Diagnostic Value of Optical Coherence Tomography Angiography for Choroidal Neovascularization in Age-Related Macular Degeneration: A Systematic Review and Meta-Analysis

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Keywords

Optical coherence tomography angiography · Age-related macular degeneration · Meta-analysis · Diagnosis · Sensitivity · Specificity

Abstract

Objective: This study aims to evaluate the diagnostic value of optical coherence tomography angiography (OCTA) in detecting the choroidal neovascularization (CNV) in age-related macular degeneration (AMD). **Methods:** A systematic review and meta-analysis was performed by searching Pubmed, Science Direct, Embase, and Web of Science. The pooled sensitivity and specificity with 95% confidence intervals (CIs), area under the summary receiver operator characteristic curve (sROC), and the total accurate classification rate were used to evaluate OCTA's diagnostic value of CNV in AMD patients. **Results:** Seven studies involving 517 eyes were included in the analysis. The mean age of subjects in each study ranged from 58.5 years to 81.7 years. Fluorescein angiography was applied as the gold standard in 5 studies. There were 350 eyes diagnosed with CNV, OCTA detected 301 eyes correctly, while among the 167 eyes without CNV, OCTA identified 150 correctly. The total accurate classifica-

tion rate was 87.23%. The Spearman's rank correlation coefficient was 0.5, indicating that there was no significant threshold effect in the current study ($S = 8$, $p = 0.103$). The pooled sensitivity and pooled specificity were 0.89 (95% CI: 0.82, 0.94) and 0.96 (95% CI: 0.85, 1.00), respectively. The area under sROC was up to 0.911. **Conclusion:** The specificity of OCTA for the detection of CNV in AMD patients is extremely high; however, the sensitivity still needs to be improved. In general, the meta-analysis revealed that OCTA had a high diagnostic value for the detection of CNV in AMD patients.

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Introduction

Optical coherence tomography angiography (OCTA) is a newly developed technology based on widely used optical coherence tomography [1, 2]. OCTA has many advantages over conventional OCT, as it can assess the retina microcirculation quantitatively and in a 3-dimensional way and ensure better image quality with shorter scanning time [3, 4]. The application of OCTA in the auxiliary diagnosis of ocular diseases such as glaucoma [5, 6], diabetic retinopathy [7, 8], age-related macular degenera-

tion (AMD), foveal hypoplasia [9], central serous retinopathy [10, 11], and retinal artery occlusion [12] has gained popularity within just several years.

Before OCTA, except for OCT, the following 2 diagnostic tools were frequently used in clinical practice for ocular diseases detection: fluorescein angiography (FFA) and indocyanine green angiography (ICGA). However, FFA and ICGA usually require the intravenous administration of dye [13, 14] and 10–30 min to finish the imaging process [15]. What's more, both FFA and ICGA are invasive methods, which might lead to nausea or even allergic reactions. OCTA, on the contrary, is a noninvasive detection method, which is an immense advantage compared with FFA and ICGA. For progressive diseases, such as AMD, follow-up and regular monitoring are quite important, which means frequently detection of the retina is needed. Therefore, it is not feasible to apply FFA or ICGA for AMD patients, while OCTA is an optimal choice.

Choroidal neovascularization (CNV) is an important sign, indicating the progression of AMD, and patients' visual acuity would be damaged severely if not prevented or treated in time. For the time being, FFA remains the gold standard for the CNV detection. However, due to occurrence of dye leakage, hemorrhage, or media opacities, retinal pathology can be obscured. Besides, while segmentation of different layers could provide detailed visualization of functional vasculature and is of great scientific significance, FFA or ICGA is not designed for acquiring segmentation of different layers. In contrast, OCTA could easily obtain the segmentation of different layers, the localization of the lesion depth of CNV, as well as the size delineation.

In recent years, several studies assessed and reported the diagnostic accuracy of OCTA for CNV detection in AMD patients; however, results are inconsistent and the sensitivity reported varied a lot. Given the lack of solid data demonstrating the exact accuracy of OCTA for CNV detection, this study aims to evaluate the overall diagnostic value of OCTA in the detection of CNV in AMD patients by conducting a comprehensive systematic review and meta-analysis.

Methods

Databases and Search Strategy

PubMed, Science Direct, Embase, and Web of Science (from inception to April 15, 2020) were searched for diagnostic test, case-control studies, cases series, cross-sectional, or cohort studies published in English with the following terms and their combination:

OCTA, diagnose, diagnosis, sensitivity, specificity, FFA, age-related macular degeneration, maculopathy, AMD, Geographic Atrophy, GA. The full search strategy is shown in the appendix (see Appendix 1).

Inclusion Criteria

Studies were included only when the following four criteria were met:

1. The subjects should be AMD patients, regardless of early AMD or late AMD.
2. The diagnose method should be OCTA.
3. At least 1 gold standard should be used for CNV diagnosis. Either FFA or ICGA would qualify, and any study using both measurements would qualify too.
4. There should be extractable data for sensitivity and specificity calculation.

Exclusion Criteria

Studies were excluded if any of the following criteria were met:

1. Patients of other diseases.
2. Only OCTA was used for CNV diagnosis, without gold standard to make comparison.
3. Study design is case report, letter, editorials, or reviews.
4. Study was not written in English.
5. Studies without extractable data.

Data Extraction

The following information of each study was extracted: name of first author, year of publication, the country or area where the study was conducted, sample size (number of eyes included in the final analysis), study design, mean age of included subjects in each study, the gold standard used for comparison in each study, and the type of OCTA applied. In addition, the numbers of true positive, true negative, false positive, and false negative were extracted for quantitative estimation of diagnostic accuracy.

Statistical Analysis

The pooled sensitivity and specificity with 95% confidence intervals (CIs) as well as the total accurate classification rate were used to evaluate the diagnostic ability of OCTA for CNV detection in AMD patients. The summary receiver operator characteristic curve (sROC) was accurately drawn so as to estimate the area under the sROC. The threshold effect was assessed by the Spearman correlation coefficient, with a *p* value of below 0.05 indicating significant threshold effect. Funnel plot was used to check publication bias in an intuitive way. The meta-analysis process was based on Bayesian theory, and all the analysis was carried out using an open source R program (Version 4.0.0). The package "meta4diag" and "INLA" were used for calculation of overall effects. The significance level was set to be 0.05, 2-tailed.

Results

Paper Selection

A total of 1,168 studies were identified by searching PubMed, Science Direct, Embase, and Web of Science. After 223 duplicates were removed, 945 records were re-

Fig. 1. Flowchart of article selection.

Table 1. Characteristics of included studies

Authors	Country/area	Eyes analyzed, <i>n</i>	Study design	Mean age, years	Gold standard	Type of OCTA
Ahmed et al. [17]	Austria	156	Cross-sectional	75.3±9.17	FFA, ICGA	SS-OCTA (Topcon Corporation, Tokyo, Japan)
Carnevali et al. [21]	Italy	44	Diagnostic test	CNV: 76.5±6.9 No CNV: 73.8±6.8	ICGA	HD-OCT (Carl Zeiss Meditec, Dublin, USA)
Faridi et al. [19]	America	52	Case-control	Non-nAMD: 81.7±5.4 nAMD: 76.7±9.1	FFA	SD-OCT (Optovue Inc., Fremont, CA, USA) SD-OCT (Optovue Inc., Fremont, CA, USA)
Gong et al. [20]	China	86	Case series	67	FFA	SD-OCT (Optovue Inc., Fremont, CA, USA)
Moult et al. [22]	America	19	Cross-sectional	79.7±8.3	FFA, ICGA	SS-OCTA (Massachusetts Institute of Technology)
Nikolopoulou et al. [18]	Italy	70	Cross-sectional	70.9±10.27	FFA	SD-OCT (Optovue Inc., Fremont, CA, USA)
Usman et al. [23]	Pakistan	90	Cross-sectional	58.5±5.05	FFA	Not specified

nAMD, neovascular AMD; CNV, choroidal neovascularization; SS-OCTA, swept-source optical coherence tomography angiography; HD-OCT, high-definition optical coherence tomography; SD-OCT, spectral-domain optical coherence tomography; FFA, fluorescein angiography; ICGA, indocyanine green angiography.

viewed for title and abstract, and 864 records were further excluded. Among the remaining 81 articles, 74 were further excluded due to ineligible study design, lack of extractable data, non-English publication [16], or other rea-

sons based on our inclusion and exclusion criteria. Eventually, 7 studies [17–23] were included for quantitative meta-analysis, and the detailed paper selection process is shown in Figure 1.

Fig. 2. Forest plot of sensitivity of OCTA in diagnosing CNV. TP, true positive; FP, false positive; TN, true negative; FN, false negative; OCTA, optical coherence tomography angiography; CNV, choroidal neovascularization.

Table 2. Diagnosis

Study	OCTA diagnosis	FFA diagnosis	
		positive	negative
Ahmed et al. [17]	Positive	81	0
	Negative	26	49
Carnevali et al. [21]	Positive	18	0
	Negative	4	22
Faridi et al. [19]	Positive	32	0
	Negative	0	20
Gong et al. [20]	Positive	45	11
	Negative	7	23
Moult et al. [22]	Positive	16	0
	Negative	1	2
Nikolopoulou et al. [18]	Positive	44	2
	Negative	6	18
Usman et al. [23]	Positive	65	4
	Negative	5	16

OCTA, optical coherence tomography angiography; FFA, fluorescein angiography.

Characteristics of Included Studies

The characteristics of 7 included studies are shown in Table 1. A total of 517 eyes were included in the analysis. Two studies were carried out in USA, 2 in Italy, 1 in China, 1 in Pakistan, and 1 in Austria. Four studies adopted cross-sectional design, and the remaining 3 were diagnos-

tic test, case-control, and case series studies, respectively. The mean age of subjects in each study ranged from 58.5 years to 81.7 years. FFA was applied as the gold standard in 6 studies, and ICGA was used as the gold standard in 3 studies. SD-OCT (Optovue Inc., Fremont, CA, USA) is the most frequently used OCTA type.

Total Accurate Classification Rate

There were 350 eyes diagnosed with CNV (Table 2), OCTA detected 301 eyes correctly, while among the 167 eyes without CNV, OCTA identified 150 correctly. The total accurate classification rate was 87.23%.

Threshold Effect

The Spearman's rank correlation coefficient was 0.5, and there was no significant threshold effect in the current study ($S = 28$, $p = 0.267$).

Sensitivity

The sensitivities in studies by Ahmed et al. [17], Carnevali et al. [21], Faridi et al. [19], Gong et al. [20], Moult et al. [22], Nikolopoulou et al. [18], and Usman et al. [23] were 0.78 (95% CI: 0.69, 0.85), 0.84 (95% CI: 0.70, 0.93), 0.92 (95% CI: 0.84, 0.99), 0.88 (95% CI: 0.79, 0.94), 0.89 (95% CI: 0.78, 0.97), 0.88 (95% CI: 0.80, 0.94), and 0.91 (95% CI: 0.85, 0.96), respectively (Fig. 2). The pooled sensitivity was 0.89 (95% CI: 0.82, 0.94).

Specificity

The specificities in studies by Ahmed et al. [17], Carnevali et al. [21], Faridi et al. [19], Gong et al. [20], Moult

Fig. 3. Forest plot of specificity of OCTA in diagnosing CNV. TP, true positive; FP, false positive; TN, true negative; FN, false negative; OCTA, optical coherence tomography angiography; CNV, choroidal neovascularization.

Fig. 4. Forest plot of area under the sROC. sROC, summary receiver operator characteristic curve.

Fig. 5. Funnel plot of OCTA in diagnosing CNV. OCTA, optical coherence tomography angiography; CNV, choroidal neovascularization; DOR, diagnostic odds ratio; SD, standardized deviation; LDOR, log (diagnostic odds ratio).

et al. [22], Nikolopoulou et al. [18], and Usman et al. [23] were 0.99 (95% CI: 0.93, 1.00), 0.97 (95% CI: 0.87, 1.00), 0.97 (95% CI: 0.84, 1.00), 0.70 (95% CI: 0.54, 0.84), 0.91 (95% CI: 0.44, 1.00), 0.90 (95% CI: 0.75, 0.98), and 0.81 (95% CI: 0.63, 0.94), respectively (Fig. 3). The pooled specificity was 0.96 (95% CI: 0.85, 1.00).

Summary Receiver Operator Characteristic Curve

Results of hierarchical sROC (Fig. 4) showed that the circles were on the top left corner of the figure, indicating a good diagnostic value. The area under sROC was fur-

ther calculated, which turned out to be 0.911, higher than 0.90, also indicating a good diagnostic value of OCTA for CNV detection in AMD patients.

Publication Bias

The funnel plot (Fig. 5) was not symmetrically distributed, indicating that there might be publication bias in this study, which is a limitation due to limited number of included studies.

Discussion

Our study aimed at exploring the diagnostic value of OCTA for CNV detection in AMD patients. Over the past several years, since the use of OCTA was proposed, several studies were conducted to assess its diagnostic value for CNV detection; however, the conclusions contradicted with each other, and the reported sensitivities ranged from 0.78 to 0.92 [17–23]. The sample size of each study varied from 19 to 156 [17–22], which is one of the reasons why the reported sensitivity varied a lot across these studies. By conducting a systematic review and meta-analysis, this article attempts to provide a more accurate and evidence-based estimation of OCTA's diagnostic value for CNV detection in AMD patients by pooling all published studies together. The main finding is that OCTA has an extremely high specificity in detecting CNV in AMD patients. Meanwhile, the sensitivity is also good, though still needs to be improved. In general, OCTA is a suitable alternative choice for CNV detection other than FFA or ICGA.

CNV is a typical trait of wet AMD, and it indicates the progression of disease, thus early detection of CNV in AMD patients is of great value so that early intervention could be carried out for patients to avoid progression to blindness. Jia et al. [24] and coworkers firstly applied swept-source OCTA system in a cross-sectional study involving 5 normal subjects and 5 subjects with neovascular AMD to visualize and quantify CNV, and they verified these CNV cases with FFA. They reported that OCTA provided more distinct vascular network patterns that were less obscured by subretinal hemorrhage. Since then, several other researchers reported the good performance of OCTA in detecting CNV in AMD patients. This meta-analysis provided a similar finding with stronger evidence based on a relatively large pooled sample size.

CNV also plays an important role in other ocular diseases like polypoidal choroidal vasculopathy [25], pachychoroid neovascularopathy [26], and central serous retinopathy [27]. However, for other ocular diseases, recent evidence showed that the performance of OCTA for CNV detection might not be as good: de Carlo TE [28] and coworkers enrolled 72 eyes with different ocular diseases including AMD, central serous chorioretinopathy, etc., and used OCTA to detect the CNV. Their study revealed a sensitivity of merely 50%.

It was worth mentioning that the gold standard of diagnosis of exudative AMD might have changed in recent years, Cohen and Mrejen [29] pointed out that combined

FFA and OCT, which showed superiority to FFA alone in determining the incidence and prognosis of various CNV subtypes [30–32], came to be considered the new gold standard for diagnosis of exudative AMD. They further pointed out that OCTA might further change the diagnostic paradigm. The use of OCTA is now limited by difficulty of image acquisition, artifacts, a slow learning curve of obtaining reliable images, etc., but visualization of CNV and exudation is sufficient for clinical practice for many cases, and invasive examinations could even be avoided for many certain cases. With the increase of sensitivity, OCTA might be a promising tool for diagnosing exudative AMD later on.

CNV has different subtypes [33, 34], which might affect OCTA's diagnostic accuracy. Current evidence showed a high detection rate for type II CNV, but not for other types [17, 35, 36]. Ahmed et al. [17] reported that most undetected eyes were with type I CNV. Mrejen et al. [35] found that the ability of OCTA for type I CNV detection greatly depended on the height of the pigment epithelial detachment, and reported that the detection rate was excellent when the PED height was below 250 μm , and the performance was poor when PED >250 μm . Similarly, Yeo et al. [36] used SS-OCTA to detect 3 types of CNV, revealing that the sensitivities for type I, type II, and type III CNV were 73.5, 100, and 88.9%, respectively. With OCTA, type II CNV usually shows a sharp demarcation, while type I CNV usually shows a minor demarcation to the surrounding vasculature [37, 38]. Mrejen et al. [35] proposed that the poor performance of OCTA on detection of type I CNV with PED >250 μm might be caused by segmentation artifact and OCT signal attenuation.

CNV is not the only symptom or sign that OCTA could detect; OCTA could be useful for many other progressive ocular diseases, like glaucoma [39] and uveitis [40]. Nowadays, the clinical practice of AMD diagnosis is changing. There is a trend that OCTA is gradually becoming the main examination method for AMD, and even for other retinal diseases. Giocanti-Auregan et al. [41] compared the practice of imaging tools in 3 cohorts carried out in year 2014, 2016, and 2018 and found that the frequency of FA application dropped rapidly from 70.2% in year 2014 to 22.1% in year 2018, while OCTA was more and more frequently used over time. Similarly, Le Rouic et al. [42] retrospectively reviewed cases of 3,487 patients examined for a retinal disease between 2015 and 2018, and randomly selected 1,170 eyes for analysis. They found that OCTA was performed in 49.4% of the studied eyes, while FFA was only performed in 6.5% of the studied

eyes. What's more, the rate of FFA application dropped over time.

However, conventional FFA could not be completely replaced because OCTA also has limitations. Currently, OCTA has a relatively small field of view [43]. Besides, OCTA is unable to evaluate alterations in vascular permeability or leakage [38], while FFA and ICGA can. For patients with occult lesions that appear quiescent on OCTA, FFA could detect this type of lesion by leakage [44]. What's more, artifact, a common condition referring to extra or missing pieces of information in image examinations, is another drawback of OCTA. There are several types of artifact, including projection artifact [45], segmentation artifact, motion artifact, and other artifacts. Projection artifact, a condition where vascular structures of superficial layers are also displayed incorrectly in deeper layers, was reported to be the most common artifact type [45]. Projection artifact limits the OCTA visualization of pathologic vessels of the outer retina [46] and thus could lead to misinterpretation and misdiagnosis. Nonetheless, the diagnosis accuracy of OCTA could be improved through "artifact removing." A recently proposed projection-resolved algorithm was reported to be effective for removing projection artifact [47]. Projection-resolved-based OCTA shows significantly greater CNV vascular area and vascular connectivity compared with conventional OCTA [47, 48]. With the improvement of algorithms and devices, the diagnostic value of OCTA for CNV detection could be further enhanced in the future.

In conclusion, the specificity of OCTA in detecting CNV in AMD patients is extremely high; however, the sensitivity still needs to be improved. In general, the meta-analysis revealed that OCTA has a high diagnostic value for the detection of CNV in AMD patients.

Limitations of This Study

Due to limited publications, there might be a potential publication bias as indicated by the funnel plot. In the future, an updated meta-analysis assessing OCTA's detection ability for CNV in AMD patients would still be of great value. In addition, subgroup analysis by CNV sub-

types is not done due to limited publications. OCTA's ability to detect different types of CNV should be explored in the future.

Statement of Ethics

Ethical approval and consent are not applicable since this is a meta-analysis, we do not include individuals, and we include published studies.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

There is no funding for this study.

Author Contributions

Chang-Xi Chen and Jin-Da Wang contributed to study design and concept; Chang-Xi Chen and Jin-Da Wang contributed to database search; Kai Cao and Chang-Xi Chen contributed to data extracting; Kai Cao contributed to data analysis; Kai Cao and Jin-Da Wang contributed to manuscript writing, and Mei-Ling Liu and Mayinuer Yusufu contributed to manuscript revising.

Data Availability Statement

Data will be available upon reasonable request.

Appendix 1

Full Search Strategy

([Optical Coherence Tomography Angiography] or [Optical Coherence Tomography Angiogram] or OCTA) AND (diagnose or diagnosis or sensitivity or specificity) AND ([fluorescein angiography] or FFA or [indocyanine green angiography] or ICGA) and ([Age-related macular degeneration] or maculopathy or AMD or [Geographic Atrophy] or GA).

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