Title: Defective angles of localized retinal nerve fiber layer reflect the severity of visual field defect- a cross-sectional analysis

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Author’s response to reviews:

Response to comments of the editors and reviewers

Defective angles of localized retinal nerve fiber layer reflect the severity of visual field defect- a cross-sectional analysis” (BMC Ophthalmology, BOPH-D-19-00297)

We highly appreciate the valuable comments and suggestions of the reviewers. Changes to the manuscript were highlighted in red. We found these comments and suggestions to be very useful for improving the manuscript and have responded to these in a point-by-point manner as follows:

Response to the comment of Reviewer #1, Professor Kim, Yong Kim:

Q1: Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format. Please overwrite this text when adding your comments to the authors.

A1: We thank Dr. Kim for the comments and will follow the instructions accordingly.
Response to the comment of Reviewer #3, Doctor Elbendary, Amal:

Introduction

Q1: First paragraph lacks reference. RNFL defect is commonly used for detecting early glaucomatous eyes. This statement dates to at least 20 years earlier before the advent of OCT. Modify it accordingly, adding a suitable reference. The same applies to this statement that dates back to 2003, "In recent years, Woo et al has established a convenient quantitative method….."

A1: We thank Dr. Elbendary for this comment. We have rephrased “commonly used” to “a tool of choice.” We chose to rephrase it instead of adding a suitable reference since it is indeed difficult to find a recent reference that describes RNFL photography as a common tool. However, as can be seen from the articles published in 2019 by Kim et al and Lee et al as presented below, RNFL photographs for detecting early RNFL changes are still widely and commonly used for either evaluating open angle glaucoma or training of artificial neural network in glaucoma screening. In our glaucoma clinic, RNFL photography for diagnosing and identifying the progression of glaucoma in conjunction with OCT is still a routine. Therefore, it may not be a routine in many developing countries, but claim of “commonly used” is not overstated.


We have rephrased “in recent years” to “Woo et al previously established” as shown below:

Woo et al previously established a convenient quantitative method for analyzing localized RNFL defect using RNFL photograph by measuring the angles around the disc.”

Q2: Brief definition of angle α and β should be added to the end of first paragraph before coming across validation of their values in the second paragraph

A2: We thank Dr. Elbendary for this comment. Brief definition of angle α and β has been added, as shown below:

They first defined the reference line as the line between the macula center and the optic disc center. Angle α is the angular width between the reference line and the proximity of RNFL defect, while angle β (+c) is the sum of angular width(s) of localized RNFL defect.

Methods:

Q3: Myopic eyes are included or excluded?

A3: We thank Dr. Elbendary for this comment. Myopic eyes were included. Since the purpose of this study was to verify the correlation between the RNFL defective angles and the severity of visual field defect, we decided not to exclude myopic eyes.

Q4: The aim of the work is to correlate RNFL defects to VF analysis. Nonetheless, basic VF information is lacking. Since all patients represent mild stages of glaucoma, indicate the VF minimal criteria for glaucoma diagnosis in inclusion criteria. Grading of VF severity should be clear, adopting any of the staging systems criteria e.g Hodapp E, Parrish RKII, Anderson DR. Clinical Decisions in Glaucoma.

A4: We thank Dr. Elbendary for this comment. Our minimal criteria for glaucoma diagnosis was based on Anderson-Patella’s criteria. We have added the VF information as follows:

Glaucomatous eyes were defined using the Anderson-Patella’s criteria. Visual field defects had to be compatible with RNFL defects and repeatable on at least two consecutive tests.
Q5: This article adopts the same angle measurement techniques of woo et al, 2003. It can't be considered the authors original work. Cite the above-mentioned reference in methodology section

A5: We thank Dr. Elbendary for this comment. We have cited the reference accordingly, as shown below:

The method [2] of angle measurements for evaluating localized RNFL defect was as follows (Fig 2).

Results

Q6: Baseline data: add mean refraction of study sample

A6: We thank Dr. Elbendary for this advice. Mean spherical equivalence (D) has been added to Table 1. Mean spherical equivalence was -0.5D.

Q7: Name of statistical test is restricted to footnotes of the corresponding table

A7: We thank Dr. Elbendary for this suggestion. Name of the statistical test was removed from the title of Table 2 and 3 and was added to the footnotes of each table.

Q8: How can you explain the high prevalence of central scotoma (76%) in a sample of mild glaucomatous eyes? According to the famous HPA classification of glaucoma, all points in the central 5 degrees must have sensitivity of at least 15dB. The definition of central scotoma as 10 central degrees of 30-2 program in the current study miscalculate the outcoming values. Lack of correlation between angle α and central scotoma may be explained by the fact that central 10-2 VF program is essential to confirm presence or absence of central scotoma. If medical records lack central 10-2 program, then you can't conclude lack of correlation. Redefine central scotoma by restricting deviation within the central 5 degrees of 30-2

A8: We thank Dr. Elbendary for this comment. By redefining the central scotoma using central 6 degrees instead of central 9 degrees of 30-2, correlation was 0.039 (-0.377 – 0.299) with a P value of 0.816. No correlation was found after redefining central scotoma using 30-2 program. Indeed, we lack 10-2 results and therefore was not able to confirm the presence or absence of central scotoma. This limitation was included in the discussion section.
Q9: Were macular NFL thickness was calculated? If possible, correlate these values to RNFL angle $\alpha$.

A9: We thank Dr. Elbendary for this comment. The average total macular thickness was 269.3 (16.4) $\mu$m and was added to Table 1. No correlation ($P = 0.214$) was found between RNFL angle $\alpha$ and average total macular thickness. This finding was also added to the result section.

Q10: Statistical relations in table 2 are too Simple and better expressed as text

A10: We thank Dr. Elbendary for this advice. We have removed table 2. The correlation between angle $\alpha$ and central scotoma is now expressed in the result section.

Q11: Table 4 appears heterogenous. The first row in table 4 is mere repetition of table 3 and had to be deleted. This table should indicate only correlation between OCT & VF parameters. The same applies to text where the explanation of table 3 had been repeated twice in page 4 (140-142, 147-148)

A11: We thank Dr. Elbendary for this advice. First row of table 4 (now table 3) has been deleted. The repetition of table 3 (now table 2) has been revised as follows:

In comparison to table 2, sectoral RNFL thickness of the OCT (Table 3), which were adjusted whether it was superior temporal, inferior temporal, or combined according to the RNFL defect, showed no significant correlation with MD ($P = 0.34$), PSD ($P = 0.41$), and VFI ($P = 0.14$).

Q12: Former reviewer comments were not addressed properly within the revised manuscript. Authors replied to some inquiries, yet they didn't modify, highlight or show the corresponding changes in text. All, modifications and responses to reviewers’ recommendations should be added, implemented and highlighted within the revised manuscript e.g

- Issue of glaucoma subgroup analysis (POAG vs NTG) and corresponding $\beta$ values
- Grading of VF severity and corresponding $\beta$ values
- No of RNFL defects and corresponding $\beta$ values
- Correlating Superior and inferior RNFL defects to visual field indices
- Correlating superior and inferior angular measurements of RNFLD with the superior temporal and inferior temporal RNFL thickness of the OCT.
A12: We thank Dr. Elbendary for this comment. These subgroup analyses were valuable methodologies for identifying the significance of β values. However, we were concerned about whether the small sample size as a result of subgrouping would have diminished the credibility and power of the statistical results. Thus, we did not include these analyses in the manuscript despite going to the extent of running through all of the above statistical analyses and presented the results in the previous reviewer’s responses. We are willing to include and modify the manuscript accordingly if the reviewers do not think this is an issue.

Q13: The control group is crucial to validate your methods. Normal people were found to have split RNFL defects characterized by lesser width than glaucoma patients, lacking the characteristic wedge shape. Quantification of these data in control subjects is beneficial to understand or propose whether certain angle values are critical, risk factors for future glaucoma development.

A13: We thank Dr. Elbendary for this comment. We agree that a control group with normal subjects having RNFL defect will be beneficial in understanding the significance of the angle values. However, this is a retrospective study. Medical records of these subjects would be difficult to collect since normal subjects often do not visit ophthalmology clinic, and record of fundus photography is even rarer for these subjects. Acquiring these data based on incidental finding would be a difficult but crucial task. We thank the reviewer for this great advice and will collect normal subjects with RNFL defects for future studies.

Discussion

Q14: Avoid copying results section while discussing the outcome, confusing the readers with p values, No of tables.

A14: We thank Dr. Elbendary for this advice. P values and table numbers have been deleted in the discussion section. The redundancies of result and discussion sections have been revised.

Q15: Avoid writing methodology technique while discussing your results (line 211-215). This part should be included in methodology section. On discussion, you need to point out that the subjectivity is one of the limitations in the study.

A15: We thank Dr. Elbendary for this advice. Subjectivity has been pointed out in the limitation. The methodology technique has been moved to the method section.
Q16: You can't conclude that your method has a stronger correlation with visual field parameters than OCT parameters based on evaluation of single parameters (sectorial RNFL). The current study and Previous studies showed that average RNFL correlated with MD, PSD and VFI (Discriminating ability of spectral domain optical coherence tomography in different stages of glaucoma, SJO,2012).

A16: We thank Dr. Elbendary for this advice. We have changed “stronger” correlation to “noninferior” correlation.

Q17: Line 166-168 page 8: the sentence (with unanimous) is poorly constructed

A17: We thank Dr. Elbendary for this advice. The sentence has been revised as follows:

In this study, we showed that the measurement of RNFL angle defect around the disc proposed by Woo et al [2] is an effective way to estimate the severity of visual field defect.

Q18: Conclusion results can't be generalized to all glaucoma stages since all eyes in this sample were categorized as mild stage. Limit your conclusion to early stages of glaucoma. Avoid citation of any authors in conclusion section. Since RNFL defects were not graded according to severity, the conclusion should be modified. It is more appropriate to conclude that the quantification of localized RNFL defects is potentially useful for glaucoma diagnosis and that the width of RNFL defects was correlated to visual field indices in early stages.

A18: We thank Dr. Elbendary for this comment. The conclusion has been revised as follows:

In summary, our study suggested that the quantification of localized RNFL defects is potentially useful for glaucoma diagnosis and that the width of RNFL defects was correlated to visual field indices in early stages of glaucoma.

Limitations

Q20: The main limitation is: Low inclusion rates over long period of time (5 years), Subjective techniques in the era of quantitative imaging analysis limit the applicability of this study. Low inclusion rate possibly reflects the well-known low prevalence rate of localized RNFL defects in glaucoma (20%), although it has high specificity being restricted to glaucomatous eyes, yet it lacks sensitivity.

A20: We thank Dr. Elbendary for this comment. Limitations stated above have been added and modified as follows:
First, the subjectivity of angle measurements using ImageJ software limits the applicability, but this technique may be valuable if it is encompassed as one of the parameters of the OCT in the future. Second, inclusion rate is low due to high RNFL photography quality requirements.

Q21: Language needs editing and attention not to implement personal expressions in scientific writing (we were not surprised …ect.

A21: We thank Dr. Elbendary for this advice. Personal expressions have been deleted.