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Research Article

Quantitative analysis of Age Related Macular Degeneration in Optical Coherence Tomography Angiography images

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Abstract

Age-related Macular Degeneration (AMD) is a common eye condition that leads to about 8% of all blindness worldwide. It is leading cause of vision loss among people age 50 and older. Optical coherence tomography angiography (OCTA) is recent non-invasive technique used for detection of various eye related diseases. It provides vascular information related to an eye. Mainly, it is used for detection of choroidal neovascularization region inside an eye. Quantitative analysis of OCTA helps in finding abnormalities and guiding the treatment for eye related diseases like diabetic retinopathy and age related macular degeneration. Vessel density is one of the quantitative measurement which has gained popularity and provides ability to quantify OCTA images in order to measure effectiveness of provided treatment. Local thresholding and global thresholding methods are used for binarization of OCTA images. Vessel density changes with respect to image size, device used, location scanned, plexus under consideration and the type of techniques used for binarization of an image. There is no standard technique for calculation of vessel density in OCTA images. There is no surety that the results obtained using one of the techniques will be similar to other techniques. Proposed method based on Otsu and component labelling algorithm provided better results as compared to all other methods by giving exact mapping with vessels in OCTA images.

Keywords: *Age related macular degeneration(AMD); Choroidal neovascularization(CNV); Vessel Density; Optical Coherence Tomography Angiography(OCTA); Thresholding; Otsu.*

Introduction

Age-related Macular Degeneration (AMD) is a common eye disease and a leading cause of vision loss among people age 50 and older[1][5]. AMD is the third leading cause of blindness all over the world[2]. It causes damage to the macula which is a small spot near the center of the retina and the part of the eye needed for sharp, central vision[1]. It lets us see objects that are straight ahead. If left unnoticed, AMD can cause irreversible damage to the macula leading to blindness and complete vision loss. In some people, AMD advances so slowly that vision loss does not occur for a long time. In others, the disease progresses faster and may lead to a loss of vision in one or both eyes[1]. Early on there are often no symptoms. Over time, however, some people experience a gradual worsening of vision that may affect one or both eyes. This may gradually turn into a dramatic loss of the central vision. However, the loss of central vision in AMD can interfere with simple everyday activities, such as the ability to see faces, drive, read, write, or do close work, such cooking or fixing things around the house[3]. Other symptoms includes blurred vision, straight lines appearing wavy, inability to see in dim light, dark and distorted vision or seeing spot and vision loss.

Age is a major risk factor for AMD. Other risk factors for AMD includes smoking, family history, blood pressure, highcholesterol, fat intake and obesity[3][4].There are three stages of AMD defined in part by the size, number of drusen under the retina and the presence of choroidal neovascularization (CNV) as shown in Fig 1. Drusen are yellow deposits under the retina and are made up of lipids, a fatty protein[3][4]. CNV is part of the spectrum of exudative or wet AMD. It consists of an abnormal growth of vessels from the choroidal vasculature to the neurosensory retina through the Bruch's membrane. Early AMD is diagnosed by the presence of medium-sized drusen, which are about the width of an average human hair. People with early AMD typically do not have vision loss. People with intermediate AMD typically have large drusen, pigment changes in the retina, or both. Intermediate AMD may cause some vision loss, but most people will not experience any symptoms In addition to drusen, people with late AMD have vision loss from damage to the macula. There are two types of late AMD namely, geographic atrophy (also called dry AMD) and neovascular AMD (also called wet AMD). In dry AMD, there is a gradual breakdown of the light-sensitive cells in the macula that convey visual information to the brain. These changes cause vision loss in the patients. In wet AMD, abnormal blood vessels grow under the retina. These vessels can leak fluid and blood, which may lead to swelling and damage of the macula. The damage may be rapid and severe, unlike the more gradual course of geographic atrophy. It is possible to have both geographic atrophy and neovascular AMD in the same eye, and either condition can appear first[3][4].

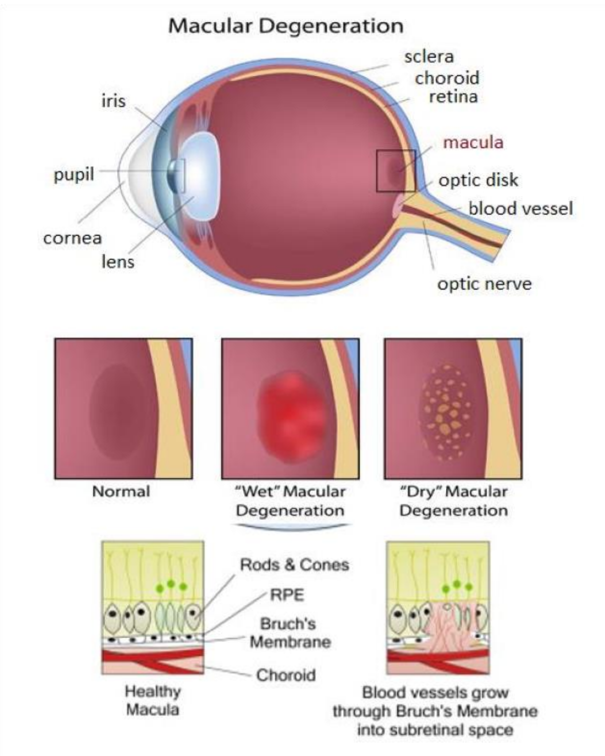

Fig. 1. Age related Macular Degeneration[5]

Traditional multimodal imaging methods, such as Fluorescein Angiography(FA), Optical Coherence Tomography and Optical Coherence Tomography Angiography are used to detect AMD at different stages. These are commonly used techniques for detection of AMD. OCTA in comparison is a non-invasive technique that acquires volumetric angiographic information without the use of dye as in FA.As it is non-invasive technique, patients do not suffer from any side effects such as vomiting and nausea which was observed in FA technique. Each three-dimensional scan set takes approximately six seconds to obtain. The en-face images (OCT angiograms) can then be scrolled outward from the internal limiting membrane (ILM) to the choroid to visualize the individual vascular plexus and segment the inner retina, outer retina, choriocapillaris, or other area of interest. The en-face acquisition areas currently range from 2 * 2 mm to 12 * 12 mm with the scan quality greatly decreased with a widened field of view since the same number of OCT b-scans is used for all scanning areas. The 12 * 12 mm scan is only available on research prototypes. The 3 * 3 mm OCT angiograms appear to be higher resolution than the currently available FA/ICGA images[6].

The wet type of AMD acts approximately 10-15 % of individuals around the whole world. It accounts for approximately 90% of all cases of severe and rapid vision loss[5][7]. AMD is the most significant cause of irreversible blindness. There is not as-of-yet an approved treatment or cure for AMD. Thus, it becomes important to deal with such deadly disease. According to transparency market research, the AsiaPacific region accounts for more than one third of the macular generation cases globally and the prevalence is estimated to increase more rapidly than in Europe and Americas[4]. With detection it becomes important to do quantitative analysis of OCTA images. OCTA is used for monitoring CNV in wet AMD providing both functional(blood flow) and morphological(fluid accumulation) information available in single scan[8][9].This helps in guiding decisions for treatment of AMD and evaluating responses on CNV to its therapy[8]. Thus, assessment of OCTA images can help to and proper treatment and cure for this disease. Quantitative image analysis involves utilizing digital images to provide data and information.

Vessel density is one of the quantitative measure which can help doctor in understanding effects of treatment provided and finding standardized treatment for such hazardous disease. It is defined as the percentage of the angiocube occupied by retinal vessels. It has gained increasing popularity, and represents a promising imaging endpoint for future clinical trials.

Literature Survey

With increase in age, risk of developing age related diseases causing irreversible blindness increases. There is no effective treatment or cure on such diseases. AMD is one of the leading cause of blindness all over the world. Lot of research had been carried out in detection and analysis of AMD. Optical coherence tomography angiography (OCT-A) is a recent imaging modality that allows non-invasive, rapid, depth-resolved visualization of all the chorioretinal vascular layers. Vessel density is measured as ratio of number of white pixels to total number of pixels in image. Various methods are used in literature to calculate vessel density. Few of them are given below which help in quantitative analysis of OCTA. Seven different threshold strategies were used to binarize en face angiograms and calculate vessel density. The algorithms included the Macular Density algorithm v 0.6.1, a manual thresholding technique, three ImageJ auto thresholding algorithm (i.e., mean, default, Otsu), a semiautomatic method using a fixed threshold, and a method combining pre-processing filters with multilevel threshold strategies. Default and Otsu algorithms had an excellent reliability at every plexus[10].

A novel implementation of local fractal dimension to calculate vessel density and FAZ area was demonstrated. Vessel density in superficial layer (31.49%) was lower than the deeper layer (45.96%).The agreement between the manually segmented and local fractal dimension segmented FAZ area was 0.97[11]. Retinal Vessel segmentation is a procedure to extract the various blood vessels to diagnose various diseases such as diabetic retinopathy. Analysis of various automatic segmentation techniques using hybrid filters, clustering based matched mapping, local adaptive histogram equalization and deep learning method was carried out. Hybrid filter works well for noisy images and provides enhanced image and high accuracy[12].

Quantitative parameters from retinal microvasculature were measured on binarized and skeletonized OCTA images and compared with single OCTA images without averaging. Averaging improves image quality and helps in reducing noise. Sample size used was very small and default segmented images are used for averaging[13]. Vessel density was calculated for superficial retinal layer in the macula area. To analyze angiography signals, the global Otsu and Mean as global thresholding methods and local Otsu, Phansalkar, Niblack, and Saubora as adaptive local thresholding methods were used. These methods were used for binarization algorithm in OCTA images using ImageJ software without noise removal filter to obtain the vascular signal as white region. The reproducibility of various binarization methods reveals that local adaptive threshold methods are more appropriate when investigating vessel density using OCTA images[14].

Based on review there are a number of promising OCTA parameters that can be used to diagnose the presence of CNV and to monitor the activity and progression of the lesion, pre- and post-treatment morphological characteristics, CNV dimensions, and automated quantitative parameters such as vessel density. The OCTA parameters described in this review are promising for the future development of clinical trial endpoints, but require further validation before they can be widely used[15].

Through the survey measure gap was that very few research were carried out to detect AMD based on OCTA images. Based on authors knowledge no research was found on automated quantitative analysis of AMD in OCTA image. Also high computational time was required for segmentation of blood vessels as retinal structure is complex in nature. It is difficult to calculate vessel density manually. Hence, no ground truth available. OCTA is a promising technique and dataset availability is also a big challenge.

Proposed Methodology

A. Architecture

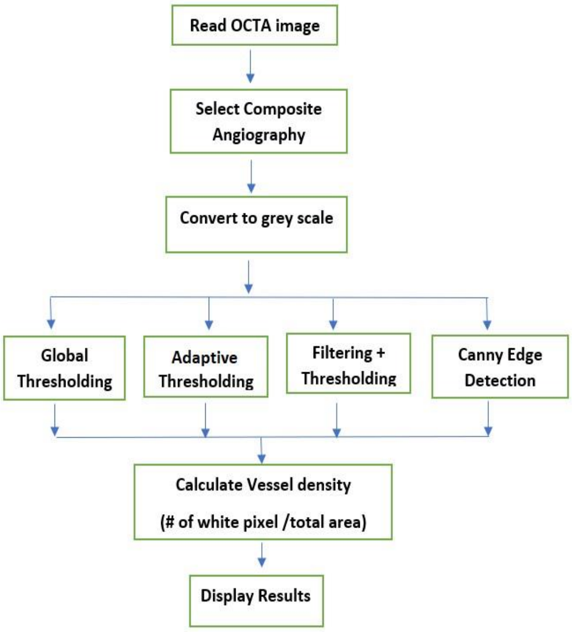

Fig. 2. Overview of proposed system

A. Algorithm Overview

An overview of developed algorithm is shown in Fig. 2. An OCTA image of patient is taken as input image. The image have different regions such as superficial, deep, outer retina, choriocapillaris and composite angiography. Images used were two different images one was before treatment image and other was after treatment image of same patient. In order to find vessel density we take into account composite angiography region as CNV region can be seen in that region. After this image is binarized using different methods in order to find vessel density. These methods are global thresholding, adaptive thresholding, pre-processing followed by thresholding, Otsu followed by component labelling and canny edge detection as shown in Fig 3.

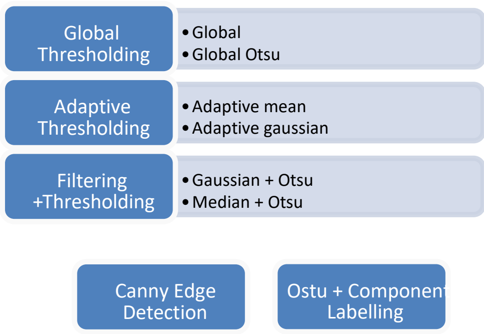

Fig. 3. Algorithms used for binarization of OCTA image.

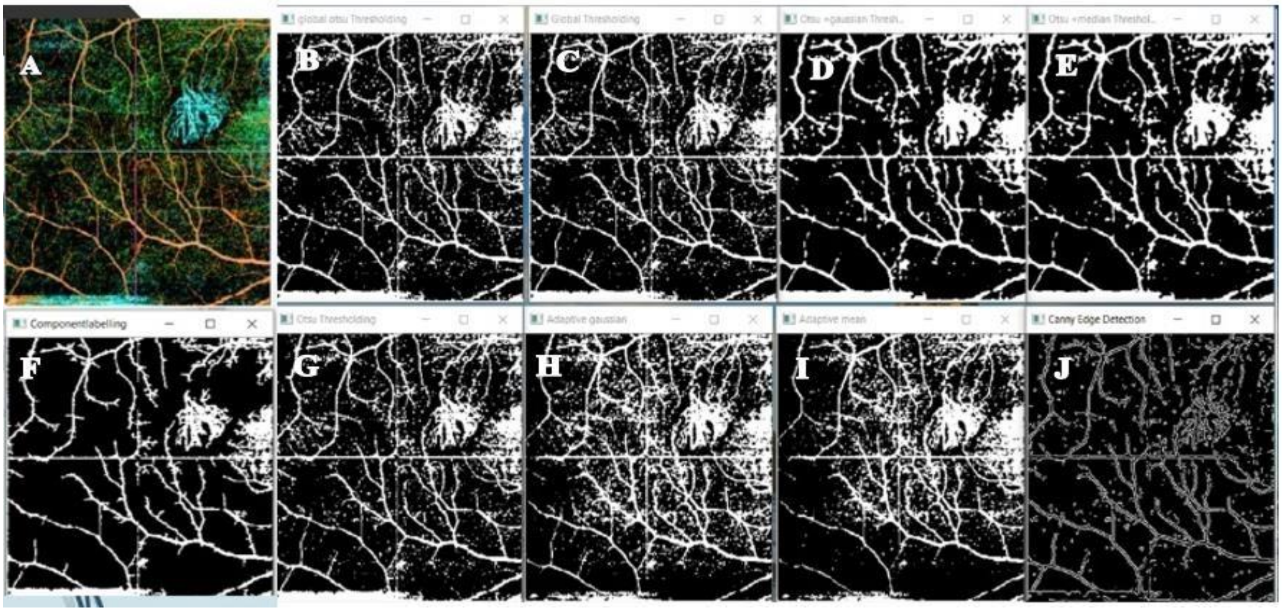

Fig. 4. Binarized images. A - input image, B – global otsu , C- global, D – otsu +gaussian, E – otsu + median, F – connected component labelling, G – otsu, H – adaptive gaussian, I – Adaptive mean, J- canny edge

1) Global Thresholding : In global thresholding, single threshold value is used to binarize entire image. As it works on assumption that image has bimodal histogram, so the object of interest can be easily extracted using single threshold value say T[10]. Here, using same on OCTA image and trying multiple threshold value, the optimal threshold value obtained was 127 and result for the same is shown in Fig. 6. Global thresholding produces binary image which have only two intensity values either 0 or 1, the one with 0 is considered to be the vessels and hence density is calculated for the same. The famous global thresholding techniques is Otsu technique, which is used to perform automatic image global thresholding. It selects the thresholding by maximizing the inter-class variance. Otsu's method is based on discriminant analysis. The Otsu algorithm works creating a two clusters by applying a threshold, which minimizes and maximizes the intra-class and inter-class variances between clusters. Using this strategy, the algorithm provides a single intensity threshold that separates pixels into two classes, foreground and background[10]. This threshold is obtained , by maximizing inter-class variance or by minimizing intra-class intensity variance.
For 2 classes, minimizing the intra-class variance is equivalent to maximizing inter-class variance

$$\sigma_b^2(t) = \sigma^2 - \sigma_w^2(t) = \omega_0(\mu_0 - \mu_T)^2 + \omega_1(\mu_1 - \mu_T)^2$$
$$= \omega_0(t)\omega_1(t)[\mu_0(t) - \mu_1(t)]^2 \quad (1)$$

where,
μ – *class means* and weights $w_0$and w_1 are the probabilities of the two classes separated by a threshold t given as below :

t−1

$w_0(t) = \sum p(i)$ (2)
i=0

L−1
$w_1(t) = \sum p(i)$ (3)
i=t

$\mu\ (t) = \frac{\sum_{i=0}^{t-1} ip(i)}{}0$ (4)
$w_0(t)$

$\mu_1(t) = \frac{\sum_{i=t}^{L-1} ip(i)}{}$ (5)
$w_1(t)$

2) Adaptive Thresholding : Unlike global thresholding the adaptive thresholding does not use single threshold to differentiate images into foreground and background region. Here, threshold value is calculated for smaller regions and therefore, there will be different threshold values for different regions in the image. For an image with variable lighting intensities in different areas adaptive thresholding provide better results. In order to differentiate every pixel into foreground or background the adaptive thresholding algorithm uses different threshold based on small neighborhood region around it. Because of this reason there is different thresholds for different regions of the same image[10][11]. The adaptive method decides how the threshold value is calculated which can be based on mean or gaussian-weighted sum of neighborhood respectively named as Adaptive-Mean and Adaptive-Gaussian. In order to differentiate given OCTA image the block size used was 199 and 247 respectively.

Table 1. Results -Vessel Density in percent

Sr.	Methods	Patient 1		Patient 2		Patient 3	
		Before	After	Before	After	Before	After
Global Thresholding							
1.	Global	37.26	38.946	30.067	46.957	25.181	24.744
	Global Otsu	37.26	38.946	33.154	48.974	29.332	24.26
Local Thresholding							
3.	Adaptive mean	45.511	45.245	35.624	42.531	32.634	27.33
4.	Adaptive gaussian	44.817	43.97	37.402	42.153	35.685	30.817
Filtering +Thresholding							
5.	Gaussian + Otsu	37.565	38.321	36.113	53.923	31.458	24.616
6.	Median + Otsu	36.884	38.161	33.617	51.062	28.78	22.338
Edge Detection							
7.	Canny Edge	17.29	07.20	08.837	05.157	06. 952	11.80
8.	Component	27.811	35.071	27.552	46.811	23.404	19.52

Filtering + Thresholding : In above techniques no preprocessing was done. But OCTA image contain projection artifacts and noise. In order to remove noise filtering was performed using gaussian and median filter which helped in smoothening, sharpening, edge detection and noise removal. A filter is defined by a kernel, which is a small array applied to each pixel and its neighbours within an image. In most applications, the centre of the kernel is aligned with the current pixel, and is a square with an odd number (3, 5, 7, etc.) of elements in each dimension[13][17]. For gaussian blur 5*5 filter size was used and median blur 3*3 filter was used. Results presented in Fig4. shows that the results are varying and could not provide sufficient accuracy.

3) Canny Edge Detection : The process of canny edge detection algorithm can be broken down to 5 different steps[16]. At first preprocess image using gaussian filter for noise removal and smoothening input OCTA image. After preprocessing image find the intensity gradients. Non-Maximum suppression(NMS) is applied to get rid of false response to edge detection. After this double thresholding is used to determine possible edges. At last step all the other edges which are not connected to strong edges and are weak are suppressed. After applying it on OCTA image the edges are highlighted well as shown in Fig. 4. But in order to determine the vessel density values went down as algorithm do not consider entire region and only considered the edges.

4) Connected Component Labelling : In this method Otsu thresholding was applied to obtain binarized image and image itself not completely resemble the vessels. Hence, connected component labelling algorithm helped in finding or grouping the pixels into components based on pixel connectivity[18].

Connectivity between pixel used was 4 and results are presented in Fig 4. After applying all these algorithms, vessel density is calculated by considering ratio of number of white pixels to total area and results are presented in the Table 1.

Result And Discussions

In present study, seven different algorithms were applied on OCTA images of three AMD patients. From every patient images before treatment and after treatment were acquired using OCTA technique. Below Table 1 shows the vessel density values of OCTA images(before, after) with different thresholding algorithms. Table 1 shows the vessel density values of OCTA images(before, after) with different thresholding algorithms. From Table 1 we get that vessel density using global thresholding and adaptive is similar. But due to noise the results are not correct. After preprocessing using median and gaussian the acceptable results are found but still some noise was present and due to noise fluctuation in results were observed. Canny edge detection is another approach whose results compared with other techniques are much variable but logically correct. Also using edge detection lot of noise is removed and exact vessel boundaries are obtained. Hence we can see that before treatment vessel density is high as compared to after treatment which is indication of recovery in patient, whereas, if it is low then patient state is deteriorating. In Table 2 vessel densities are expressed in form of mean and standard deviation which gives an idea about dispersion of vessel density obtained using different methods. Fig. 5 and Fig 6. represent the boxplot of vessel density values obtained using different binarization techniques and gives information about dispersion or deviation of results before and after treatment.

Table 2. Mean and Standard Deviation (SD) Vessel Density

SR	Methods	Before	After
1	Global	30.836 ± 4.961	36.882 ±9.185
2	Global Otsu	33.248 ± 3.237	37.393 ± 10.149
3	Adaptive Mean	37.923 ± 5.502	38.368 ±7.883
4	Adaptive Gaussian	39.3013±3.962	38.98±5.8195
5	Gaussian + Otsu	35.045±2.604	38.953±11.97
6	Median+Otsu	33.093±3.329	37.187±11.746
7	Canny Edge	11.026±4.495	8.052 ± 2.778
8	Component labelling	26.255±2.019	33.80±11.17

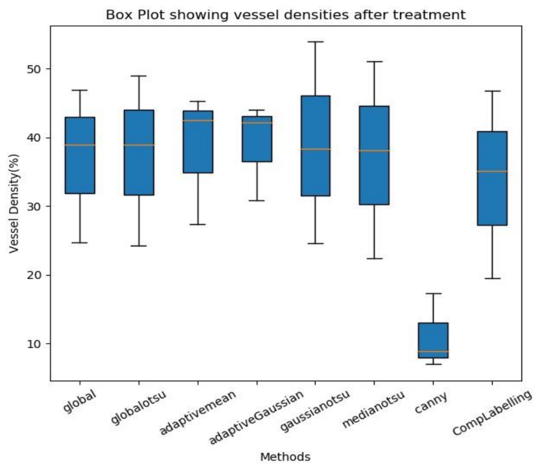

Fig. 5. Box plot showing vessel densities before treatment

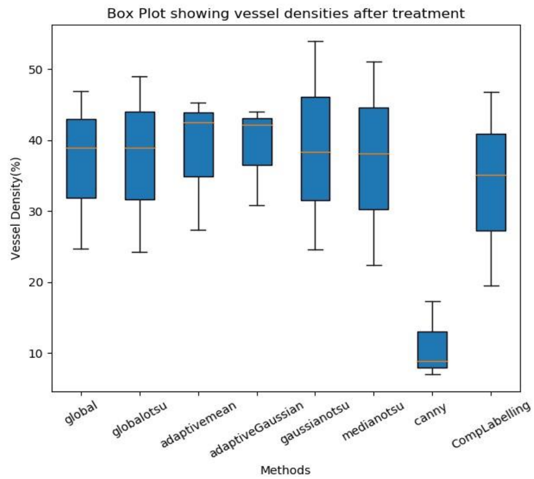

Fig. 6. Box plot showing vessel density after treatment

Conclusions

Quantitative assessment OCTA images can help to find proper treatment and cure for various eye related diseases. Vessel density is used as quantitative measurement for assessment of CNV region in OCTA images. Various methods can be used to obtain vessel density in OCTA images like Local Otsu, Global Otsu, local thresholding methods ,manual and fixed thresholding. No method outperformed the others , but the performance is dependent on the selected OCTA image. Canny edge detection gives good results compared to others as it removes noise but at the same time vessels are not accurately measured. Filtering along with thresholding gives better results but still presence of noise makes result to be inaccurate. Component labeling algorithm was able to segment blood vessels accurately but it fails in presence of unclear images. All methods provide promising results with certain limitations. In future, along with vessel density other quantitative measures like total area of CNV, vascular area of CNV can be implemented and evaluated which can be helpful for assessment of wet AMD.

We may use different methods such as image registration for obtaining clear OCTA scan, image enhancement methods like Frangi filters, Gabor filters and hybrid approaches for noise removal and vessel enhancement to obtain better accuracy. The systems performance can be improved by using more accurate dataset and advance techniques.

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