The role of haemorrhage and exudate detection in automated grading of diabetic retinopathy

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ABSTRACT

Background/aims Automated grading has the potential to improve the efficiency of diabetic retinopathy screening services. While disease/no disease grading can be performed using only microaneurysm detection and image-quality assessment, automated recognition of other types of lesions may be advantageous. This study investigated whether inclusion of automated recognition of exudates and haemorrhages improves the detection of observable/referable diabetic retinopathy.

Methods Images from 1253 patients with observable/referable retinopathy and 6333 patients with non-referable retinopathy were obtained from three grading centres. All images were reference-graded, and automated disease/no disease assessments were made based on microaneurysm detection and combined microaneurysm, exudate and haemorrhage detection.

Results Introduction of algorithms for exudates and haemorrhages resulted in a statistically significant increase in the sensitivity for detection of observable/referable retinopathy from 94.9% (95% CI 93.5 to 96.0) to 96.6% (95.4 to 97.4) without affecting manual grading workload.

Conclusion Automated detection of exudates and haemorrhages improved the detection of observable/referable retinopathy.

INTRODUCTION

Computer detection of diabetic retinopathy in digital photographs could offer economic benefits to diabetic retinal screening programmes by reducing the costs of grading and quality assurance.[1] Delivery of a quality-assured, systematic screening programme, as recommended at the conference 'Screening for Diabetic Retinopathy in Europe—15 years after St Vincent' (17–18 November 2005, Liverpool),[2] is a major challenge. An automated system that can safely reduce the number of 'no disease' cases presented for manual grading would help to meet these targets.

Many automated systems for detection of lesions of diabetic retinopathy have been assessed in terms of their performance for detecting the target lesion types.[3–8] Automated grading of images with signs of diabetic retinopathy can be performed using algorithms designed to detect only a subset of the lesion types associated with diabetic retinopathy,[9–13] relying implicitly on the co-occurrence of lesions. For example, assessments of automated grading have been made using microaneurysm detection,[9] red lesion detection,[10] combined haemorrhage and exudate detection,[11] combined detection of red lesions and bright lesions, and assessment of image quality,[12] and combined detection of red lesions and exudates and assessment of image quality.[13] Unlike these studies, our earlier study compared an automated system against manual graders routinely employed within a screening programme, and was thus able to determine the impact of introducing an automated grading system into a screening programme.[1 14] We used microaneurysm/dot haemorrhage detection and quality assessment based on our previously developed techniques.[15–17] With a test set of 6672 patients, this earlier study found that manual workload was reduced by 60%, while achieving a slightly better sensitivity for detecting diabetic retinopathy than manual graders.

The current study develops this work in two ways. First, there was a far larger number of patients with observable/referable retinopathy. Second, we investigated whether detection of these patients is improved by algorithms designed to detect lesions other than microaneurysms.

GRADING SCHEMES AND TERMINOLOGY

Retinal images were graded using the Scottish Diabetic Retinopathy Grading Scheme current in 2005 which is summarised in table 1. This scheme is based on the 4:2:1 rules derived from the ETDRS grading scheme, adapted for non-stereoscopic single disc/macula field photographs, and is similar to the 'International clinical diabetic retinopathy and diabetic macula oedema severity scale.'[18] Patients with mild or no retinopathy are recalled for annual screening. Patients are recalled for rescreening after 6 months if they have four or more retinal blot haemorrhages in one hemisphere of either eye (observable retinopathy) or exudates >1 and ≤ 2 disc diameters of the centre of the fovea (observable maculopathy). Patients are referred to the hospital eye service if they have referable retinopathy (four or more retinal blot haemorrhages in both hemispheres equivalent to Airlie House retinal photograph 2a, intraretinal microvascular abnormalities (IRMA), new vessels, venous beading) or referable maculopathy (exudate or blot haemorrhage ≤ 1 optic disc diameter from the fovea).

In this paper, 'non-referable retinopathy' refers to patients with no retinopathy or mild retinopathy (R0 and R1 in table 1). All disease more severe than

Table 1 Scottish Diabetic Retinopathy Grading Scheme current in 2005[22]

Retinopathy	Description	Outcome
R0	No diabetic retinopathy anywhere	Rescreen 12 months
R1 (mild)	Background diabetic retinopathy—mild ► At least one dot haemorrhage or microaneurysm with or without hard exudates	Rescreen 12 months
R2 (observable)	Background diabetic retinopathy—observable ► Four or more blot haemorrhages (ie, ≥AH standard photograph 2a) in one hemi-field only (inferior and superior hemi-fields delineated by a line passing through the centre of the fovea and optic disc)	Rescreen 6 months
R3 (referable)	Background diabetic retinopathy—referable Any of the following features: ► Four or more blot haemorrhages (ie, ≥AH standard photograph 2a) in both inferior and superior hemi-fields ► Venous beading (≥AH standard photograph 6a) ► IRMA (≥AH standard photograph 8a)	Refer ophthalmology
R4 (proliferative)	Proliferative diabetic retinopathy Any of the following features: ► New vessels ► Vitreous haemorrhage	Refer ophthalmology
R6 (inadequate)	Not adequately visualised. Retina not sufficiently visible for assessment	Technical failure
Maculopathy	Description	Outcome
M1 (observable)	Lesions within a radius of >1 but ≤2 disc diameters of the centre of the fovea ► Any hard exudates	Rescreen 6 months
M2 (referable)	Lesions within a radius of ≤1 disc diameter of the centre of the fovea ► Any blot haemorrhages ► Any hard exudates	Refer ophthalmology

mild retinopathy will be referred to as 'observable/referable retinopathy.' This includes observable retinopathy, R2, referable retinopathy, R3 and R4, observable maculopathy, M1, and referable maculopathy, M2.

METHODOLOGY

Material

Images and their gradings were collected from the diabetic retinal screening programmes of NHS Grampian, NHS Greater Glasgow and NHS Tayside. Photographs were acquired using Canon EOS 20D and D30 digital cameras and Canon CR5-45NM, CR6-45NM, CR-DGi non-mydriatic fundus cameras (Canon Medical Equipment Business Group, Kanagawa, Japan). Images sizes were 1536×1024, 1728×1152 and 2160×1440 pixels.

All patients were manually graded by 'disease/no disease' graders who final-graded patients with no retinopathy. Patients with any signs of diabetic retinopathy were then manually graded by 'full-disease' graders who final-graded patients with mild retinopathy and observable retinopathy. Patients who had referable retinopathy were further graded by the programmes' level-three grader, an ophthalmologist.

Reference standard grading

Reference standard grading was performed by a clinical research fellow (SP or GJW). In this study, a blot haemorrhage was defined as a retinal haemorrhage with a diameter greater than the width of the retinal vein at the optic disc.

For practical reasons, reference grading was performed on a stratified sample of 7586 patients as shown in figure 1. This sample included all available patients with observable and referable retinopathy, according to any grading level (1350) and a sample of patients with no or mild retinopathy (6236) drawn from a screened population of approximately 25 500.

Disagreements between the reference grading and the final screening programme grade, concerning status of observable/referable retinopathy, were arbitrated by the lead clinician (JAO).

According to the reference standard grading, 1253 patients in the study set had observable/referable retinopathy, and 6333 patients had mild or no retinopathy or were ungradeable. The median age was 65 years with interquartile range 19.

Automated method development

Automated methods for analysis of retinal images were developed as modules corresponding to lesion types. For microaneurysms, the number of detected lesions was obtained. For other lesions, a numerical value was obtained representing the confidence that the image contains the lesion type. These counts and confidence values were combined as described below.

A training set of patients, separate to the test set, comprising 200 patients with observable/referable retinopathy and 400 without, was used to develop the automated methods.

Image quality

Our previously described techniques were used to locate the optic disc and fovea, to determine whether the image was of the right or left eye, and to assess image quality.[16 19]

Microaneurysm detection

Microaneurysm detection was performed using methods we have described previously.[15 17] This method does not distinguish between microaneurysms and dot haemorrhages.

Blot haemorrhage detection

Potential blot haemorrhage locations were determined using a version of the microaneurysm detection algorithm which had been adapted to detect dark objects having a range of sizes. Properties of the detected objects, such as area, contrast,

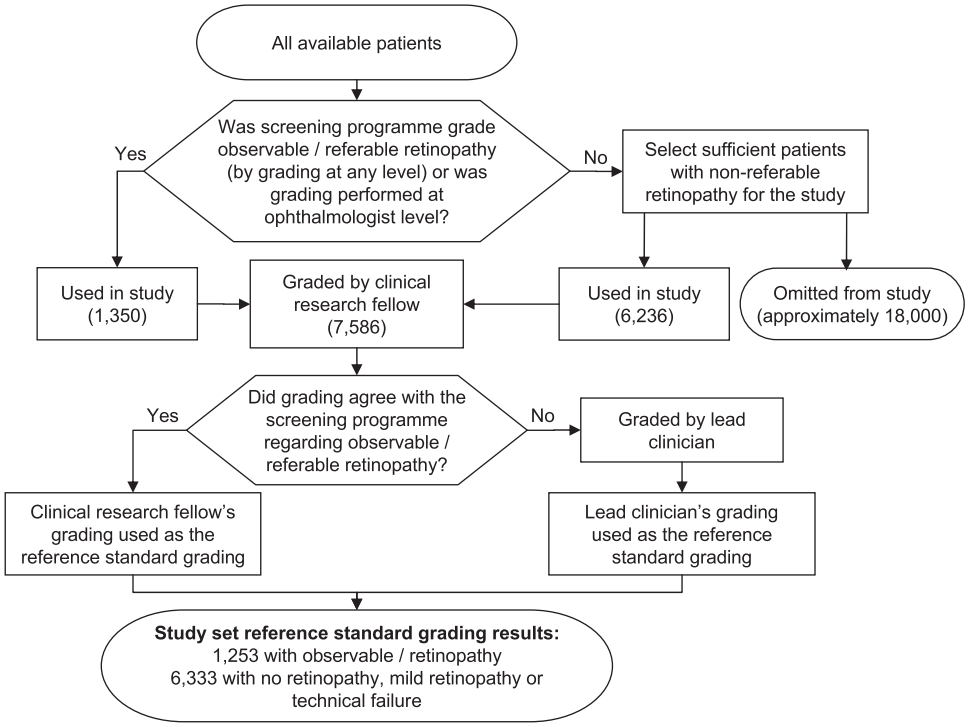

Figure 1 Flow chart illustrating the study method including selection of the study set and the reference standard grading.

directionality and whether the object appeared to lie on a vessel, were evaluated. An automated classifier was trained to separate true blot haemorrhages from false detections using the training set. A confidence value was obtained for each potential lesion location.[20]

Exudate detection

Potential exudate locations were detected using a version of the microaneurysm detection algorithm which had been adapted to detect bright objects having a range of sizes. The objects were automatically classified, as exudate, drusen or background, based on size, shape and colour properties of the objects.[21]

Disease/no disease detection

Two methods were compared for performing disease/no disease detection: combined quality assessment and microaneurysm detection[14] and a new method encompassing quality assessment, microaneurysm detection, blot haemorrhage detection and exudate detection.

In the new method, five image-based lesion measures, $L_1 \ldots L_5$, were obtained, as listed in table 2. For blot haemorrhages and exudates, $L_2 \ldots L_5$, these represented the confidence that the lesion was present in the image. They were calculated as the sum of the n highest confidence values for individual potential lesions. The optimum value of n, for each lesion type, shown in table 2, was the value which gave the maximum area under receiver operator characteristic (ROC) curves for detection of images with the lesion in the training set images.

A linear classifier was then trained to predict disease by optimising weights, α_i, $i=1 \ldots 5$, so as to obtain the maximum area under the ROC curves for observable/referable retinopathy detection, using the expression:

$$D = \sum_{i=1}^{5} \left[\alpha_i \max \left(L_i^{\text{Left}}, L_i^{\text{Right}} \right) \right]$$

where D represents a confidence for observable/referable retinopathy, and 'Left' and 'Right' refer to values obtained for the left and right eye images. Note that for four or more blot haemorrhages in either or both hemifields, the weight is zero, implying that this lesion configuration did not contribute to the overall assessment of disease. A threshold on D was chosen that gave 50% specificity for detection of observable/referable retinopathy (in the training set), chosen to be close to the value of 52% attained in our previous work for the specificity of observable/referable retinopathy detection.[14] If D was above this threshold, the patient was deemed to have disease that requires referral to manual grading.

Table 2 Image-based lesion measures

	Image-based lesion measure	Portion of photograph used	No of candidates used (n)	Weight (α_i)
L_1	Number of detected microaneurysms	Whole photograph	–	2
L_2	Confidence value for four or more blot haemorrhages in superior or inferior hemifield	Whole photograph	8	0
L_3	Confidence value for blot haemorrhage ≤1 DD from the centre of the fovea	≤1 DD from the centre of the fovea	3	0.4
L_4	Confidence value for exudates ≤1 DD from the centre of the fovea	≤1 DD from the centre of the fovea	3	6
L_5	Confidence value for exudates ≤2 DD from the centre of the fovea	≤2 DD from the centre of the fovea	2	5

DD, disc diameter.

Table 3 Cross-tabulation of the screening programme and the reference standard grading

	Reference standard grade							
No of cases	**TF**	**R0**	**R1**	**M1**	**R2**	**M2**	**R3**	**R4**
Screening programme grade								
TF	464	18	7	0	0	10	2	1
R0	117	3985	470	1	1	9	4	3
R1	48	34	1138	19	0	27	13	11
M1	5	1	12	71	0	42	14	2
R2	2	1	8	1	12	10	5	1
M2	5	1	10	9	3	509	40	18
R3	2	1	1	1	2	23	187	55
R4	0	0	3	0	0	3	7	137

The grade codes are explained in table 1. Cases of mixed retinopathy (R1–4) and maculopathy (M1–2) were assigned to the most severe grade using the ordering: R1, M1, R2, M2, R3, R4.

RESULTS

Screening programme and reference standard grading

Table 3 illustrates a cross-tabulation of the screening programme and the reference standard grading for the 7586 patients in the study; 85.7% of episodes received the same grade by the screening programme and the reference standard.

Automated detection of images with lesions

Figure 2 shows ROC curves for the detection of individual images containing microaneurysms, haemorrhages and exudates using the respective lesion detectors. The data were weighted to correct for the higher prevalence of observable/referable retinopathy in images in the test set (12.9%) than in the screened population, found to be 3.2% of images in an earlier study.[14]

Automated detection of patients with observable/referable retinopathy

Table 4 shows that the new method reduced cases of misclassified observable/referable retinopathy (p=0.001). Misclassified cases were also reduced in the following subsets of observable/referable retinopathy: referable retinopathy (M2, R3 and R4) (p<0.001) and referable maculopathy (M2) (p=0.001).

The proportion of patients with non-referable retinopathy who were 'final graded' by the automated system was 49.1% using microaneurysm detection alone and 49.0% using blot haemorrhage and exudate detection.

The average time to process each image was 320 s on a 3 GHz processor. This would allow up to 390 000 images to be processed annually on a computer unit with four processor cores. For microaneurysm detection and quality assessment, the time is 120 s per image on the same processor.

DISCUSSION

This multicentre study showed that the inclusion of automated identification of blot haemorrhages and exudates improves upon our previously published algorithms for disease/no disease detection of diabetic retinopathy.

The addition of automated detection of exudates and blot haemorrhages improved the detection of observable/referable retinopathy mainly due to the improved detection of referable maculopathy, resulting in a reduction by 38% in the number of missed cases of observable/referable retinopathy. The proportion of patients receiving a final grading by the automated system was unaffected by the inclusion of haemorrhage and exudate detection. The improvement to detection of observable/referable retinopathy may have occurred because automated detection of exudates and blot haemorrhages was assisting the detection of maculopathy when microaneurysms were unclear.

Despite there being excellent detection of images with four or more blot haemorrhages per hemifield (figure 2), the weighting for observable/referable retinopathy detection of the output of this lesion detector became zero after optimisation of the linear classifier during the training phase (table 2). Therefore, blot haemorrhages outside the macula were not used in the study.

This study was undertaken within the context of a systematic single-field photographic screening programme. Application to multiple-field photography requires adjustment to only the image-quality assessment and optic disc and fovea detection

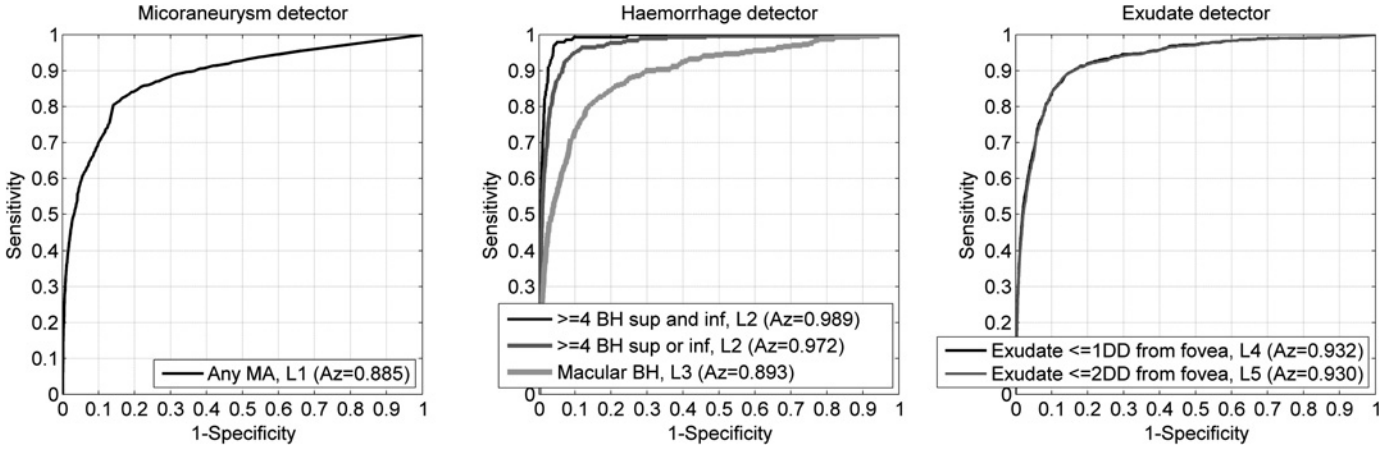

Figure 2 Receiver operator characteristic curves illustrating the performance, per image, of the detectors for microaneurysms, haemorrhages and exudates against the presence of these lesion types (regionally, for haemorrhages and exudates) as provided by the reference standard graders. Az, area under the curve. $L_1 \ldots L_5$ refer to the designations in table 2.

Table 4 Number of patients referred and not referred for manual grading by the automated system for each grade of retinopathy by the two automated detection methods

	Technical failure (R6)	No retinopathy (R0)	Mild retinopathy (R1)	Observable macul-opathy (M1)	Observable retinopathy (R2)	Referable maculopathy (M2)	Non-proliferative referable retinopathy (R3)	Proliferative referable retinopathy (R4)	Observable/ referable retinopathy (M1+R2+M2 +R3+R4)	Referable retinopathy (M2+R3+ R4)	Total
Disease/no disease grading—using microaneurysm detection only											
Not referred	9	2562	336	7	0	45	5	7	64	57	2971
Referred	634	1479	1313	95	18	588	267	221	1189	1076	4615
Percentage referred (95% CI)	98.6 (97.4 to 99.3)	36.6 (35.1 to 38.1)	79.6 (77.6 to 81.5)	93.1 (86.5 to 96.6)	100 (82.4 to 100)	92.9 (90.6 to 94.6)	98.2 (95.8 to 99.2)	96.9 (93.8 to 98.5)	94.9 (93.5 to 96.0)	95.0 (93.5 to 96.1)	60.8 (59.7 to 61.9)
Disease/no disease grading—using microaneurysm, blot haemorrhage and exudate detection											
Not referred	8	2553	347	8	0	26*	3	6	43*	35*	2951
Referred	635	1488	1302	94	18	607	269	222	1210	1098	4635
Percentage referred (95% CI)	98.8 (97.6 to 99.4)	36.8 (35.3 to 38.3)	79.0 (76.9 to 80.9)	92.2 (85.3 to 96.0)	100 (82.4 to 100)	95.9 (94.0 to 97.2)	98.9 (96.8 to 99.6)	97.4 (94.4 to 98.8)	96.6 (95.4 to 97.4)	96.9 (95.7 to 97.8)	61.1 (60.0 to 62.2)

Percentages are included with 95% CI. Cases of mixed retinopathy (R1–4) and maculopathy (M1–2) were assigned to the most severe grade using the ordering R1, M1, R2, M2, R3, R4.
*Significant reductions in misclassified cases.

modules. While there are minor differences between grading protocols,[18 22 23] the definitions for mild retinopathy (see R1, table 1) are similar and based on Airlie House photographs. As long as it is accepted that only disease more severe than mild retinopathy (known as observable/referable retinopathy in this paper) needs to be detected, the main conclusions of this study will be generalisable to other screening protocols.

It was impractical to reference grade all available screened patients, and thus a complete comparison with the performance of manual grading was not possible. The true number of screening programme false negatives is not known.

In the current study, six cases of proliferative retinopathy were misclassified by the automated system. Grading is subjective, and on review we do not believe they are clear errors, as defined by NHSQIS's Clinical Standards for Diabetic Retinopathy Screening.[24] These six cases are included in online supporting material. In comparison, the screening programmes failed to refer 17 patients with proliferative retinopathy to ophthalmology. Similarly, the automated system misclassified 26 patients with referable maculopathy and three patients with non-proliferative referable retinopathy. In comparison, the screening programmes failed to refer 88 patients with referable maculopathy and 36 with non-proliferative referable retinopathy.

Previous publications confirm that human graders miss or disagree about patients with observable/referable retinopathy. We have reported that level 2 graders miss significant eye disease,[14] and others have shown that human experts have a sensitivity between 62% and 85% for detecting referable retinopathy.[13]

Automated grading should be assessed against the best available alternative system which, in the UK, is routine manual grading by Allied Health Professionals.[25] Automated grading could assist the global expansion of retinal screening to the 171 million people affected by diabetes worldwide.[26]

In conclusion, using a large number of patients with observable/referable retinopathy, we have shown that automated disease/no disease grading can be improved by including automated detection of exudates and haemorrhages, and is safe compared with manual screening.

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Competing interests Implementation in Scotland is being considered. If this occurs, it is likely that there will be some remuneration for the University of Aberdeen, NHS Grampian and the Scottish Government.

Contributors JAO was the principal investigator. JAO, PFS, KAG, SP, GJW, ADF, GS, PM and GJP contributed to the study design. GPL, WNW, ADF, KAG and SP performed data collection. The reference grading was performed by SP, GJW and JAO using a grading database which SP designed and developed. ADF developed the automated methods, set up the analysis and generated the results. JAO performed quality assurance. GJP performed and checked the validity of the statistical analyses. All participated in the interpretation of the data. ADF wrote the first draft of the paper. All authors reviewed and revised the paper for important intellectual content. JAO takes responsibility for the content.

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