Quantification of wet 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. Late stage AMD is divided into dry AMD and wet AMD. Drusen and Choroidal Neovascularization(CNV) are the major causes of dry and wet AMD. An OCTA is the latest non-intrusive and safe technology that can provide detailed internal and external structure information of CNV. Detecting and analysing CNV is very effective for proper treatment and assessment of wet AMD. The proposed work aims to provide automated method and application to detect and analyse CNV region in OCTA images. Proposed methodology is divided into two modules which include CNV segmentation step based on connected component labelling algo- rithm and other one is CNV quantification step based on Otsu thresholding. This provides two important quantification measures namely CNV area and CNV vessel density. Performance of proposed system was measured using various parameters and was found better when compared with state of art methods. The jaccard similarity score was 0.9379 ± 0.023 and false negative rate was 0.0026 ± 0.003.

Keywords— Choroidal Neovascularization(CNV), CNV area, CNV vessel density, Con- nected Component labelling , Optical Coherence Tomography Angiography(OCTA, Otsu thresholding.

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1 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, 4]. AMD is the third leading cause of blindness all over the world [5]. 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. AMD behaviour is unpredictable as in some cases it grows slowly and vision loss is for small time period. For others it progresses faster and may lead to a blindness in one or both eyes [1].

Initially there are often no symptoms. With the time, people suffering from AMD experiences a gradual weakening of vision and if not treated leads to complete vision loss. This may gradually turn into a dramatic loss of the central vision. The loss of central vision in AMD can affect simple day to day activities, such as the ability to drive, read, see faces, write, to do daily work such preparing food or fixing and mending things around the house [1]. Other symptoms may include 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, high-cholesterol, fat intake and obesity [3, 2]. 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 yellowish deposits which are made of a fatty protein, lipids, and it is present under the retina [3, 2]. 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 Bruchâs membrane.

Based on size of drusen and choroidal neovascularization(CNV), AMD stages are defined. AMD have three major stages: early, intermediate and late. Late AMD can be of two type dry and wet. Early stage of AMD is asymptomatic and can be diagnosed by size of drusen. The one with medium sized drusen having width of an average human hair indicates the presence of early AMD. Intermediate AMD is also asymptomatic in many cases but in some cases it may cause vision loss. In intermediate stage retinal pigments changes and drusen are bigger in size and more in number. In case of late AMD along with drusen there occurs CNV which damages macula of human eye and leads o complete blindness. 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, CNV occurs i.e abnormal blood vessels grow under the retina. These blood vessels are abnormal and can sometimes leak fluid and blood, which can cause swelling and damage to the macula. The damage can be fast and severe, unlike the more gradual course of dry AMD. It is possible to have both types of late AMD in the same eye [3, 2].

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. It becomes easy to quantify CNV using OCTA images [7].

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 [4, 14]. 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 Asia-Pacific 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 [2]. 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 [13, 12].This helps in guiding decisions for treatment of AMD and evaluating responses on CNV to its therapy [13]. Thus, assessment of OCTA images can help to and proper treatment and cure for this disease. 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 pixels occupied by retinal vessels. It has gained increasing popularity, and represents a promising imaging endpoint for future clinical trials.

2 Literature Review

With increase in age, risk of developing age related diseases which causes 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. Few promising methods for detection and analysis of AMD are given below.

The novel method for detection and segmentation of drusen in colour fundus images was proposed. It combines colour information of the objects with its boundary information for accurate detection and segmentation of drusen. The accuracy of system was 96.62%. However, this method requires higher calculation time.[12]. Supervised learning methods such as neural net- work along with constrained graph search also pro- vided promising result for segmenting retinal layers with CNV in OCT images. The performance of sys- tem was measured in terms of true positive fraction rate, which was $82.12 \pm 11.70\%$. The work further suggested that, by using abnormal segmentation method for only local region can increase accuracy and reduce computational time of the system [15].

With the development in technology, the need of dye based modalities tends to decrease. In OCTA different features such as shape, branching pattern, anastomoses loops, vessel termini and perilesional hypointense halo were used for CNV detection[3]. As technology evolves, OCTA provides exciting results when compared with traditional multimodal imaging techniques for detection of wet AMD. This study shows that, although, fluorescein angiography remains golden standard for determining the presence of fluid, the OCTA may now offer non-invasive monitoring of CNV, thus helping treatment decision during follow-up [13].

Deep learning method such as modified VGG16 neural network with batch normalization is used for screening and assessment of AMD from fundus images. The accuracy of system was 92.5%. They suggested that pre-processing of images can improve accuracy by eliminating lens glare and non-uniform illumination among other noisy data [6].

Deep Convolutional Neural Network and linear Support Vector Machine together form a potential method for AMD detection and classification. The accuracy of this system ranges from 92% to 95%. The work suggested that fine tuning of algorithm and using larger dataset can help in improving accuracy of this method and give more optimized results [9].

Quantitative analysis of OCTA images was done in order to provide better and efficient treatment decision. The accuracy of system was 97.1%.Only four features were extracted and detection was done by random forest classifier [8]. The method for automatic analysis of the choroid in OCT images was proposed. This algorithm analysed the texture of choroid portion below retinal pigment epithelium layer. The result obtained were satisfactory and accuracy of proposed system was 81% [10].

An automated saliency detection model was proposed for CNV area detection for OCTA. Evaluation was performed on scans of 7 participants. The accuracy of system was 83%.The major limitation of the proposed work was that it tends to include less area from CNV due to projection artifacts removal step [11].To overcome this issue novel method based on unsupervised and parallel machine learning technique named density cell like P system with active membrane was introduced. This method improved the accuracy of detection to 87.2% on 22 subjects. However, this method was unable to distinguish noise from vessel information if noise pixel was bright and found in vicinity of vessels [16].

As detection and analysis of AMD remains an open challenge in current world, there is need to develop robust and optimized technique in order to provide effective treatment for such deadly disease.

3 Data Acquisition

Patients with wet AMD were selected at National Institute of Ophthalmology, Pune. OCTA data of patients with CNV were obtained after taking proper consent and permission of the enrolled patients. Topcon's Swept Source (SS) OCT Angio was used to acquire OCTA images of the patients.

It is the only system which combines high quality OCT Angio with Swept Source OCT and is empowered with proprietary image processing algorithm named OCT Angiography Ratio Analysis (OCTARA). This algorithm provides highly sensitive angiographic detections including visualization of vascular structures in deeper , superficial, outer and choroidal layers of an eye. It provides a clear image of microvascular flow network and performs rapid scanning at 100,000 A scans per second. Incorporated with SMARTTrack eye tracking system provided accurate tracking by detecting eye movements and blinks simultaneously. Topcon is integrated with multimodal platform i.e Fluorescein Angiography(FA), Fundus Auto Fluorescein(FAF), OCT and color fundus images all in single device. As OCTA is based on 1050nm light source, it is performed without injecting dye and causing any side effect or discomfort to the patient . OCTA scanning area can be $3mm \times 3mm$, $4.5mm \times 4.5mm$ or $6mm \times 6mm$.

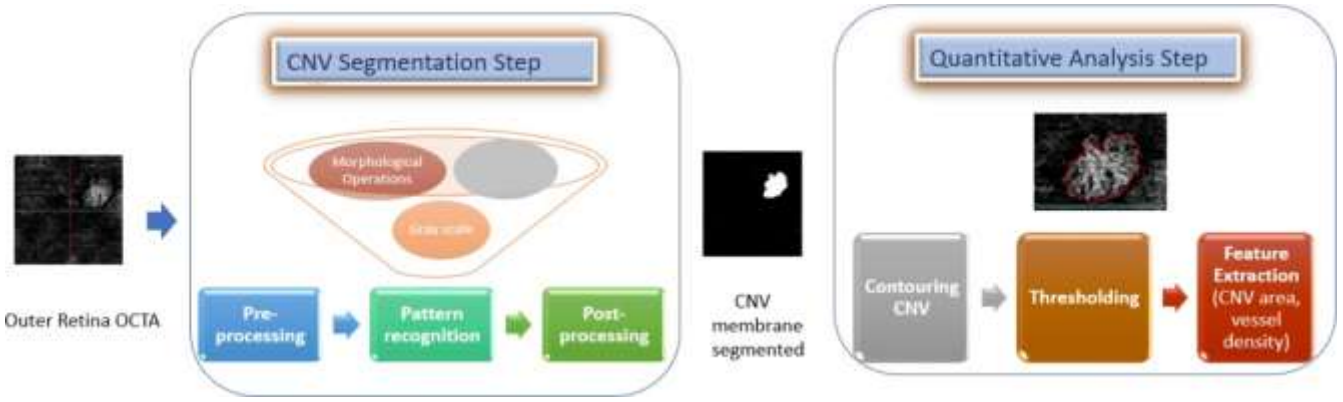

Figure 1: Overview of proposed methodology

Twenty participants with CNV lesion were recruited. Data from 7 participants were excluded due to low image quality (structural OCT signal strength index less than 50), , shadowing, noise due to sever artifacts, not clear visualization, distorted images . Data from 9 other participants were excluded because an experienced grader could not identify the presence of CNV on OCT angiography. Data from the remaining 4 participants were used in this study. Also one image was taken from images in google to check correctness. Images were not specific to eye or scanning area. They were selected irrespective of both parameters. To make algorithm more robust data augmentation techniques were used and total 15 images were used for final analysis.

4 Proposed Methodology

An overview of the proposed and developed algorithm is shown in Fig. 1. Entire process is divided into two main modules or steps. CNV segmentation step and Quantitative analysis steps were developed to obtain CNV area, CNV size and CNV vessel density. This two steps incorporated with different algorithm to finally obtain accurate results. In CNV segmentation step, pre-processing was first performed to reduce projection artifacts and motion artifacts from the outer retina OCTA image. After removal of noise, the CNV region was more clear and distinct. After that CNV pattern recognition was carried out using binarization techniques and connected component labelling algorithm. Finally, post-processing operations were applied to generate the CNV lesion mask. In quantitative analysis step, the contoured CNV region obtained is binarized using Otsu and finally features like CNV area, CNV vessel density, CNV size were extracted. The following sections will describe the process of CNV segmentation and quantification in detail. The algorithm was software written in python 3 and python IDLE IDE was used for implementation.

This step provides perfectly segment out CNV lesion from input OCTA image provided. The entire procedure is depicted in Fig.1. As OCTA consist of different layers, namely, outer, deeper, superficial and choriocapillaris, proposed approach take outer and superficial region into consideration. As CNV lesion can be seen in outer retina it is selected as input to our algorithm.

4.1 Preprocessing

Imaging, projection and motion artifacts are usually generated in OCTA imaging which can cause inaccurate results , segmentation error and limits the functionality of OCTA, thus provide inappropriate diagnosis results. They are developed during acquisition of OCTA , eye motions, intrinsic characteristics of eye or display. It is important to remove these artifacts before segmenting CNV lesions. In previous work [15], outer retina image was subtracted from filtered inner retina image. It was observed that some portion of CNV get eliminated in this process and filtering is again a time consuming operation. In this algorithm, outer retina (O) was subtracted from superficial image (S) as CNV region does not appear in superficial OCTA image and this is done without filtering which save time and gives clear and distinct CNV region as output. Outer and superficial image were resized to 350×350 and converted to grey scale before subtracting them. Along with CNV lesion there was some small noisy pixels areas in subtracted image.

O’ (350*350) = O(350*350) â S(350*350) (1)

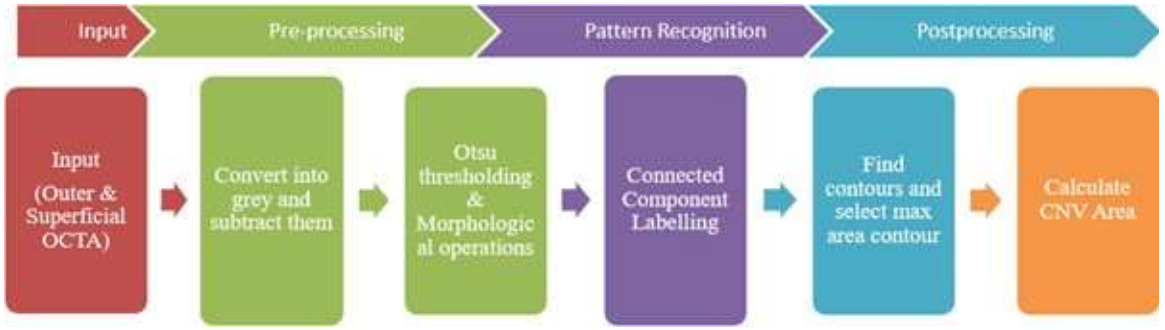

Figure 2: CNV Segmentation Step

where, O' (350,350) is clear outer retina OCTA image.

4.2 Pattern Recognition

As images were subtracted some part of CNV was missed out. To regain that portion clear outer retina image was further binarized using Otsu method as it perform automatic image thresholding. It gives optimized threshold value that divides pixels into two classes, background and foreground respectively. The advantage of using Otsu was there was no need to provide threshold as it is adaptive thresholding technique. The threshold was determined itself by algorithm by minimizing inter- class variation or maximizing intra-class variance. The threshold T corresponds to 't' value of Max $\sigma_b^2(t)$.

$$\sigma_b^2(t) = \omega_0(t)\omega_1(t)[\mu_0(t) - (\mu)(t)]^2$$

where,

μ - class means and weights are the probabilities of the two classes separated by a threshold 't'. This are computed from 'L' bins of histogram. given as below.

$$\omega_0(t) = \sum_{i=0}^{t-1} p(i)$$

$$\omega_1(t) = \sum_{i=t}^{L-1} p(i)$$

$$\mu_0(t) = \frac{\sum_{i=0}^{t-1} ip(i)}{\omega_0(t)}$$

$$\mu_1(t) = \frac{\sum_{i=t}^{L-1} ip(i)}{\omega_1(t)}$$

On applying Otsu thresholding binarized image was obtain and in order to regain small portion of CNV which was missed out during subtraction morphological dilation was performed which expands the shapes and area of an image by adding pixels to the boundaries of objects. CNV lesion area was accurately segmented but applying morphological operations added some noise and to make lesion more distinct, connected component labelling was further carried out which resulted in removal of additional noise added to image during morphological dilation step. This algorithm is generally used after a segmentation algorithm to count the number of regions segmented and detect connected regions in image by labelling each pixels in the image based on pixel connectivity. This algorithm uses 4 pixel connectivity i.e pixel have 4-neighbours. The recursive connected component labelling was applied to label the pixels and find out connected region. For pixel p[i][j] the 4-neighbourhood pixels are p[i][j-1], p[i][j+1],p[i-1][j] and p[i+1][j].

4.3 Postprocessing

As this algorithm labels out all white pixel region the biggest region among all the region is selected and contoured. This region is nothing but CNV lesion area which is then represented by creating new all zero pixel image and contoured region is pasted on this newly formed image. Hence on this way we obtain CNV membrane mask.

CNV area was equivalent to the number of white pixels in postprocessed image.

4.4 Pseudocode

Label (i,j):

1. Store (i,j);
2. If P[i][j-1] is 1 and unlabelled, Label (i,j-1);
3. If P[i][j+1] is 1 and unlabelled, Label (i,j+1);
4. If P[i-1][j-1] is 1 and unlabelled, Label (i-1,j);
5. If P[i+1][j-1] is 1 and unlabelled, Label (i+1,j);

Figure 3: Quantitative analysis step

4.4.1 Steps

- Scan the image left to right and top to bottom and find an unlabelled unity valued pixel i.e white pixel and assign new label L to the pixel.
- Recursively assign a label L to all its unity valued neighbourhood pixels.
- Stop when all unity value pixels are labelled.
- Go to step 1.

$$CNV area(mm^2) = CNV area(pixel) * (\frac{3mm}{350})^2 \quad (1)$$

$$CNV\ area(pixel) = Max\{n(r_1),\ n(r_2),\ n(r_3),\ ..,\ n(r_n)\} \quad (2)$$

where, are the white pixel regions obtained using component labelling algorithm and n(r) â total number of pixel in region r.

4.5 Quantitative Analysis Step

Quantitative analysis is done by finding vessel density of CNV region. The output of CNV segmentation is used as input to this step. In this step contoured image is binarized as shown in Fig. 3 and vessel density of CNV is calculated as percentage of vessel occupied by the CNV lesion.

On consulting health professionals and on showing results of various thresholding techniques like global ,local, adaptive it was found that Otsu give better results and hence was selected and applied to the contoured region in outer retina. This resulted in image with segmented blood vessel.

$$CNV vesseldensity(\%) = \frac{Vesselarea(pixel)}{CNV area(pixel)} * 100 \quad (3)$$

$$Vesselarea(pixel) = \sum_{i=0}^{w} B(m, n) \quad (4)$$

where,B(m, n) is binary image obtained after applying Otsu and w is number of white pixels in B(m, n).In this way algorithm gives out two important measures as an output which helps doctor to analyze patients and guide them in giving proper treatment.

5 Results and Discussions

The outer retinal angiogram of a patient with wet AMD having CNV lesion was used as an example to show the workflow of our proposed algorithm. Figure 5 shows the results obtained by proposed algorithm step by step. Fig.4(A) is original outer retinal angiogram of participants with CNV and artifacts. Superficial retinal region image is shown in Fig. 4(B) was used to remove the bigger vessels projections and some artifacts from the outer retina. The result shown in Fig. 4(C) is clear CNV image which still has some projections of small vessels and some of the CNV region is eliminated. Fig. 4(D) represent the binarized image obtained after applying Otsu thresholding on Fig. 4(C). As some part of CNV was eliminated in subtraction step it is regained back by performing morphological dilation of binarized image in Fig. 4(D). The resultant image after applying morphological operation can be seen in Fig.4(E). Along with CNV noise is also inculcated in image which is further removed by applying connected component labelling algorithm whose result is shown in Fig.4(F). Three different regions are obtained after from which

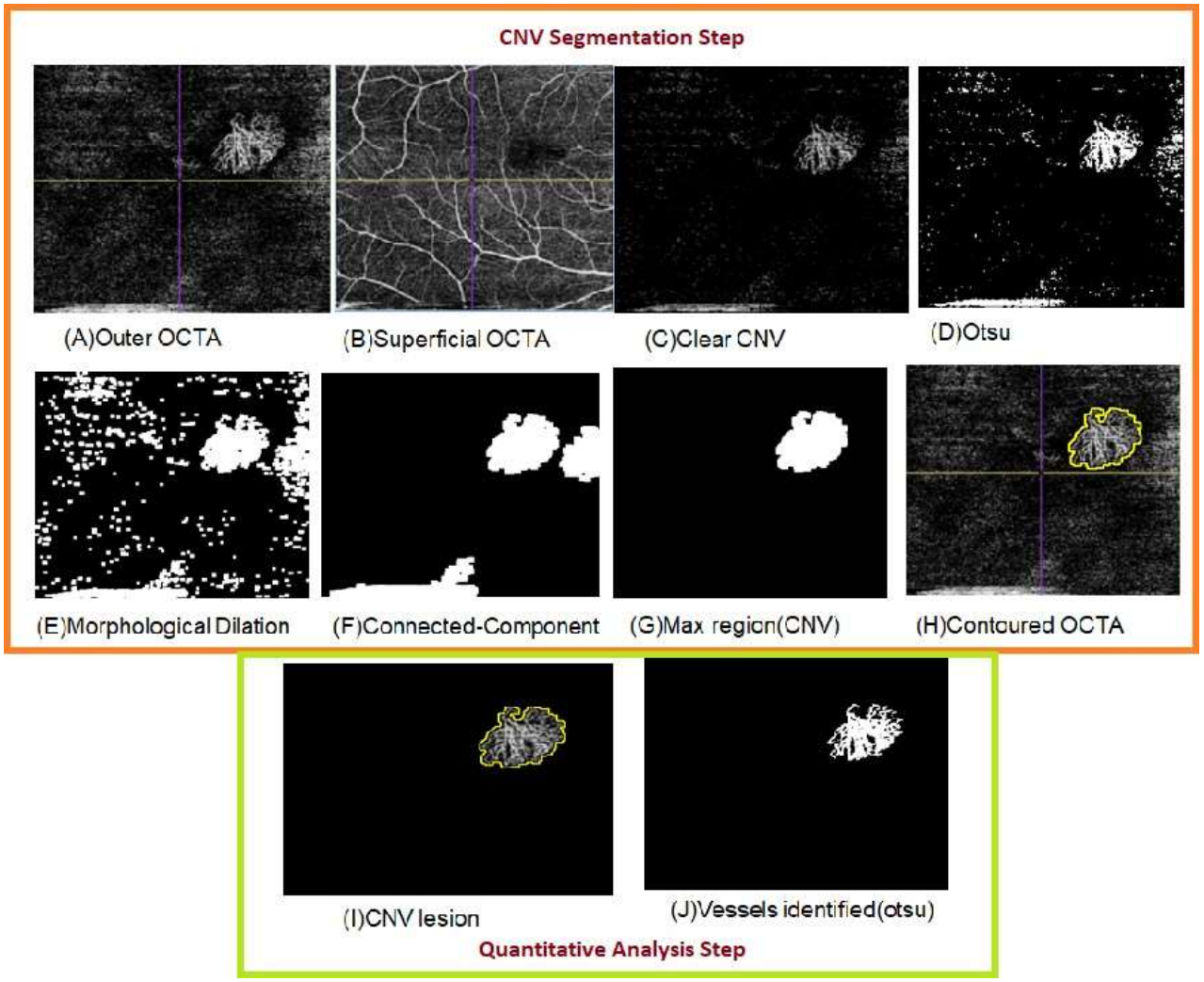

Figure 4: Workflow of proposed algorithm

maximum area region is selected as shown in Fig.4(G) which is nothing but final CNV membrane mask. This entire process is part of CNV segmentation step where CNV region is segmented out and contoured is drawn on outer OCTA image. Quantitative analysis is done on this CNV contoured region where complete black pixel image of same dimension as outer is constructed and CNV region is copied on it from contoured image as shown in Fig. 4(I). On applying Otsu finally vessels in CNV region are segmented and shown in Fig. 4(J). In this way given proposed methodology works by anticipating this two main steps. It provide CNV lesion area and CNV vessel density as an output.

The results obtained using proposed algorithms were very closely matched with the that of manual delineation by experts. More than 95% similarity was present between ground truth and segmented region. The CNV area was measured in square millimetre and CNV vessel density was given in percentage. Fig.6 shows the result of our proposed algorithm on three different participants. First column represents the input outer OCTA image of three participants. Second column represents CNV area segmented by proposed methodology and area is shown in upper left corner of image. Third column indicates the contour of CNV drawn on outer OCTA and it can be easily verified that obtained segmented region match exactly with the actual CNV region. The last column shows the segmented vessel in CNV region and vessel density is given at upper left corner in terms of percentage.The time required to process new image is less than 2 seconds. Hence, this make proposed algorithm more efficient.

Figure 5: AMD quantification App

Performance of the system was evaluated against previously developed algorithm and against manual delineation performed by health professionals.The comparison of proposed methodology with previous approach is shown in Table 1. Results obtained from proposed systems were compared with the manual results by computing the jaccard similarity metric, accuracy, False Negative Rate (FNR) and False Positive Rate (FPR), sensitivity/recall, specificity, precision and F1 score. All this results are shown in Table 2.

Hence proposed algorithm works well and gives more accurate results.Jaccard similarity metric J(S,M)between segmented image S(i,j) and manual segmented image M(i,j) is given by which is defined as,

$$J(S,M) = (|S \cap M|)/(|S \cup M|) \quad (5)$$

$$FalseNegativeRate = \frac{FN}{(TP + FN)} \quad (6)$$

$$FalsePositiveRate = \frac{FP}{(TN + FP)} \quad (7)$$

$$Accuracy = \frac{(TP + TN)}{(TP + TN + FP + FN)} \quad (8)$$

$$Specificity = \frac{TN}{(TN + FP)} \quad (9)$$

$$Sensitivity = \frac{TP}{(TP + FN)} \quad (10)$$

$$Precision = \frac{TP}{(TP + FP)} \quad (11)$$

$$F1Score = 2 * \frac{Precision * Recall}{Precision + Recall} \quad (12)$$

An application was developed using python library tkinter which helped doctor to operate and get adjusted with proposed methodology more easily and sophisticatedly. Fig.5 represents the graphical user interface for this application. Different buttons are provided where user can browse outer and superficial OCTA image and perform AMD quantification. Once it is done message box appeared and confirm that the process is completed. After this CNV area and vessel density can be visualized using two distinct button from and application.

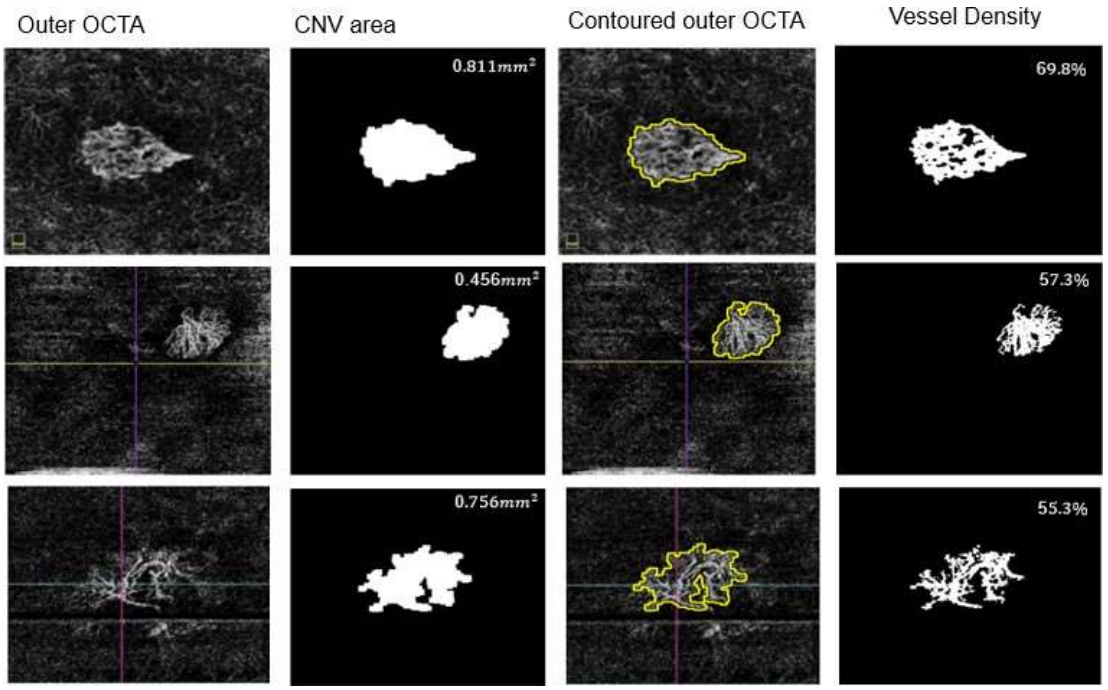

Figure 6: Results of the participants - CNV area and CNV vessel density

Table 1: Mean and standard deviation of the Jaccard coefficient and error rates on 15 cases

Metrics	Jaccard Score	FPR	FNR
Saliency [9]	0.834 ± 0.125	0.043 ± 0.046	0.134 ± 0.109
Dec P system [10]	0.872 ± 0.053	0.024 ± 0.029	0.069 ± 0.054
Proposed Approach	0.937 ± 0.023	0.182 ± 0.26	0.002 ± 0.003

Table 2: Comparative results of proposed and state of art methods.

Metrics	Values
Jaccard Score	0.9379 ± 0.023
FNR	0.0026 ± 0.003
FPR	0.182 ± 0.26
Accuracy	0.989 ± 0.004
Specificity	0.9066 ± 0.047
Sensitivity	0.99 ± 0.003
Precision	0.99 ± 0.004
F1 Score	0.99 ± 0.002

6 Conclusions

Age-related macular degeneration is a retinal complication, causing abnormalities in the retina. It is a leading cause of visual deficiency and irreversible blindness in the developed world. It is important to tackle this disease with proper detection and analysis techniques in order to find the proper treatment or cure for the same.

Proposed methodology provides the development of a desktop application as a part of an fully automated CAD system for wet AMD detection and quantification using OCTA images. Entire process is divided into two different modules and time required to process images is very less. First is CNV segmentation step in which combination of pre-processing techniques, binarization techniques are used to provide CNV area. Second one is CNV quantification step which uses output of previous step and proceed with CNV lesion to further segment vessels and provide vessel density in percentage. Most interesting part of this system is entire process takes less than 2 seconds and this make it more efficient. The proposed pipeline can be used by any system and is completely offline. The desktop application can contribute to the medical practitioners in decision making and also in quantification of wet AMD thus helping the patient in avoiding an irreversible vision loss that would have caused to their eyesight.

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