Author’s response to reviews

Title: Semi-automated quantification of hard exudates in colour fundus photographs diagnosed with diabetic retinopathy

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Author’s response to reviews:

We express our sincere thanks for providing constructive and encouraging reviews for our manuscript. We tried to address all the reviewer(s) comments in the revised manuscript and the same are provided, for your kind perusal, in the following.

Editor comments:

1. Please describe how this study’s methods differs from/is superior to the method of Sasaki; specifically, do the authors have any statistical evidence to support superiority/differences of their method compared to that of Sasaki?

Response: The differences and superiority of the proposed method vis-à-vis Sasaki et al.’s method is enumerated in the following.

(i) Sasaki et al.’s method performs sequence of steps including removing of spurious regions interactively using ImageJ software which is slightly tedious, whereas the proposed method performs all operations automatically except removing outliers.

(ii) Sasaki et al.’s method uses max-entropy thresholding on the green channel of the colour fundus photograph which could detect only few bright hard exudates. On the other hand, the proposed algorithm uses two pronged methodology to detect both bright and faint hard
exudates. In particular, specific pre-processing steps which include top-hat filtering and adaptive histogram equalization are performed to make hard exudates regions more distinguishable from background. Further, for thresholding, distinct empirically determined thresholds are employed for bright and faint exudates.

(iii) Superiority of the proposed method over Sasaki et al.’s method is established both qualitatively and quantitatively. Statistically, proposed algorithm detected more than 80% of the HEs in 96% of eyes whereas Sasaki et al.’s method detected more than 80% HEs in only 3% of the eyes. More specifically, Sasaki et al.’s method missed HEs, in 70% of eyes, up to 50%.

This has been added on page 9, 1st and 2nd paragraph.

2. The statistical analysis should include subheadings. For measures of intraobserver or interobserver repeatability, the use of intraclass correlation would be more suitable.

Response: Subheadings are included as suggested. Intraclass correlation coefficients, capturing intra-observer and inter-observer repeatability, are reported using variant of Pearson’s correlation coefficient.

3. Please state what is the specificity of this method compared to the previous method(s).

Response: The statistical analysis performed in this work is based on observer grading, due to absence of ground truth segmentation of hard exudates. In this setting, estimating parameters such as specificity is challenging.

4. Could this method be used to detect drusen?

Response: Yes, the proposed method detects drusen as well. However, thorough performance analysis has to be performed to deploy this for clinical studies. This aspect of the algorithm is now discussed in the discussion section of the manuscript. We would like to thank the reviewers for raising this point.

5. Please clarify that hard exudates are not only derived from lipid deposits (cf. pages 2 and 4).

Response: Hard exudates are the largely made of lipid residues of serous leakage from damaged capillaries and consist of lipid-laden macrophages or noncellular materials including lipid and
proteinaceous substances. This is also clarified in the main manuscript (first paragraph of Background section) as suggested along with references.

6. Please include citations regarding the characteristics of hard exudates.

Response: We cited more papers (enumerated below) that describe the characteristics of the hard exudates (HEs) as suggested.


7. Please correct the numerous misspellings throughout the manuscript.

Response: We ran the document through spell check (US English) and corrected the misspellings.

Reviewer comments:

Reviewer 1: This retrospective study by Marupally et al. develop the semi-automated method of quantification of hard exudates in diabetic retinopathy. The author compared their developed method with previously shown method. My comments are shown as below.

1. The author excluded cotton wool spots, optic disc and retinal vessel refections. Is there possibility that this method could detect drusen?

Response: Yes, this method also detects drusen. However, thorough statistical analysis corroborating the efficacy of the algorithm in this regard is yet to be performed. We thank the reviewer for raising this important point.
Page 2 and page 4: Hard exudates is not only derived from lipid deposits. A few papers should be cited about hard exudate characteristics.

High-Resolution Imaging by Adaptive Optics Scanning Laser Ophthalmoscopy Reveals Two Morphologically Distinct Types of Retinal Hard Exudates.


Histopathology of the starfigure of the macular area in diabetic and angiospastic retinopathy.


Response: We cited more papers, as suggested, describing the characteristics of the hard exudates (HEs). We thank the reviewer for pointing us to recent literature which reported classification of HEs based on AOSLO imaging.

Reviewer 2: Authors proposed a novel semiautomatic method to detect hard exudates on color fundus photographs. The manuscript is well written, and several concerns are shown below.

1. They stated the priority of their methods comparing to Sasaki's method. They should show the statistical differences between them.

Response: Superiority of the proposed method over Sasaki et al.’s method is established both qualitatively and quantitatively. Statistically, proposed algorithm detected more than 80% of the HEs in 96% of eyes whereas Sasaki et al.’s method detected more than 80% HEs in only 3% of the eyes. More specifically, Sasaki et al.’s method missed HEs, in 70% of eyes, up to 50%.

2. Authors should prepare the subheading for statistics. For the intraobserver or interobserver repeatability, the ICCs would be more suitable.

Response: Intraclass correlation coefficients, capturing intra-observer and inter-observer repeatability, are reported using variant of Pearson’s correlation coefficient. Accordingly, for images analyzed on measurements obtained using ImageJ-based and proposed method, we obtained an ICC of 99.02% and 99.94%, respectively for grader-A, and an ICC of 98.27% and 99.60%, respectively for grader-B. This has been added on page 7, last paragraph.
3. The results suggest that the proposed method had higher sensitivity than the previous one. How was the specificity?

Response: The statistical analysis performed in this work is based on observer grading due to absence of ground truth segmentation of hard exudates. In this setting, estimating parameters such as specificity is challenging.

4. There are many misspellings.

Response: We ran the document through spell check (US English) and corrected the misspellings.