

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cross sectional study: does combining Optical Coherence Tomography measurements using the 'Random Forest' decision tree classifier improve the prediction of the presence of perimetric deterioration in glaucoma suspects?
AUTHORS	Asaoka, Ryo; Sugimoto, Koichiro; Murata, Hiroshi; Aihara, Makoto; Mayama, Chihiro

VERSION 1 - REVIEW

REVIEWER	Takehiro Yamashita Assistant Professor Department of Ophthalmology, Kagoshima University Graduate School of Medical and Dental Sciences Japan
REVIEW RETURNED	13-May-2013

THE STUDY	<p>The authors used visual field damage as a gold-standard to classify glaucomatous eyes. However, visual field damage itself is not necessarily a gold-standard. For diagnosing or classifying glaucoma, it is essential to see the agreement of ocular fundus change and visual field change. The authors evaluated the visual field change and structural change on OCT, but not diagnosing ability for glaucoma. Therefore, it is not appropriate to describe, "It is useful for the diagnosis of glaucoma". The authors should rewrite the Title, Abstract and Discussion section based on this limitation.</p> <p>Another concern is lack of control subject. The subjects of this study consisted of glaucoma eyes and glaucoma suspect eyes. These problems should be discussed as limitations.</p>
GENERAL COMMENTS	<p>Sugimoto et al reported combining optical coherence tomography measurements using the 'Random Forest' decision tree classifier. This is an important and hot topic for readers; however, the following should be addressed.</p> <p>1. Title, Abstract and Discussion. The authors used visual field damage as a gold-standard to classify glaucomatous eyes. However, visual field damage itself is not necessarily a gold-standard. For diagnosing or classifying glaucoma, it is essential to see the agreement of ocular fundus change and visual field change. The authors evaluated the visual field change and structural change on OCT, but not diagnosing ability for glaucoma. Therefore, it is not appropriate to describe, "It is useful for the diagnosis of glaucoma". The authors should rewrite the Title, Abstract and Discussion section based on this limitation.</p> <p>Another concern is lack of control subject. The subjects of this study consisted of glaucoma eyes and glaucoma suspect eyes. These</p>

	<p>problems should be discussed as limitations.</p> <p>2. Page 6, line 9-22. This study comprised 179 consecutive patients and 178 subjects were analyzed (page8, line 5). A number of consecutive patients may be incorrect. So, the authors should correct the number of consecutive patients and describe a number of patients that excluded by the criteria.</p> <p>3. Page10, line3 – Page 11, line 2 The description about the OCT measurements in the first and second paragraphs of Discussion is somewhat confusing. This should be described in Introduction.</p> <p>4. Table 1 There is no maximum MD in range of both groups. The number of cases in gender is different from Table and the text. This must be a typographical error.</p>
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REVIEWER	Tin Aung, Singapore National Eye Centre No competing interest
REVIEW RETURNED	05-Jun-2013

THE STUDY	<p>There are 2 major issues with the methodology:</p> <ol style="list-style-type: none"> not including normal individuals- Not including normal patients is a problem since one may not know if the classifiers have enough sensitivity to discriminate between normal individuals vs “glaucoma suspects”. not providing details about the severity of glaucoma-It is important to summarize the VF characteristics as mild, moderate and severe in this study to enable comparison across studies, since the AUC mostly depends on the severity of glaucoma. <p>Both issues could influence the ROCs.</p> <p>Specific Comments:</p> <ol style="list-style-type: none"> Any particular reason for excluding angle closure glaucoma? Were secondary glaucomas included? What were the exact definitions of glaucoma suspects and glaucoma cases? Please summarize patients excluded from analysis and the reasons. Page 11 line 15: ‘suspect’ is misspelt as ‘subject’. Not restricting those with higher axial length (myopic subjects) may have increased the artefacts in SDOCT – and may falsely label glaucoma suspects as glaucoma. The authors over-emphasized the advantages of the RF method throughout discussion. The authors mentioned the similarities of optic disc parameters in discriminating glaucoma but failed to prove this in their study The authors should discuss limitations of this study Points 9, 16 and 22 of STARD chart should be addressed explicitly. The pages referenced were not accurate.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: Takehiro Yamashita
Assistant Professor
Department of Ophthalmology, Kagoshima University Graduate School of Medical and Dental Sciences
Japan

Sugimoto et al reported combining optical coherence tomography measurements using the 'Random Forest' decision tree classifier. This is an important and hot topic for readers; however, the following should be addressed.

1. Title, Abstract and Discussion.

The authors used visual field damage as a gold-standard to classify glaucomatous eyes. However, visual field damage itself is not necessarily a gold-standard. For diagnosing or classifying glaucoma, it is essential to see the agreement of ocular fundus change and visual field change. The authors evaluated the visual field change and structural change on OCT, but not diagnosing ability for glaucoma. Therefore, it is not appropriate to describe, "It is useful for the diagnosis of glaucoma". The authors should rewrite the Title, Abstract and Discussion section based on this limitation.

Thank you very much for this important comment. Subjects underwent OCT and VF measurements if glaucomatous structural change was confirmed at the glaucoma clinic (Page 7 Line 16). This point was added in the Methods section and also the Title and Abstract sections were re-written as requested.

Another concern is lack of control subject. The subjects of this study consisted of glaucoma eyes and glaucoma suspect eyes. These problems should be discussed as limitations.

Thank you very much for this important comment, with which we support. The limitation is outlined in the Discussion section (Page 12 Line 35). Also, some relevant changes were made throughout the manuscript.

2. Page 6, line 9-22.

This study comprised 179 consecutive patients and 178 subjects were analyzed (page8, line 5). A number of consecutive patients may be incorrect. So, the authors should correct the number of consecutive patients and describe a number of patients that excluded by the criteria.

Thank you very much. In the leave-one-out process, 178 patients were used as a training dataset and the remaining one patient was used as a testing dataset (the 'leave-one-out' method). This process was repeated 179 times so that each patient is used as a testing data set once. We can add more details about the leave-one-out process, if necessary.

3. Page10, line3 – Page 11, line 2

The description about the OCT measurements in the first and second paragraphs of Discussion is somewhat confusing. This should be described in Introduction.

We thank the reviewer for this comment. The descriptions were moved to the Introduction section (Page 5 Line 21).

4. Table 1

There is no maximum MD in range of both groups. The number of cases in gender is different from Table and the text. This must be a typographical error.

Thank you very much. The maximum number is described in Table 1. The gender was counted for the number of eyes rather than patients.

Reviewer: Tin Aung, Singapore National Eye Centre
No competing interest

There are 2 major issues with the methodology:

1. not including normal individuals- Not including normal patients is a problem since one may not know if the classifiers have enough sensitivity to discriminate between normal individuals vs “glaucoma suspects”.

We thank this reviewer for this important comment. The purpose of the current study was discriminating perimetric and pre-perimetric glaucoma. This point is now clearly described in the Introduction (Page 6 Line 16) and Discussion (Page 12 Line 35). Also, some relevant changes were made to the title, Abstract and Discussion (Page 12 Line 25, Page 14 Line 10). Moreover, the limitation of not including a normative population is now discussed (Page 12 Line 35).

2. not providing details about the severity of glaucoma-It is important to summarize the VF characteristics as mild, moderate and severe in this study to enable comparison across studies, since the AUC mostly depends on the severity of glaucoma.

Thank you very much for this comment. We agree with the reviewer. The range of MD is given in Table 1, as well as the mean and standard deviation values. Also, the histogram is shown below (figure 1). We are happy to add this histogram as an additional Figure, if necessary.

Both issues could influence the ROCs.

This possibility is now deliberated in the Discussion section (Page 12 Line 35).

Specific Comments:

1. Any particular reason for excluding angle closure glaucoma?

2. Were secondary glaucomas included?

These cases were excluded because of the possibility of different structural and VF features (Page 7 Line 22).

3. What were the exact definitions of glaucoma suspects and glaucoma cases?

Thank you very much. The details are now clearly described in the Methods section (Page 7 Line 9-24, Page 7 Line 26-Page 8 Line 1).

4. Please summarize patients excluded from analysis and the reasons.

Thank you very much for this comment. No patients were excluded, unless they did not meet the inclusion criteria for VFs (Page 7 Line 26-Page 8 Line 1) and OCT (Page 8 Line 11), as described in the Methods section.

5. Page 11 line 15: ‘suspect’ is misspelt as ‘subject’.

This misspelling was rectified. Thank you very much (Page 12 Line 23).

6. Not restricting those with higher axial length (myopic subjects) may have increased the artefacts in SDOCT – and may falsely label glaucoma suspects as glaucoma.

Thank you very much for raising this point. There was a significantly negative relationship between Image quality and AL, as suggested by this reviewer and illustrated in the figure 2 below. Hence we agree with this reviewer and this will further support our suggestion that using multiple parameters is advantageous, because the influence of noise would be large when only a single parameter is interpreted.

$$Y = -0.7323 X + 96.0183, R^2 = 0.02578, p < 0.01$$

7. The authors over-emphasized the advantages of the RF method throughout discussion. Thank you very much. The description in the discussion was modified (Page 13 Line10).

8. The authors mentioned the similarities of optic disc parameters in discriminating glaucoma but failed to prove this in their study
Thank you very much. The AROC associated with m-RNFL was significantly larger than cp-RNFL, rim area and GCC. We didn't discuss this in the manuscript, because it was not our purpose to compare between conventional OCT parameters, but to compare them with the Random Forest method (and decision tree method).

9. The authors should discuss limitations of this study
The limitations were added to the Discussion section (Page12 Line 35).

10. Points 9, 16 and 22 of STARD chart should be addressed explicitly. The pages referenced were not accurate.
These statements were rectified, thank you.

VERSION 2 – REVIEW

REVIEWER	Takehiro Yamashita M.D.,Ph.D. Assistant professor Department of ophthalmology, Kagoshima University Graduate School of Medical and Dental Sciences Japan
REVIEW RETURNED	25-Jun-2013

GENERAL COMMENTS	This manuscript contains an important clinical message for glaucoma diagnosis and the authors have been highly responsive to previous reviews; the paper has improved substantially from its original submission.
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