Author’s response to reviews

Title: Diagnostic accuracy of optical coherence tomography angiography for choroidal neovascularization: a systematic review and meta-analysis

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Version: 1 Date: 12 Jun 2019

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Corrections

Author(s): Rui Wang, M.D., Zhenzhen Liang, Ph.D., Xin Liu, Ph.D.

Article title: Diagnostic accuracy of optical coherence tomography angiography for choroidal neovascularization: a systematic review and meta-analysis.

Manuscript Number: BOPH-D-19-00342

Dear Editor:

Thank you for your comments and suggestions. We have revised accordingly, and corrections were listed below point by point. The related contents have also been marked in the manuscript. In addition, we updated the search literature with a deadline of June 2019. Figures and tables had been replaced and corrected.

Reviewers’ comments:

Reviewer 1:

Q1: Discuss the Fluorescein Angiography compared to OCT-A in the parameters.

A1: Based on your advice, we collected information about reference standards from each article and listed them in Table 1 (On page 24). It showed that 9 studies included in this meta-analysis were only used fluorescein angiography (FA) as a reference standard while 7 studies used
indocyanine green angiography (ICGA) or multimodal imaging. We analyzed and discussed if different reference standards was the source of heterogeneity (On page 11, line 2 to 5 and page 14, line 10 to page 15, line 2). It showed that the sensitivity was different between two groups. The sensitivity of FA reference group was lower than other reference standards (0.92 versus 0.83, p<0.01). We also discussed parameters including sensitivity and specificity of OCTA compared to FA on page 14, line 13 to page 15, line 2.

Q2: Please describe what you mean: Negotiations were utilized to settle down disagreements to achieve consistent conclusions.

A2: In order to ensure the quality of this meta-analysis, the process of extracting data was done by two people independently. If there was disagreement in extracting the data and information of each article, we would resolve the disagreement through discussion by a third reviewer to ensure that the information and data extraction of each article was correct. Now we changed this sentence into ‘A third reviewer was consulted to settle down disagreements and achieve consistent conclusions.’(On page 6, line 22 to page 7, line 1).

Reviewer 2:

Q1: The diagnostic accuracy of OCTA for CNV, from the clinical aspect, it mainly depending on the size of CNV; the activity of the CNV; and the primary causes of CNV, and etc. Firstly, The small and stable CNV, might have a higher diagnostic accuracy with OCTA. However, if the CNV accompany with huge hemorrhage or PED known as a subtype of Type I CNV, which is commonly seen in polypoid choroidal vasculopathy in Asian patients. The accuracy may be poor because poor optical transmission of hemorrhage. Authors should consider the different type of diseases. Different proportion of different diseases may influence sensitivity and specificity. The previous reported OCTA accuracy of CNV was varies in nAMD patients, the Six publications providing information on the diagnostic accuracy (sensitivity, specificity or calculations of positive and negative predictive values) of OCTA in nAMD varies from about 65% to100% in specificity and sensitivity.

A1: Meta-analysis is a comprehensive analysis of multiple medical studies with the same research topic. The purpose of meta-analysis is to increase the sample size and reduce the differences caused by random errors and increase the efficiency of testing. Heterogeneity is evitable among studies so the analysis of heterogeneity source is necessary in each meta-analysis. As you said, CNV is caused by multiple diseases such as age-related macular degeneration, central serous chorioretinopathy, myopia and polypoid choroidal vasculopathy. Therefore, to assess the overall diagnostic value of OCTA for CNV, a variety of these diseases should be included, which is more in line with the actual situation on clinical. The heterogeneity
of a meta-analysis may be derived from research types, races, sample sizes, reference standards, etc., in addition to causes of the disease and types of the device. This is why the previously reported the heterogeneity of CNV in AMD patients was still large. Thus, based on your advice, we tried our best to extract the information provided in included articles to analyze sources of heterogeneity in as many aspects as possible. Finally, ethnicity, type of study, etiology, reference standard, type of device and sample size were added in a meta-regression model to explore sources of heterogeneity from sensitivity, specificity (On page 25 and page 26) and overall diagnostic value (On page 11, line 7 to 11). As you said that small and stable CNV might have a higher diagnostic accuracy with OCTA and CNV accompany with huge hemorrhage or PED might lead to a false negative result affecting the diagnostic value of OCTA, we intended to classify different types of CNV to conduct a subgroup analysis based on your advice. However, the information about the type of CNV in each study was not sufficient to investigate whether the sensitivity and specificity of OCTA in the diagnosis of type 1 CNV were different from those of other types. It appeared that most articles used more than two types of CNV to analyze the diagnostic value (Table 1 on page 24). In addition, fewer studies reported the size of CNV in detail, so we failed to list the size of CNV in Table 1. However, we analyzed ethnicity and compared the Asian people with other races. The result suggested that the difference was not statistically significant (On page 10, line 20 to page 11, line 11 and page 15, line 3 to 6). We also compared AMD with other diseases to explore whether the etiology is a source of heterogeneity. The result suggested that there was no statistically significant difference between AMD and other diseases (On page 10, line 20 to page 11, line 11). We conducted this meta-analysis based on only published articles, so some information in these articles might be insufficient which might lead to some limitations. Therefore, according to your advice, we wrote these limitations in the discussion (On page 15, line 10 to 19).

Q2: The projected artifact affected false positive rate, and different machine varies with CNV diagnosis accuracy. How the authors avoid the bias caused by projected artifact?

A2: Considering projected artifact in different devices may affect diagnostic outcome of OCTA in detecting CNVs, we made a subgroup-analysis to explore whether or not the type of OCTA device affecting CNV diagnosis accuracy. Since 10 of 16 studies used only AngioVue device, we compared the diagnostic value of only AngioVue device group with other OCTA devices group. The result of joint model of meta-regression model showed that diagnostic value was different between these two subgroups and it might be the potential source of overall heterogeneity (On page 11, line 7 to line 11 and page 14, line 2 to 10). The sensitivity and the specificity of AngioVue group were 0.90 and 0.96, respectively, while in other devices group, they were 0.83 and 0.98, respectively.