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Title Page

Title: Accuracy of trained rural ophthalmologists versus non-medical image graders in the
diagnosis of diabetic retinopathy in rural China.

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Precis

Non-medical personnel in rural China graded images obtained by nurses on patients with high cataract prevalence, meeting standards of the United Kingdom's National Diabetic Eye Screening Programme, and surpassing the performance of trained local ophthalmologists.
Abstract

Background/aims To determine the diagnostic accuracy of trained rural ophthalmologists and non-medical image graders in the assessment of diabetic retinopathy (DR) in rural China.

Methods Consecutive patients with diabetes mellitus were examined from January 2014 to December 2015 at ten county-level facilities in rural Southern China. Trained rural ophthalmologists performed a complete eye examination, recording diagnoses using the United Kingdom National Diabetic Eye Screening Programme (NDESP) classification system. Two field, mydriatic, 45° digital photographs were made by nurses using NDESP protocols, and graded by trained graders with no medical background using the NDESP system. A fellowship-trained retina specialist graded all images in masked fashion and served as reference standard.

Results Altogether, 375 participants (mean age 60 +/-10 years, 48% men) were examined and 1277 images graded. Grader sensitivity (0.82-0.94 (median 0.88)) and specificity (0.91-0.99 (median 0.98)), reached or exceeded NDESP standards (sensitivity 80%, specificity 95%) in all domains except specificity detecting any DR. Rural ophthalmologists’ sensitivity was 0.65-0.95 (median 0.66) and specificity 0.59-0.95 (median 0.91). There was strong agreement between graders and the reference standard (kappa=0.84-0.87, P<0.001) and weak-moderate agreement between rural doctors and the reference (kappa= 0.48-0.64, P<0.001).
Conclusion This is the first study of diagnostic accuracy in DR grading among non-medical graders or ophthalmologists in LMICs. Non-medical graders can achieve high levels of accuracy, whereas accuracy of trained rural ophthalmologists is not optimal.
INTRODUCTION

China faces the world’s largest diabetes mellitus (DM) epidemic, with the prevalence in Chinese adults increasing from <1% in 1980,[1] to 11.6% in 2010,[2]. This represents an estimated 114 million affected persons, the largest number of any country in the world, placing an enormous public health burden on Chinese health services,[3]. Of note, half of the Chinese adult population suffers from pre-diabetes (50.1%), suggesting that DM prevalence will continue to rise,[2].

Diabetic Retinopathy (DR), together with diabetic macular edema (DME) is a major microvascular complication of DM. It is the leading cause of blindness and visual impairment in the working-age population worldwide, except in relatively few countries such as Iceland and the UK, where established screening programmes have led to DR no longer being the most common cause of blindness in this age group.[4]. Approximately 75% of those with DM in China will experience DR/DME within 15 to 20 years of diagnosis,[5]. Early diagnosis and prompt laser treatment prevents blindness in more than 90% of cases, therefore regular and accurate DR screening is critical,[6]. DR is a particular concern in rural China, as a recent population study showed that only 10% of patients with diabetic eye disease are diagnosed and treated in such settings,[7]. Moreover, 43% of those with DM in rural China have DR/DME, 6.3% with vision-threatening disease, both higher than for most other reported populations,[7].
In rural China, 81% of patients with DM do not receive an annual eye examination,\cite{8} as recommended by Chinese guidelines adopted from the American Academy of Ophthalmology,\cite{9} and 69% have never received an eye examination,\cite{8}. This is largely due to uneven distribution of providers, with 80% of Chinese ophthalmologists located in urban areas,\cite{10}. Therefore, it is necessary to explore alternate DR screening approaches in order to reduce demands on the small cadre of rural Chinese ophthalmologists, so capacity is freed for seeing those requiring treatment. To achieve this, critical evaluation of the accuracy of different models of rural DR screening is required.

The aim of the present study is to compare the accuracy of two methods of DR screening: trained rural doctors performing complete eye examinations with grading of DR severity, and trained non-medical graders remotely examining retinal photographs taken by ophthalmic nurses.

**METHODS**

**Study Setting**

This study was undertaken in Guangdong Province, Southern China. Data were collected from the Comprehensive Rural Eye Service Training (CREST) programme, an ongoing, five year collaboration
between Zhongshan Ophthalmic Center (ZOC) and ORBIS International.[11]. The ten hospitals involved were chosen for geographic coverage of the province, and their ability to perform independent cataract surgery, indicating readiness for training in management of more complex diseases. The CREST programme aims to create a rural model of comprehensive eye care, including the specific goal of developing capacity to diagnose and treat DR, including DME. From the outset, the project was designed to compare the accuracy and efficiency of two screening methods in the assessment of DR,[12], trained rural ophthalmologists and non-medical graders using digital images.

The protocol for the current study was approved in full by the Ethics Committee at Zhongshan Ophthalmic Center (ZOC), Sun Yat-sen University, Guangzhou, China, and patients, providers and graders taking part provided oral informed consent. The tenets of the Declaration of Helsinki were followed throughout.

**Study Design and Participants**

This was a retrospective analysis of consecutive patients screened for DR in the CREST programme between 1 January 2014 and 31 December 2015. Eligibility criteria included:

- Age $\geq 18$ years.
- Diagnosis of DM according to the International Diabetes Classification.[13]
• Receipt of a complete eye examination in a rural clinic in the CREST network.

• Existence of a record in the project’s Electronic Medical Record (EMR) system.

• Retinal photography completed in at least one eye.

Training and Diagnostic Methods

Rural ophthalmologists

At each CREST facility, at least two ophthalmologists underwent training in identifying and grading both glaucoma and DR involving two phases: two months at ZOC (the project coordinating center), consisting of didactic lectures, observation of clinics and surgery and practical sessions on Goldmann applanation tonometry, slitlamp biomicroscopy, indirect ophthalmoscopy and gonioscopy, proctored by senior sub-specialists; and a hands-on training phase, during which sub-specialists in glaucoma and DR from ZOC travelled to the ten CREST hospitals on a rotating basis to supervise pan-retinal photocoagulation (PRP), focal laser and trabeculectomy surgery. Hands-on training also included a graded checklist review of all phases of a complete eye examination. Areas graded as weak on one training visit would receive additional emphasis on the next; a total of 65 training visits were completed from 1 January 2014 to 31 December 2015.
Rural ophthalmologists’ assessment of severity of DR/DME status was determined by complete bilateral eye examinations on all patients aged 40 years and above, including all persons known to have DM. Examinations included evaluation of the following: visual acuity, intraocular pressure (IOP), pupillary response including presence of afferent pupillary defect, gonioscopy, anterior segment, and examination of the fundus and optic nerve with 90D lens and indirect ophthalmoscopy after pharmacological dilation of the pupil. Ophthalmologists recorded their diagnoses in the CREST Electronic Medical Record (EMR) system using the United Kingdom National Diabetic Eye Screening Programme (UK NDESP) grading framework.[14].

Trained non-medical graders

All retinal images were acquired (3Nethra Classic, Forus, Inc., Bangalore, India) by 17 ophthalmic nurses at the ten centers after having successfully completed a one-week training provided by technicians from Forus. Photographers captured two 45° fields per eye at 1024x768 resolution, one image centered on the macula and the other on the optic nerve, in accordance with UK NDESP DR screening protocol.[15] Nurses were trained to identify and repeat inadequate images as a quality control measure. Images were uploaded to a software system created specifically for the project (CSIRO, Perth, Australia) and transferred to ZOC for grading. Retinal photographs were taken on the same day as the rural
ophthalmologist’s diagnosis. Rural doctors were not shown these images and were masked to the results of DR grading at the time of their clinical assessment.

Four graders based at ZOC with secretarial or data entry backgrounds, and without any history of medical training, received one-month of intensive grader’s training, supervised by a trained ophthalmologist who completed his grading training at the University of Wisconsin-Madison Fundus Photograph Reading Center in the United States. Graders’ training focused on ocular anatomy, retinal disease, DR signs and severity based on the UK NDESP DR grading protocols, with a marked examination at the end of the training course. This was further supplemented by routine quality assurance monitoring exams every three months for the first year, followed by one to two routine exams per year thereafter, all requiring the grading of standard image sets downloaded from the Reading Centre at Moorfields Eye Hospital NHS Foundation Trust’s website.[16].

Two graders assessed each photograph independently and graded it according to the UK NDESP National Grading system. All disagreements, and an additional 10% of all images, were sent for re-grading and internal quality assurance. These images were referred to an arbitrator, the ophthalmologist who supervised grader training, and his decision was taken as final. The arbitrator was not the same
ophthalmologist as the reference standard (see below), and evaluated the images in a fully masked, independent way.

Image quality was rated “adequate” or “inadequate” for grading in accordance with NDESP guidelines. An image was deemed adequate if it met the following criteria:

- Macular image: Center of fovea >2DD (disc diameters) from edge of image, and vessels visible within 1DD of center of fovea.
- Disc image: Complete optic disc >2DD from edge of image, and fine vessels visible on surface of disc.

Reference Standard

A reference standard was used to assess the accuracy of assessments by the non-medical graders and local ophthalmologists. This reference standard was a senior retina specialist with full medical and surgical retina training to the fellowship level, and was not included in the training of the non-medical graders or the rural ophthalmologists. DR grading of all retinal images using the grading system and protocols outlined above was carried out by the reference standard, masked to any prior diagnoses or grades from the rural physicians or graders.
Statistical Methods

Data were entered into an Excel spreadsheet and data were analyzed using IBM SPSS Statistics v23 software (IBM Corporation, Armonk, NY). Sensitivity and specificity (with 95% Confidence Intervals), positive and negative predictive values, area under the receiver operating characteristic (ROC) curve and kappa statistic comparing both rural ophthalmologists and graders with the reference standard were calculated for the following:

- **Any Diabetic Retinopathy (Any DR)** - defined as grades R1 (mild nonproliferative phase), R2 (moderate or severe nonproliferative phase), R3a (active proliferative phase) and R3s (stable proliferative retinopathy). A grade of R0 was defined as no diabetic retinopathy.

- **Diabetic Retinopathy (DR) requiring treatment** - defined as R3a grade. Grades of R0, R1, R2 or R3s were defined as DR not requiring treatment.

- **Diabetic Macular Edema (DME) requiring referral** - defined as grade of M1 (any macular edema). A grade of M0 was defined as no diabetic macular edema.

In addition, the non-medical graders’ diagnostic accuracy was assessed separately for those cases where there was no intervention by the arbitrator, and when intervention by the arbitrator was mandated by protocol, to investigate possible effects of the arbitrator’s involvement.
Logistic regression models were used to examine the association between various characteristics of the rural physicians and correct diagnosis of DR requiring treatment, defined as agreement with the reference standard. The Generalised Estimating Equations procedure was used to adjust for the correlation between two eyes of the same patient, and for repeated measures. Variables found to be significant at the 0.05 level in simple univariate models were entered into the multiple regression models, after investigation of potential co-linearity of variables, and further developed through removal of non-significant variables by backward elimination.

RESULTS

Participant Characteristics

Rural Ophthalmologists, Graders and Reference Standard

A total of 28 rural ophthalmologists were involved in the study (mean age 37.0 years, standard deviation (SD) 7.3 years, 77% male), who had a median 10.5 years of experience in ophthalmic practice (inter-quartile range 5.25-19.0) and a median 5.5 years providing cataract surgery independently (inter-quartile range 0.0-15.8). The four graders had a mean age of 28 years (SD 3.37) and 75% were female. The reference standard was a 35-year-old male who had completed retina fellowship training 24 months prior to taking part in the study.
Patients

Between January 2014 and December 2015, 6824 patients were recorded in the CREST EMR system, of which 537 (7.87%) were identified as having DM. A total of 375 persons (69.8%, mean age 60.3 [10.4] years, 47.7% male) among this cohort successfully completed retinal photography in at least one eye, and were eligible for the study. These patients had a median 6-year known duration of DM (inter-quartile range 2-10 years), and 240 (64.0%) were identified by the rural ophthalmologist as having cataract on dilated slitlamp examination.

Images, diagnosis and grading

Among 375 participants, 357 (95.2%) had at least one image in each eye, and 18 (4.8%) had images for only one eye, for a total of 732 eyes and 1277 images, which serve as the basis for all subsequent analyses. Grading by the reference standard showed 394 (55%) eyes had no DR, 323 (45%) had any DR, including the 68 (9%) eyes with DR requiring treatment. DME requiring referral was seen in 172 (25%) of eyes (Table 1). Rural doctors failed to record DR and DME status in the EMR system in 11/750 (1.47 %) and 65/750 (8.67 %) eyes respectively. Graders failed to assign grades for DR and DME status in 24/732 (3.28%) and 56/732 (7.65%) eyes respectively, and identified 312/732 eyes (42.6%) as having images of inadequate quality (though the majority of these were still gradable for certain characteristics, see below). Of these, 177/312 (56.7%) were due to fewer than two images being available for an eye,
contrary to NDESP image quality criteria,[15]. Retinal images were unavailable to the reference standard for 17 (2.3%) eyes. The reference standard failed to assign grades for DR and DME status in 33/750 (4.4%) and 55/750 (7.3%) eyes respectively, though he identified a total of 245/733 (33.4%) images as not being of adequate quality, of which, of which 103/245 (42%) were due to there being fewer than two images available for an eye.

Table 1. Diagnostic results of rural doctors, non-medical graders and the reference standard.

<table>
<thead>
<tr>
<th></th>
<th>Rural Doctors</th>
<th>Non-medical Graders</th>
<th>Reference Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DR grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R0</td>
<td>255 (35)</td>
<td>375 (53)</td>
<td>394 (55)</td>
</tr>
<tr>
<td>R1</td>
<td>237 (32)</td>
<td>160 (22)</td>
<td>148 (21)</td>
</tr>
<tr>
<td>R2</td>
<td>134 (18)</td>
<td>105 (15)</td>
<td>102 (14)</td>
</tr>
<tr>
<td>R3s</td>
<td>6 (1)</td>
<td>4 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>R3a</td>
<td>107 (14)</td>
<td>64 (9)</td>
<td>68 (9)</td>
</tr>
<tr>
<td><strong>DME grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>554 (81)</td>
<td>527 (78)</td>
<td>523 (75)</td>
</tr>
<tr>
<td>M1</td>
<td>131 (19)</td>
<td>149 (22)</td>
<td>172 (25)</td>
</tr>
</tbody>
</table>
The sensitivity and specificity of rural ophthalmologists compared to the reference standard for the various domains ranged from 0.65-0.95 and 0.59-0.95 respectively, while the non-medical graders had sensitivity and specificity values ranging from 0.82-0.94 and 0.91-0.99 respectively (Table 2). There was weak-moderate agreement between rural doctors and the reference standard in all domains (kappa= 0.48-0.64, \( P<.001 \)), whereas the agreement for non-medical graders with the reference standard was strong (kappa=0.84-0.87, \( P<.001 \)) (Table 2). Positive predictive value (PPV) and Negative predictive value (NPV) of rural ophthalmologists for the various domains ranged from 0.66-0.78 and 0.90-0.96 respectively, whereas those of the non-medical graders ranged from 0.89-0.94 and 0.94-0.99 respectively (Table 2).
Table 2. Accuracy of diagnosis among trained rural ophthalmologists and non-medical graders compared to the reference standard

<table>
<thead>
<tr>
<th>Condition</th>
<th>Non-medical Graders</th>
<th>Rural Ophthalmologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any DR a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (95% CI)</td>
<td>0.94 (0.92 to 0.97)</td>
<td>0.95 (0.93 to 0.97)</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>0.91 (0.88 to 0.94)</td>
<td>0.59 (0.54 to 0.64)</td>
</tr>
<tr>
<td>AUC ROC (95% CI)</td>
<td>0.93 (0.90 to 0.95)</td>
<td>0.77 (0.74 to 0.81)</td>
</tr>
<tr>
<td>Kappa (P value)</td>
<td>0.85 (&lt;.001)</td>
<td>0.52 (&lt;.001)</td>
</tr>
<tr>
<td>DR requiring treatment b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (95% CI)</td>
<td>0.88 (0.80 to 0.96)</td>
<td>0.66 (0.55 to 0.77)</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>0.99 (0.98 to 1.00)</td>
<td>0.91 (0.89 to 0.94)</td>
</tr>
<tr>
<td>AUC ROC (95% CI)</td>
<td>0.93 (0.87 to 0.98)</td>
<td>0.79 (0.72 to 0.86)</td>
</tr>
<tr>
<td>Kappa (P value)</td>
<td>0.87 (&lt;.001)</td>
<td>0.48 (&lt;.001)</td>
</tr>
<tr>
<td>DME requiring referral c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (95% CI)</td>
<td>0.82 (0.76 to 0.88)</td>
<td>0.65 (0.57 to 0.72)</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>0.98 (0.97 to 0.99)</td>
<td>0.95 (0.93 to 0.97)</td>
</tr>
<tr>
<td>AUC ROC (95% CI)</td>
<td>0.90 (0.87 to 0.94)</td>
<td>0.80 (0.75 to 0.85)</td>
</tr>
<tr>
<td>Kappa (P value)</td>
<td>0.84 (&lt;.001)</td>
<td>0.64 (&lt;.001)</td>
</tr>
</tbody>
</table>

Abbreviations:

DR=Diabetic Retinopathy, DME= Diabetic Macular Edema, CI= Confidence Intervals, AUC= Area Under Curve, ROC= Receiver Operating Characteristic

a *Any DR*, defined as grades R1, R2, R3a and R3s.
bDR requiring treatment, defined as R3a grade.

cDME requiring referral, defined as a grade of M1.

In 206 (54.9%) of participants (412/732 = 56.3% of eyes, 716/1277 =56.1% of images), the arbitrator was involved in the grading decision per protocol, either as part of the random 10% quality control sample or due to disagreement between graders (178/643 = 27.7% of eyes for DR and 64/617 =10.4% of eyes for DME status). In 222/357 (62.2%) and 105/332 (31.6%) of arbitrated eyes for DR and DME status respectively, the grade assigned by one or more grader was changed by the arbitrator, and in 135/357 (37.8%) and 227/332 (68.3%), no change was made to DR and DME status respectively. When images where a change in grading was made by the arbitrator were removed from consideration, grader performance was generally lower: sensitivity was 0.75-0.88 (median 0.80), specificity was 0.97-0.99 (median 0.98), AUC ROC was 0.86-0.93 (median 0.88) and kappa was 0.78-0.88 (P < 0.001).

In the univariate analysis, younger age, fewer number of years working in ophthalmic practice, shorter length of time providing cataract surgery independently, receiving didactic training in DR management and having fewer outpatient visits annually all were significantly associated with rural ophthalmologists correctly identifying patients with DR requiring treatment (Table 3). Age of the doctor, the length of ophthalmic practice and years providing cataract surgery were highly correlated (Spearman’s rho > 0.75),
and so only one of these variables were retained in the multiple regression model to avoid co-linearity.

After consideration of the three possible multiple regression models, age of the doctor provided a slightly better Quasi Likelihood under Independence Model Criterion (QIC) goodness of fit. In the final multiple regression models, younger age and receiving didactic training in DR through the programme remained significantly associated with diagnostic accuracy (Table 3).
Table 3. Logistic regression model of potential predictors of correct diagnosis by rural doctors of diabetic retinopathy requiring treatment

<table>
<thead>
<tr>
<th>Doctor characteristics</th>
<th>Simple regression</th>
<th>Multiple regression Model A</th>
<th>Multiple regression Model A reduced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>P value</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.939 (0.908 to 0.971)</td>
<td>&lt;.001</td>
<td>0.959 (0.931 to 0.988)</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.062 (0.940 to 4.521)</td>
<td>.071</td>
<td></td>
</tr>
<tr>
<td>Years working in ophthalmic practice</td>
<td>0.959 (0.922 to 0.997)</td>
<td>.035</td>
<td></td>
</tr>
<tr>
<td>Years providing cataract surgery independently</td>
<td>0.961 (0.926 to 0.997)</td>
<td>.034</td>
<td></td>
</tr>
<tr>
<td>Received didactic training in DR through programme</td>
<td>2.884 (1.393 to 5.968)</td>
<td>.004</td>
<td>2.495 (1.193 to 5.215)</td>
</tr>
<tr>
<td>Number of hands-on training sessions</td>
<td>1.008</td>
<td>0.767</td>
<td></td>
</tr>
<tr>
<td>received in managing DR</td>
<td>0.958 to 1.061</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual number of outpatient visits</td>
<td>0.999</td>
<td>0.011</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td>(0.998 to 1.000)</td>
<td>(0.999 to 1.000)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** DR=Diabetic Retinopathy CI= Confidence Interval
DISCUSSION

The sensitivity (0.82-0.94 for various domains) and specificity (0.91-0.99) of non-medical graders in this setting exceeded the DR screening standards of the British Diabetic Association (Diabetes UK) (sensitivity of 0.80, specificity of 0.95),[17,18] in all domains except “any DR” (specificity, 0.91). In contrast, rural doctors lacked diagnostic accuracy. Doctors who had received didactic training in DR management performed significantly better than their counterparts.

Screening by centrally-located, non-medical graders offers many advantages in low resource settings over reliance on rural doctors. These include allowing the time of the few available trained practitioners to be focused more fully on provision of care; ease of quality assurance at a central location; and the potential to improve DR screening quality by reducing missed diagnoses and unnecessary referrals. The explosive recent growth of DM in China,[2] is likely to make DR screening models which rely on scarce, trained rural ophthalmologists increasingly untenable.

Shortcomings of image-grading telemedicine models in this low-resource setting must also be acknowledged, principally the costs of equipment, training and on-going quality assurance. Reliable internet connections with adequate bandwidth for image transfer may also be a practical limiting factor. Cost-effectiveness analyses comparing direct clinical detection of DR with telemedicine models are
needed, and will be provided for our programme in future manuscripts. Another barrier to grading by non-medical personnel, in high-resource as well as low-resource settings, is resistance from eye care practitioners themselves. For example, a recent report on DR screening in India found that 79% of programmes used ophthalmologists or optometrists as primary screeners,[19]. However recent guidance from the Royal College of Ophthalmologists has advocated training of non-medical personnel for extended roles to increase capacity of care,[20]. Additional work is needed to explore the accuracy of non-medical personnel in other settings, given the potential advantages outlined above. Our own results show that the inclusion of trained medical expert arbitrators did improve the performance of non-medical graders, as it is designed to. It is expected that non-medical graders would operate under the supervision of trained medical professionals in most settings (at they do for example in the NHS), and thus we do not feel that the expected modest improvement associated with arbitration in any way undercuts our conclusions about the usefulness of non-medical graders in this and potentially other settings.

These results have significant implications for DR screening in low and middle income countries (LMICs). Both VISION 2020,[21] and China’s current 5-Year Blindness Prevention Plan,[22] emphasized the need to develop accurate models to detect DR in settings where there are insufficient trained ophthalmologists to provide comprehensive screening. Non-medical graders, which have not been widely used in LMICs, may provide an important part of the solution, if accuracy levels in other settings
are similar to those we observed. Conversely, our results point to very significant limitations in the
diagnostic accuracy of rural ophthalmologists in this setting, even after provision of extensive didactic
and practical training.

In June 2016, we carried out a review of publications appearing in English with no time limits in Medline,
Embase and Web of Science databases. The review terms included rural health or low income settings
and DR or retinal screening. Accuracy of grading performed by a number of different types of medical
practitioners has been examined in both low and high-resource settings, with variable results. In India,
both general practitioners (kappa=0.84) and optometrists (kappa=0.72) showed good agreement with
ophthalmologists in detecting ‘absent DR’, ‘non sight-threatening diabetic retinopathy’ or ‘sight-
threatening diabetic retinopathy,’ after 25 hours of training over 5 weeks.[23].

In Singapore, a cross-sectional study in a primary care setting against retina specialists as a reference
standard showed substantial agreement (kappa=0.66) for non-physician graders and fair agreement
(kappa=0.40) for family physicians. Non-physician graders were validated by the University of
Melbourne, and underwent a year of rigorous training and annual audits.[24]. In the UK, optometrists
using slit-lamp biomicroscopy following accreditation and assessment at a retinal clinic showed slightly
lower sensitivity (0.75 vs. 0.80) and identical specificity (0.98) compared to digital photography graded
by an ophthalmologist. The reference standard was an experienced ophthalmologist who examined and graded the referrals from both screening methods using slit-lamp biomicroscopy.[25]. A study in Scotland compared the appropriateness of DR referrals among junior doctors who had received formal training in a DR clinic over 10-12 weeks to junior doctors who were comparable in terms of overall experience, but had not received specialist ophthalmic instruction. The reference standard used was the initial assessment of the examining ophthalmologist. Junior doctors with ophthalmic training had a significantly higher ratio of appropriate to inappropriate referrals.[26]. Orthoptists receiving no additional DR training in an Australian study performed well in detecting any DR, with a mean sensitivity of 0.86 and specificity of 0.91.[27]. In Norway, 74 optometrists each screening 14 single-field retinal images for the presence or absence of DR, had sensitivity and specificity of 0.67 and 0.84 respectively, with independent assessments by two ophthalmologists acting as the reference standard. Investigators concluded that only 5% of optometrists met the existing standards for DR screening programmes (sensitivity=0.80, specificity=0.95).[28]. Our review found little information on the performance of non-medical graders in detection of DR,[24] or on grading in LMICs,[23], and no prior publications on non-medical graders in LMICs.

Strengths of the current study include independent, masked, simultaneous diagnosis and grading of DR on a large number of consecutive patients with DM by two different groups relevant to screening in LMICs:
rural ophthalmologists and non-medical graders, both compared to a fully-trained retina specialist. The study took place in an on-going programme, so that high-quality training and equipment was available for both ophthalmologists and graders. Images were acquired by local nurses (rather than photographers) on rural patients without prior experience of retinal photography and with high prevalence of cataract, all typical for programmes in under-served areas. A simple, well-documented and widely-used image-grading system, that of the UK NDESP, was employed, and reference made to well-known standards for acceptable grading accuracy, from Diabetes UK.

Limitations of the study must also be acknowledged. It was not practical for the reference standard to examine patients clinically, which precluded direct comparison with the rural ophthalmologists. Had such direct comparison been possible, performance of the rural ophthalmologists may have appeared better. However, grading of high-quality images by a certified clinical specialist is widely used as the gold standard in screening programmes. Thus, we felt that clinical examination of patients by the reference standard would not clearly have added relevant information, while comparison with the assessment of local ophthalmologists, currently the most widely-used screening approach in rural China, is highly relevant. The current study was not planned to provide information on cost-effectiveness of the two approaches, which is important in evaluating appropriate methods of screening for low-resource settings. This will be the focus of future publications. The widely-used research standard for the detection and
classification of DR, stereoscopic color fundus photographs in 7 standard fields as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) group,[29], was not employed in the current study. Although accurate and reproducible, this approach is time-consuming and uncomfortable for patients,[30]. Two-field retinal photography is more commonly-used in DR screening programmes in high as well as low-resource settings,[31], and its proven accuracy, relatively low cost and greater acceptability,[32] made it more suitable for the CREST programme and the current study.

Finally, although the CREST programme included ten county-level hospitals spread across one of China’s larger provinces, application to other settings may be made only with caution. Such county-level facilities are the major provider of care for rural populations in every region of the country, though quality of medical services may vary widely. As participants in an NGO programme, these facilities may have had access to more resources than typical hospitals in rural China. Nonetheless, the study is an important proof of principle: non-medical graders with modest training could produce highly-accurate results on images taken by recently-trained nurses of patients who had little experience with fundus photography and a high prevalence of lens opacity, which would be expected to affect image quality. On the other hand, the relatively poor performance of local ophthalmologists in a comparatively optimal setting suggests that their accuracy in more typical rural Chinese settings may also be problematic.
CONCLUSIONS

This is the first study to examine accuracy in the detection of DR among non-medical graders or trained rural ophthalmologists in LMICs, and it adds to very limited evidence,[24] on the accuracy of non-medical graders in any setting. Given the very rapid current and projected growth of DM in LMICs, and the lack of proven models for DR screening in such areas, these results are of great importance for programme planners. Our findings of very good accuracy among non-medical graders and relatively poor performance by local ophthalmologists require replication in other settings.
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