Predictive Value	93.4% (88.2 – 96.8)	94.0% (89.0 – 97.2)	94.5% (87.8 – 96.7)

95% confidence intervals shown for all estimates.

^aKappa statistic for diagnosis of CMV retinitis comparing 50 duplicate composite images