VŠB– Technical University of Ostrava
Faculty of Electrical Engineering and Computer Science
Department of Cybernetics and Biomedical Engineering

Software application for archiving and analysis of retinal records
Softwarová aplikace pro archivaci a analýzu retinálních záznamů

2020 **Mathumitha Thirunavukkarasu**

VŠB - Technical University of Ostrava
Faculty of Electrical Engineering and Computer Science
Department of Cybernetics and Biomedical Engineering

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Student: **Mathumitha Thirunavukkarasu**

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1. Study of literature dealing with the retinal imaging methods.
2. Technical specification, principle and analysis of digital imaging system RetCam 3 for diagnostic of the retinal diseases.
3. Theoretical proposal of SW application for archiving of the retinal records from the RetCam 3.
4. Proposal and realization of a database containing the retinal records, associated clinical parameters and technical aspects of the retinal records from the RetCam 3.
5. Design and realization of the SW application for visualization and editing of the retinal records from the RetCam 3.
6. Proposal and realization of advanced searching and sorting functions of the retinal images in the proposed SW application, including the statistical analysis of individual clinical parameters and technical aspects of the retinal records.
7. SW testing in the clinical practice.

References:

[1] DATE, C. J. *An introduction to database systems.* 8th ed. Boston: Pearson/Addison Wesley, 2004. ISBN 0-321-19784-4.
[2] GARCIA-MOLINA, Hector, Jeffrey D ULLMAN a Jennifer WIDOM. *Database systems: the complete book.* 2nd ed. Upper Saddle River, N.J.: Pearson Prentice Hall, c2009. ISBN 978-0-13-187325-4.
[3] RYAN, Stephen, et al. *Retina.* 5th ed. London: Saunders/Elsevier, 2013. eISBN 978-1455737802.

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Supervisor: **Ing. Jan Kubíček, Ph.D.**

Consultant: Ing. David Oczka

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doc. Ing. Jiří Koziorek, Ph.D.
Head of Department

prof. Ing. Pavel Brandštetter, CSc.
Dean

Declaration

I declare that this thesis was written by myself. I have listed all the sources and publications from which I drew.

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I hereby agree to the publishing of the master's thesis as per s. 26, ss. 9 of the Study and Examination Regulations for Master's Degree Programmes at VŠB-Technical University of Ostrava.

Ostrava, April 21, 2020

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Abstrakt

Existuje několik diagnostických medicínských zařízení s cílem diagnostiky patologií očního systému jako je systém Retcam, který představuje plně integrovaný širokoúhlý zobrazovací systém pro klinické využití. Tento systém poskytuje oftalmologické vizualizace a fotografickou dokumentaci retinálních obrazů. V rámci oftalmologického vyšetření je produkováno větší množství obrazových záznamů, proto je potřeba řešit databázové systémy, kde tyto záznamy budou ukládány a archivovány. Pro tento účel je v rámci této diplomové práce navržena softwarová web aplikace pro archivaci a analýzu retinálních záznamů, která je propojena s retinální databází pro ukládání, správu retinálních obrazů. Je využíváno SQLite pro tvorbu databáze. Retinální obrazy jsou ukládány v rámci sytému, nebo centralizované sítě přístupového sdílení. Retinální obrazy jsou ukládány ve složkách, které definuje aplikace. Pacientské formuláře jsou vytvářeny s využitím nástroje symfony php.

Klíčová slova: retinální obrazy, obrazová analýza, Retcam, načítání obrazu, pacientská databáze, webová aplikace.

Abstract

There are several diagnostic medical devices for the diagnosis of eye pathologies. therein Retcam may be a fully integrated wide field digital imaging system for the hospital and clinic. This provides ophthalmic visualization and photo documentation of retinal images. For every examination number of patients are high and therefore the images taken during the examination are more. In order to manage this, I proposed to develop a software application for archiving and analysis of retinal records. This web application connected to database to save and retrieve patient records and retinal records for further analysis of pathology conditions of eye are created in order to support the proposal. I'm using SQLite for database it's linked with server where the applicant details are received from the patient Form. Retinal images are saved within the system or Centralized Network Access Storage. And therefore, the path of the image is stored in database for easy retrieving. Retinal images from the retcam are stored in folder created by application. Patient form created using symfony php.

Keywords: Retinal images, Image analysis, Retcam, Image retrieving, Patient Database, Web application.

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LIST OF ABBREVIATIONS

AMD	Age-related Macular Degeneration
BRVO	Branch Retinal Vein Occlusion
CCD	Charge Coupled Device
CD	Compact Disk
CLAHE	Contrast Limited Adaptive Histogram Equalization
CMOS-APS	Complementary Metal Oxide Semiconductor Active Pixel Sensor
CPU	Central Processing Unit
CRVO	Central Retinal Vein Occlusion
cSLO	confocal Laser Scanning Ophthalmoscopy
CSS	Cascading Style Sheet
CT	Computer Tomography
DB	Database
DBMS	Database Management System
DCL	Data Control Language
DDL	Data Definition Language
DICOM	Digital Image and Communication in Medicine
DML	Data Manipulation Language
DOB	Date of Birth
DR	Diabetic Retinopathy
FA	Fluorescein Angiography
FAF	Fundus Auto Fluorescence
FCM	Fuzzy Clustering Means
HDD	Hard Disk Drive
HTML	HyperText Mark-up Language
ICG	Indo-Cyanine Green
ID	Identification
IMG	Image
KNN	K-Nearest Neighbours Algorithm
LAN	Local Area Network
MRI	Magnetic Resonance Imaging
OCT	Optical Coherence Tomography
OD	Oculus Dexter (Right eye)
OS	Oculus Sinester (Left eye)
PDF	Portable Document Format
PHP	HyperText Pre-processor
PR	Photo Receptors
RAM	Random Access Memory
RDBMS	Relational Database Management System
RNFL	Retinal Nerve Fibre Layer
ROP	Retinopathy of Prematurity
RPE	Retinal Pigment Epithelium
SIFT	Scale-Invariant Feature Transform
SQL	Structure Query Language
SURF	Speeded Up Robust Features
WEF	Wavelet Energy Features

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1. INTRODUCTION

Vision is one of the most significant human senses, enabling us to comprehend nature around us. The eye, this incredibly complex structure, is continually taking in the light reflected from objects close to us. The light goes through the eyeball combining to a point where a group of cells at the rear of the eye convert the light vitality into electric impulses which are then transmitted to the brain. Every single one of the eye structures contributes in a manner to the general visual process. Retina, layer of sensory tissue that covers within the back 66% of the eyeball, in which incitement by light happens, starting the sensation of vision. The retina is really an augmentation of the cerebrum, shaped embryonically from neural tissue and associated with the mind appropriate by the optic nerve.

Like any other organ of the human body, eyes are susceptible to pathologies as well. Many eye diseases have no early symptoms and no change in vision may be detected until the disease stage worsens. Although eye disorders may appear at any age, most of them are more common among adults and especially among elder people.

The optical properties of the eye that permit image formation for direct examination of the retina. Retinal imaging takes a computerized picture of the rear view of human eye. It shows the retina where light and images hit, the optic disk a spot on the retina that holds the optic nerve, which sends information to the brain, and blood vessels. For imaging retina there are more medical imaging techniques. For diagnostic and treating retinal diseases imaging and processing of retinal image is required.

The present imaging technology in medical industry can reveal all the layers of the retina. Several optical coherence tomography (OCT) devices include colour fundus photography capability. And there's a medical device that takes pictures and lasers the eye. Using imaging devices clinical physician can easily have wide view of causes of blindness, age-related macular degeneration, diabetic retinopathy, and glaucoma, etc with the help of retinal imaging and image analysis methods and their clinical implications. Retinal images have become so valuable that people with retinal disease can expect to have at least one, and sometimes several, types of images taken on each visit to the ophthalmologist.

For this purpose, a software application that runs on a remote server was developed to store retinal records. mostly, Web browsers are utilized to get to Web applications, over a network, i.e., the Internet. Some web applications are used in intranets, in hospitals. I proposed to develop an intranet web application for specific hospital purpose for an ophthalmology department. Symfony is a PHP web application framework and a set of reusable PHP components/libraries used this to develop retinal image web application. Doctrine to connect the web application to multiple table SQLite database to archive and retrieve functions of retinal records.

To develop the software application for archiving and analysis of retinal images. For this process first, I am developing the database with multiple tables for easy retrieving of retinal image for pathologies monitoring by comparing retinal images of the same patient and image captured at different times. Pre-processing of retinal image are four different types of features were considered. Fractal dimension and wavelet energy features (WEF), both used in biometric identification procedures using retinal images, and SIFT and SURF image features. These structures which made the search procedure a lot faster. This enables the clustering of images accordingly to their similarity, which facilitates the selection of the subset of images most similar to the one being queried. I am using SQLite for database

it is linked with server where the applicant details are received from the patient Form which is developed using PHP coding and jQuery.

Retinal images are saved in the system or Centralized Network Access Storage. and the path of the image is given to the database for easy retrieving. Retinal images from the retcam are stored. This software application is created to save, retrieve, edit, update, delete, export, statistical analysis of retinal images of patients. Detailed information about the software application are explained below chapters and discuss about the practical result of the software application.

As I discussed above study of literature dealing with the retinal imaging methods and technical specification, principle and analysis of digital imaging system RetCam 3 for diagnostic of the retinal diseases are described on the upcoming chapters.

Theoretical proposal of Software application for archiving of the retinal records from the RetCam 3. Information about the proposal and realization of a database containing the retinal records, associated clinical parameters and technical aspects of the retinal records from the RetCam 3 are elaborately described.

Design and realization of the software application for visualization and editing of the retinal records from the RetCam 3. Results of proposed and realization of advanced searching and sorting functions of the retinal images, including the statistical analysis of individual clinical parameters and technical aspects of the retinal records are explained.

Web application is designed for maintenance of retinal records. As the retinal records are plenty, this web application helps to overcome the time lagging in retrieving the retinal records. It will fetch the relevant record and avoids the irrelevant fetching of retinal records.

Finally, the testing retinal records with ROP and other data from the patient information are utilized in the clinical practice. Practical results of software application with all user-definable functions explained.

2. RETINAL ANATOMY

2.1. Eye Anatomy

Vision is one of the most important human senses, enabling us to understand the environment around us. The eye, this amazingly complex structure, is constantly taking in the light reflected from objects near us. The light passes through the eyeball converging to a point where a set of cells at the back of the eye convert the light energy into electric impulses which are then transmitted to the brain. Each one of the eye structures contributes in a way to the overall visual process. [6]

The eye may be considered as a slightly asymmetrical sphere with an approximate sagittal diameter of 25mm and a transverse diameter of 24 mm. In a cross-sectional view of the eye three different layers would be visible. Figure 1 and 2 illustrate the arrangement of each layer and structure in the eye anatomy.

The external layer is formed by the sclera and the cornea, both making up the supportive structure of the eye. Both cornea and sclera have essentially the same chemical composition, although the cornea is transparent while the sclera appears opaque or translucent. This difference is explained by the fibrils arrangement since the chemical composition is identical. The cornea is the clear part of the eye's protective covering and its main function is to focus the light for photoreception while the sclera mainly protects the eyeball. The sclera is a tough white outer coating of fibrous tissue which covers the eyeball and the muscles that move the eye are attached to it.

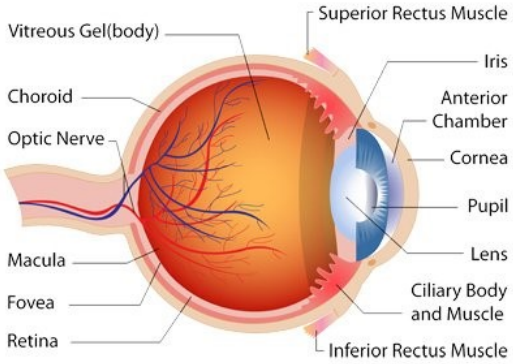


Figure 1: Anatomy of Eye [7]

The middle layer, also called uvea, contains the main blood supply of the eye and it is constituted by the choroid, the ciliary body and the iris. The outer layer of the uvea is the choroid. It is essentially a layer of blood vessels between the sclera and the retina that nourish the back of the eye. It is connected to the ciliary body in the front of the eye and to the optic nerve at the back of the eye. The ciliary body is a muscular forward continuation of the choroid which main function is the change of the lens shape when the eye is focusing on something. Lens is the structure responsible to focus light rays onto the retina. It is composed of flexible tissue which enables the change in shape of this structure. The lens become more rounded to focus on near objects and more elongated to focus on far objects. The iris is the coloured part of the eye which regulates the amount of light entering through the eye by closing when there is bright light and opening when there is low light. The darker centre in the middle of the iris is called pupil and is through it that light rays are transmitted. The iris controls the pupil size.

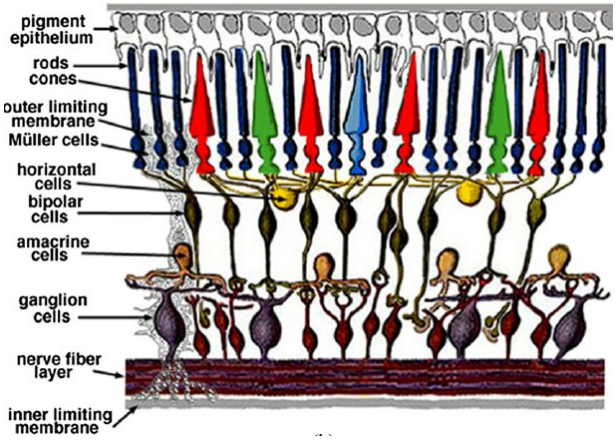


Figure 2: Representation of layers of human eye. [7]

2.2. Analysis of Retinal Images

A brief introduction to the anatomy of the eye is provided and the most common eye pathologies relevant to this work as well as their characteristic lesions are presented. From the retinal images This information is important to understand and evaluate the proposed method.

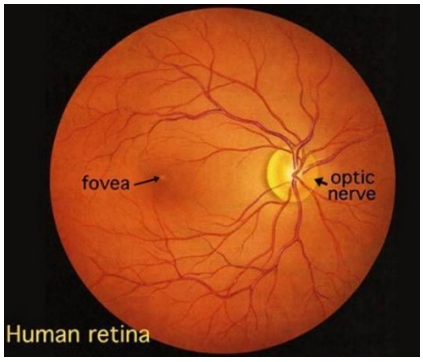


Figure 3: Retinal image of human eye. [3]

The retina is a light-responsive layer at the rear of the eye that covers over 65 percent of its inner surface. Photosensitive cells called rods and cones in the retina convert occurrence light vitality into signals that are conveyed to the cerebrum by the optic nerve. In the retina is a slight dimple called the fovea or fovea centralis. It is the focal point of the eye's pointed vision and the area of most colour recognition [3].

A slight layer (about 0.5 to 0.1mm thick) of light receptor cells covers the internal surface of the choroid. The focused beam of light is absorbed via electrochemical reaction in this pinkish multilayered structure. The human eye contains two sorts of photoreceptor cells; rods and cones. Approximately 125 million of them are associate unevenly over the retina. The group of rods(each about 0.002 mm in distance across) structures an exceedingly responsive detector, acting in light unreasonably diminish for the cones to react to. It is unable to distinguish colour, and the images it relays are not well defined [7].

Conversely, the outfit of 6 or 7 million cones (each about 0.006 mm in distance across) can be envisioned as a different, however covering, low-speed colour film. It acts in intense light, giving point by point shaded perspectives, however is genuinely inconsiderate at low light levels [32].

The rods and cones have become visible to be pointed away from the light source they notice. The light strikes the responsive pigment layer at the rear of the eye and moves the data to the close by

rods and cones. The rods and cones assimilate the dispersed light from the close by pigment layer, which makes vision more clear and keeps the responsive detectors in a progressively secured area. The rods and cones are likewise held nearer to their metabolic vitality supply. From the rods and cones, the impulse go through horizontal cells, bipolar cells, amacrine cells and retinal ganglion cells on their way to the retinal throughway prompting the optic nerve.

The optic nerve is the bundle of nerve fibers with conveys the electrical impulse from the retina to the cerebrum for computing. The purpose of divergence of that optic nerve through the retina doesn't have any rods or cones, and in this way creates a "vulnerable side".

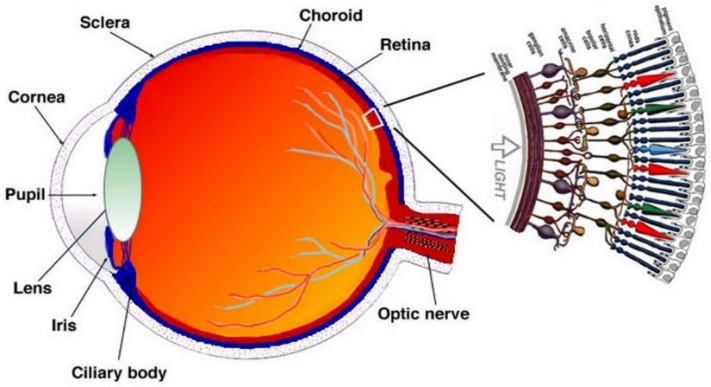


Figure 4: Schematic enlargement of retina [7]

In the retina, five types of neuron, photoreceptors, bipolar cells, retinal ganglion cells, horizontal cells and amacrine cells are wired together to form one of nature's most complex circuit boards. When light hits the retina, it stimulates photoreceptors, creating an electrical signal that is conveyed through other neurons of the retina to the optic nerve, and then on to the brain.

Photoreceptors:

There are two main types of light-sensitive cell in the eye: rods and cones. Rods enable vision in poor light, whereas cones are responsible for colour vision. Photoreceptors convert light into electrical signals that travel through other retinal neurons to reach the optic nerve.

Bipolar cell:

Responsible for transmitting signals from photoreceptors to a retinal ganglion cell.

Retinal ganglion cell:

Relays signals from bipolar and amacrine cells to the brain through long projections called axons that form the optic nerve.

Horizontal cell:

Regulates the signal that emerges from several rods and cones.

Amacrine cell:

Reaches across several bipolar cells to regulate signals directed at retinal ganglion cells. So far, around 30 subtypes have been identified.

Retinal pigment epithelium (RPE):

A layer of epithelial cells that lies beneath the photoreceptors. It forms a barrier to blood vessels in the choroid and mops up harmful substances that are shed by photoreceptors in response to light [8].

3. RETINAL DISEASES

3.1. Eye Pathology

Like any other organ of the human body, eyes are susceptible to pathologies as well. Many eye diseases have no early symptoms and no change in vision may be detected until the disease stage worsens. Although eye disorders may appear at any age, most of them are more common among adults and especially among elder people. [7]

Characteristic lesions of Diabetic Retinopathy (DR), Age-related Macular Degeneration (AMD), Retinopathy of Prematurity (ROP), Retinoblastoma and Retinal Haemorrhages were found in the dataset of retinal images used in this work. Therefore, a detailed description of these pathologies is presented below.

3.1.1. Diabetic Retinopathy

Diabetes is characterized by high blood glucose levels due to the fact that the body cannot properly use it. The reason is that the pancreas does not produce enough insulin (or that which is produced is not performing its function) which is responsible to help glucose, the main body fuel, enter the body's cells. Diabetic Retinopathy (DR) is one among the common complications of Diabetes. It is characterized by the damage of the cells at the back of the eye, i.e. at the retina, due to the high blood glucose levels.[28]

If someone have diabetes, the tiny blood vessels (capillaries) in the back of your eye can deteriorate and leak fluid into and under the retina. This causes the retina to swell, which may blur or distort human eye vision. Or it may develop new, abnormal capillaries that break and bleed. This also worsens human vision.

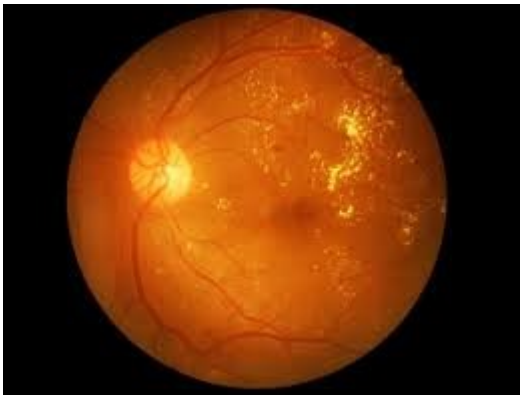


Figure 5: Retinal image of Diabetic Retinopathy [28]

The retina is responsible for the conversion of photonic energy into electrical impulses which are then transmitted to the brain through the optic nerve. To properly function, the retina needs a constant supply of blood which is provided by blood vessels. A continuous high blood glucose level causes obstruction or leakage of the blood vessels, affecting the retina functions. In some people abnormal new blood vessels may grow on the retina surface. DR can cause vision loss when it progresses to an advanced stage.

This eye disorder has four stages:

Mild Nonproliferative Retinopathy:

It is the earliest stage of the disease and it is characterized by the occurrence of microaneurysms. Microaneurysms are small areas of blood protruding from a vessel which may open and leak blood into the retinal tissue. This results in the appearing of retinal haemorrhages, edemas and exudates. In Figure

3 haemorrhages are visible as reddish spots in the retina. Macular edema is the swelling or thickening of the part of the retina responsible for the central vision and appear in the retinal image as darker areas. Exudates are lipid residues of blood vessel leakage and appear as rounded yellow areas in the retinal image.

Moderate Nonproliferative Retinopathy:

Moderate Nonproliferative Retinopathy is characterized by the blockage of blood vessels that nourish the retina.

Severe Nonproliferative Retinopathy:

As the disease progresses many more blood vessels are obstructed depriving areas of the retina with blood supply. Those deprived areas transmit signals to the body to stimulate the growth of new blood vessels for the retina nourishment.

Proliferative Retinopathy:

This is the most advanced stage of DR and is characterized by the growth of several new blood vessels which are abnormal and fragile. In case they suffer leakage, it can result in severe vision loss or even blindness.[9]

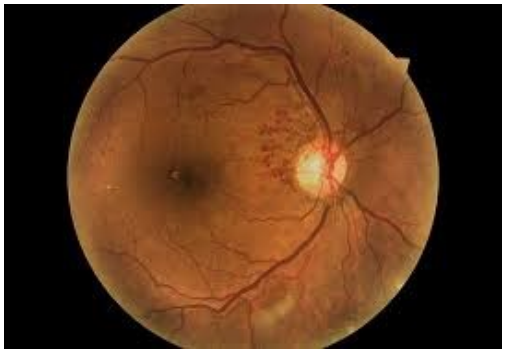


Figure 6: Retinal image of proliferative retinopathy [9]

Symptoms of an advanced stage of DR include shapes floating in the vision field, blurred vision, reduced night vision and sudden blindness. The difference between normal vision and that of a person with advanced DR is illustrated in Figure 7.

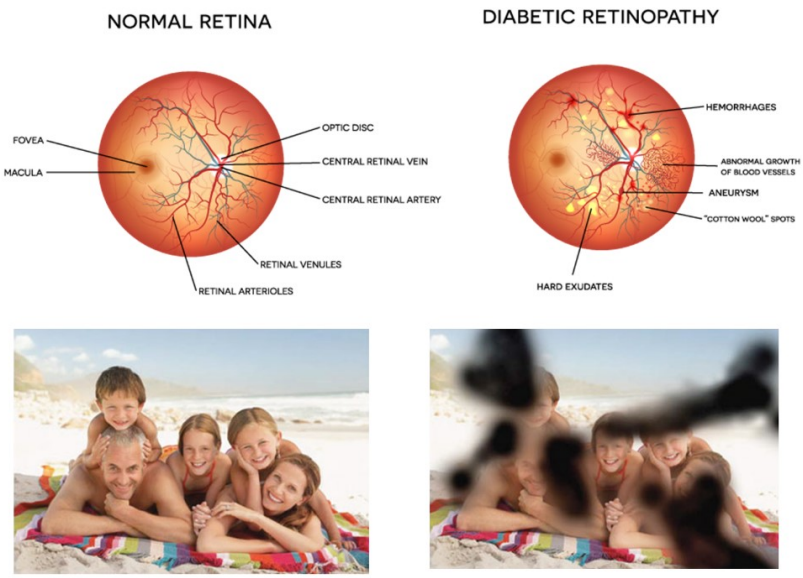


Figure 7: Person with normal Retina and by a person with Diabetic Retinopathy [28]

3.1.2 Age-related Macular Degeneration:

Age-related Macular Degeneration (AMD) is the leading eye pathology causing blindness in the elderly. AMD essentially affects the retina area at the back of the eye called macula which is the centre of vision. Although an exact cause for AMD is not known some factors may increase the chance of this disease development such as age, gender (more women suffer from AMD), genes, smoking, sunlight and diet.[2]

The macula is a retina area that contains specialized photoreceptor cells designed cone cells. Cone cells allow colour recognition and detail vision. When a person develops AMD, these cells become damaged and do not properly perform their functions.

There are two forms of AMD, dry and wet AMD, and both can progress to advanced stages and cause severe vision loss.

Dry AMD:

This form of AMD does not have many symptoms in the early stages. However, as the disease progresses the person may suffer from blurred vision and see objects brighter than they actually are. Usually people with dry AMD experience difficulty in face recognition and need more light to perform some tasks such as reading.

The most common early sign of dry AMD are drusens. Drusens are small yellow and white deposits in the retina made up of lipids and proteins. These substances are wasted products of photoreceptors cells which were not correctly disposed. Drusens form on the retina, beneath the macula, causing it to deteriorate over time. Figure 8 illustrates a retinal image affected with these lesions.

Dry AMD has three development stages. At an early stage there are no specific symptoms and only small or medium-sized drusens are formed. At an intermediate stage one or more larger drusens appear. At this stage some people see a blurred spot in the centre of their vision and often need more light to perform some ordinary tasks. At an advanced dry AMD stages, a breakdown of the light sensitivity cells that support tissue in the macula occurs. This causes a blurred spot in the centre of the vision which tends to get bigger and darker over time**.**

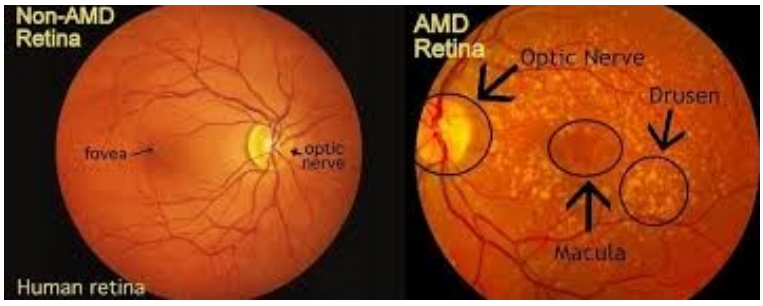


Figure 8: Retinal image of AMD with presence of drusens [2]

Wet AMD:

The dry form of AMD can suddenly turn into the wet form which is what happens with 10% of all people suffering from AMD. This form of AMD is characterized by the growth of new blood vessels under the macula. The new blood vessels can be fragile and easily leak blood and fluids causing the macula swelling and damage. Beginning stages of wet AMD straight lines may appear wavy.

Figure 9: Person with normal vision and by a person with AMD [2]

3.1.3. Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a possibly blinding eye dysfunction that essentially affects new-born babies weighing about 1250 grams or less, that are born before 31 weeks of gestation that is a full-term pregnancy has a gestation of 38–42 weeks. The smaller a baby is during childbirth, the more likely that child is to develop ROP. This disorder, which usually creates in both eyes is one among the most common causes of visual loss in adolescence and can lead to lifelong vision impairment and blindness [7].

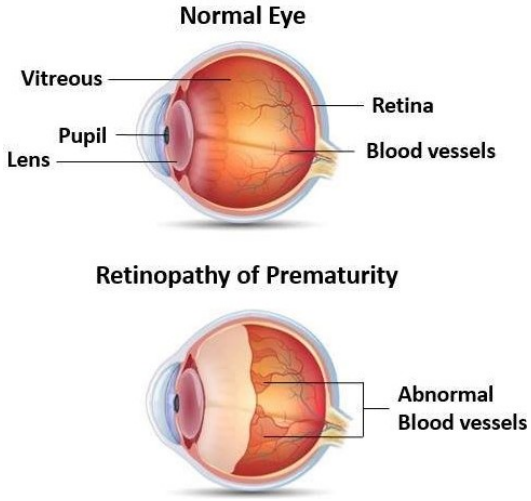


Figure 10: Human eye with ROP [25]

3.1.4. Retinoblastoma

Retinoblastoma is an eye cancer that begins in the retina, the sensitive lining on the inside of the human eye. Retinoblastoma most usually affects young children, but can once in a while occur in adults.

Retinoblastoma occurs when nerve cells in the retina create genetic mutations. These mutations cause the cells to continue growing and multiplying when healthy cells would die. This accumulating mass of cells forms a tumour [25].

Figure 11: Person with Retinoblastoma [26]

3.1.5. Retinitis

Retinitis is inflammation of the retina in the human eye, which can permanently cause damage to the retina and lead to blindness. The retina is the part of your eye that is also known as the "sensing tissue." Retinitis may be caused by a number of different infectious agents. Retinitis, also called Retinitis pigmentosa. This condition is one of the leading causes that leads to blindness in patients in the age range of 20–60 years old [26].

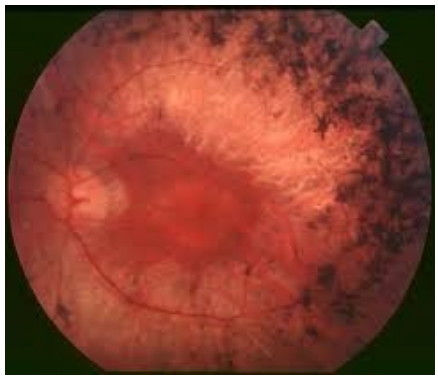


Figure 12: Retinal image of Retinitis pigmentosa [8]

3.1.6. Detached or Torn retina

Retinal detachment is a condition of the eye wherein the retina disconnects from the layer beneath. manifestation contains an expansion for the number of floaters, flashes of light, and worsening of the exterior part of the visual field. This might be depicted as a mask over the region of the field of vision. [7]

A retinal detachment is characterized by the presence of fluid under the retina. This often occurs when fluid passes through a retinal tear, making the retina to lift away from the underlying tissue layers.

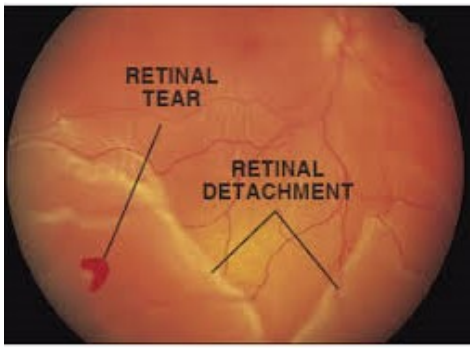


Figure 13: Retinal image of detached and torn retina [7]

A retinal tear occurs when the clear, gel-like substance in the centre of the human eye (vitreous) shrinks and tugs on the thin layer of tissue lining the back of the human eye (retina) with enough traction to cause a break in the tissue. It's often accompanied by the sudden onset of symptoms such as floaters and flashing lights. [25]

3.1.7. Retinal Vein Occlusion

Retinal vein occlusion causes an interruption, or blockage, in normal blood flow. This blockage prevents blood and other fluids from passing through, leading to leakage. This can cause swelling, which affects the macula the responsible for the vision that is necessary for daily activities, and can result in blurry and/or distorted vision [2].

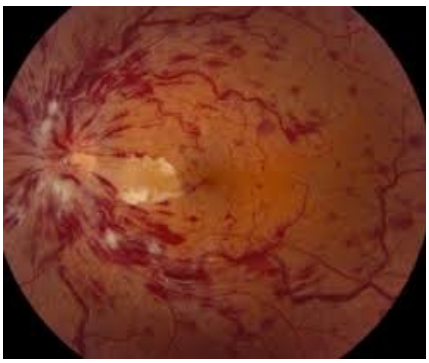


Figure 14: Retinal image of vein occlusion of retina [2]

3.1.8. Epiretinal Membrane

An epiretinal membrane is a pathological condition where a thin layer of scar tissue found on the outside of the retina in a region that is at risk for human pointed vision. The region of the eye influenced by an epiretinal membrane is known as the macula.

Epiretinal membrane is a fragile tissue-like scar or membrane that appears as though crinkled cellophane lying on the retina. This layer pulls up on the retina, which distorts the human vision. Objects may appear blurred or crooked. [2]

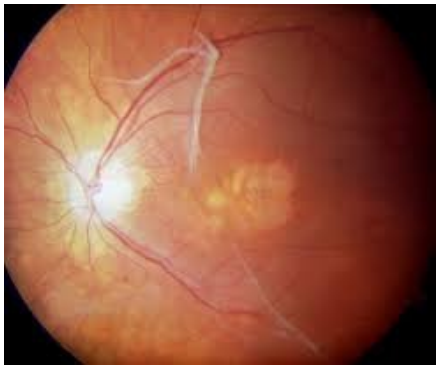


Figure 15: Image of epiretinal membrane [25]

3.1.9. Macular Hole

A macular hole is a small defect in the centre of the retina at the back of the human eye (macula). The hole may develop from abnormal traction between the retina and the vitreous layer, or it may cause an injury to the human eye. [25]

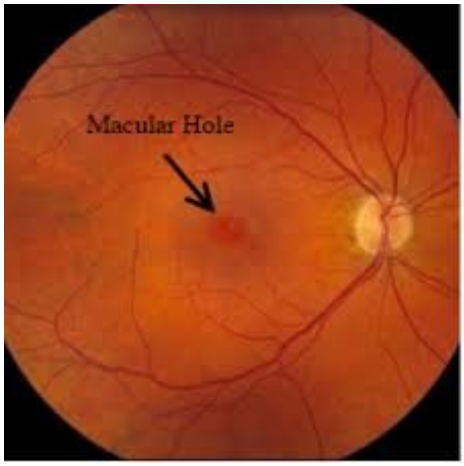


Figure 16: Retinal image of macular hole [25]

3.1.10. Macular Degeneration

In macular degeneration, the centre of your retina begins to deteriorate. This causes symptoms such as blurred central vision or a blind spot in the centre of the visual field. There are two types of macular degeneration that is wet macular degeneration and dry macular degeneration. Many people will first have the dry form degeneration, which may progress to the wet form degeneration in one or both eyes.

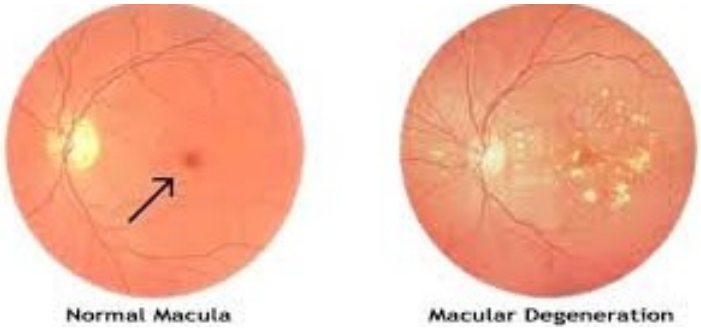


Figure 17: Retinal image of normal and degenerated macular [2]

3.2. Retinal Disease Symptoms

Many retinal disorders share some common signs and symptoms. These may include:

- Seeing floating specks or cobwebs
- Blurred or distorted that is straight lines look wavy vision
- Defects in the side vision
- Lost vision
- The sudden appearance of number of floaters tiny specks that seem to drift through field of vision
- Flashes of light in one or both eyes i.e. photopsia
- Gradually reduced side peripheral vision
- A curtain-like shadow over your visual field

4. METHODS FOR RETINAL IMAGING

4.1. Optical Coherence Tomography (OCT)

Optical coherence tomography is a magnificent procedure for capturing detailed images of the retina to analyse epiretinal membranes, macular holes and macular swelling or edema, to monitoring the extent of age-related wet macular degeneration, and to monitor the responses to treatments.

Optical coherence tomography (OCT) was first described in 1991, as a non-invasive retinal imaging technology. It produces an incorrect colour description of the tissue structures, in view of the strength of the responding light back. Throughout the years, the clinical utilization of OCT has drastically improved in sensitivity and specificity. It has been contrasted with in vivo optical biopsy. As the proposition of OCT has been getting increasingly refined; the recognizable detection, validation, determination and measurement of the tissues has in like manner, become progressively predominant and dependable [1].

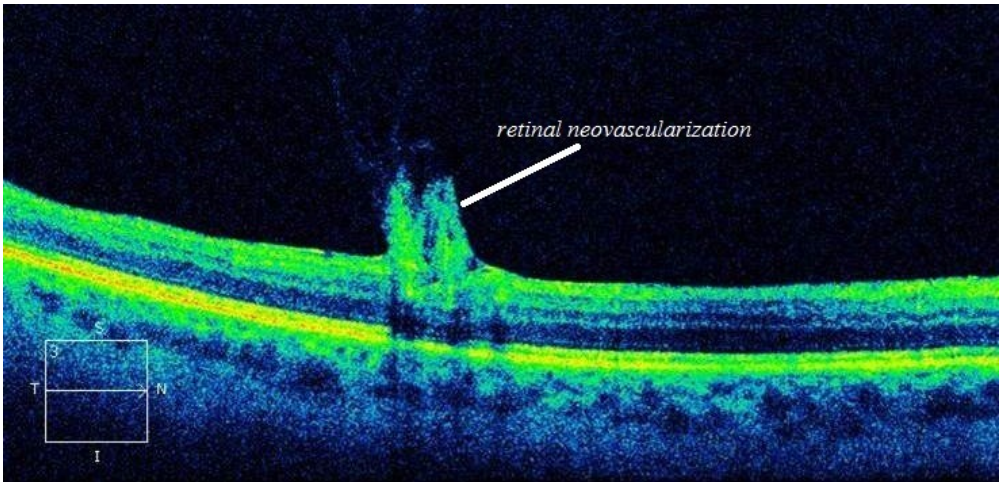


Figure 18: OCT image of retinopathy [17]

The OCT examine printout bears a pseudo-colour imaging and retinal mapping depends on various colour codes (white, red, orange, yellow, green, blue, and black respectively); white being the thickest (>470 microns) and black is thinnest (<150 microns) [17].

Ordinary retinal structures are marked as red for RNFL, and the intersection of internal and external sections of photoreceptors (PR); green for plexiform layers, and blue/dark for nuclear layers. Both PR intersections and retinal pigment epithelium (RPE) are illustrated by red lines, the first is skinnier and the last is thicker. It is difficult to recognize the laterality of the eye from the macular examination. This ought to consistently be checked with fundus video image examination. Light beams from OCT can sensibly infiltrate mild visual media opacities like cataract, posterior capsular opacification, vitreous hemorrhage, asteroid hyalosis and vitritis [17].

4.2. Fundus Auto-Fluorescence (FAF)

FAF may be used to decide the advancement of retinal disorders, including macular degeneration. FAF features a retinal pigment (lipofuscin) that increases with retinal damage or dysfunction.

Fundus autofluorescence (FAF) is a moderately new, non-invasive imaging methodology that has been created over the last decade. The FAF images are acquired using confocal laser scanning ophthalmoscopy (cSLO). It utilizes the fluorescent properties of lipofuscin to initiate images that give data over that is obtained by using increasingly standard imaging techniques, for example, fluorescein angiography, fundus photography, and regular optical coherence tomography (OCT). FAF has been a

domain of concern in ophthalmic research for more than 40 years. Be that as it may, it has as of newly become clinically applicable on account of different significant technological advances. FAF has determined to be useful in comprehension the pathophysiological procedure, diagnostics and recognizable proof of forecast markers for abnormality development, and for keep track of novel treatments [18].

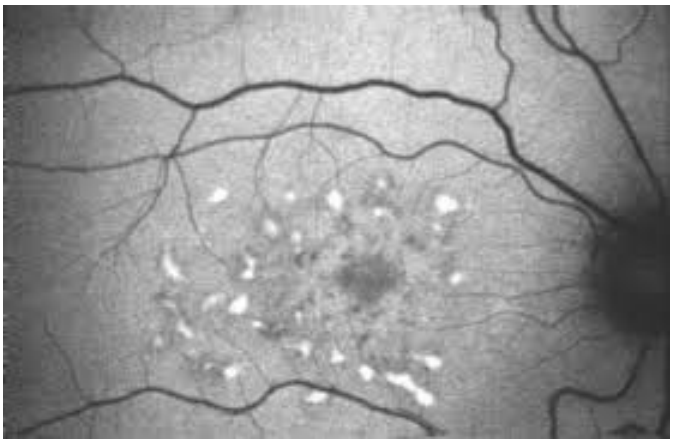


Figure 19: Fundus autofluorescence image of retinopathy [19]

Fundus autofluorescence (FAF) is a non-invasive imaging method that encounter fluorophores, spontaneously appearing molecules that absorbs and emits light of defined frequencies. To deliver autofluorescence, a fluorophore ingests a photon of the excitation frequency, which promotes an electron to an energized, high vitality state. The electron disperses some vitality through molecular collision, at that point emits a quantum of light at a lower vitality and longer wavelength as it advances back to normal state. Traditionally, FAF uses blue-light excitation, at that point accumulate emissions inside a present spectrum to structure a bright coloured map reflecting the dispensation of lipofuscin, a predominant fluorophore situated in the RPE. FAF may utilize other excitation frequencies to recognize secondary fluorophores, for example, melanin with near- infrared autofluorescence [18].

4.3. Fluorescein Angiography

Fluorescein angiography (FA) is the point at which ophthalmologist utilizes a certain camera to take photos of the human retina. These photos help ophthalmologist acquire an enhanced view of blood vessels and distinct structures in the rear of the eye.

This method uses a dye that causes blood vessels in the retina to stand out under a special light. This serves to precisely distinguish closed blood vessels, leaking blood vessels, new abnormal blood vessels and subtle changes in the rear of the human eye [20].

4.3.1. Techniques Used in Fluorescein Angiography

Standard colour and high contrast like black and white red-free separated photos are taken preceding to dye injection. The highly contrasting images are refined red-free (a green filter) to build differentiate and regularly gives a superior photo of the fundus than the colour photo. A 6-second bolus dye infusion of 2-5 cc of sodium fluorescein into a vein in the arm or forehand

A progression of highly contrasting or computerized photos are taken of the retina prior and later the fluorescein arrives at the retinal circulation (roughly 10 seconds after infusion). The early pictures take into account the acknowledgement of autofluorescence of the retinal tissues. Photographs are taken roughly once consistently for around 20 seconds, at that point less regularly. A deferred picture is acquired at 5 and 10 minutes. A few specialists like to see a 15-minute picture also [20].

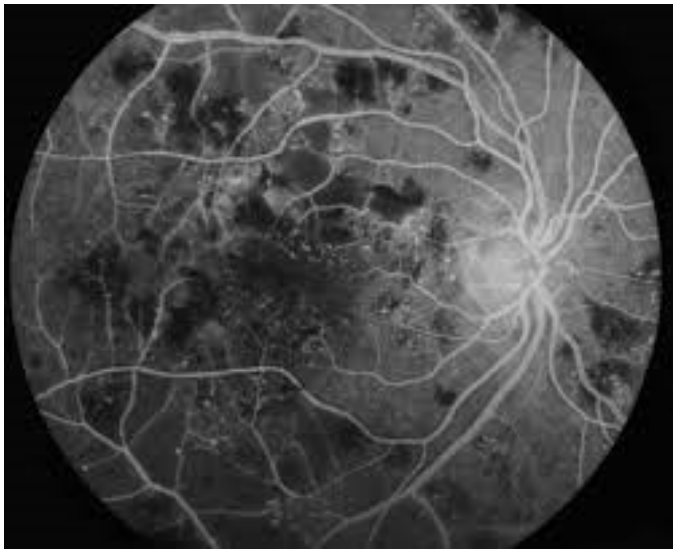


Figure 20: Fluorescein angiography of retinal image [21].

A filter is set in the camera so just the fluorescent, yellow-green light (530 nm) is recorded. The camera may anyway get impulse from pseudo fluorescence or autofluorescence. In pseudo fluorescence, non-fluorescent light is recorded. This happens when blue light reflected from the retina goes through the filter. This is commonly an issue with earlier filter, and yearly substitution of these filter is suggested. In autofluorescence, fluorescence from the eye exists without the infusion of the dye. This might be seen with retinal optic nerve head drusen, astrocytic hamartoma, or calcific scarring.

High contrast photographs give preferred difference over colour images, which aren't essential on the grounds that the filter transmits just one colour of light.

4.3.2. Clinical Application of Fluorescein Angiography (FA)

Fluorescein Angiography (FA) is generally recommended to find and diagnose eye disorder including:

- Macular edema, swelling or inflammation in the retina that distorts or blurred vision.
- Diabetic Retinopathy, damaged or abnormal blood vessels in the human eye affected by diabetes.
- Macular degeneration.
- blockage of veins inside the human eye, called BRVO or CRVO - retinal vein occlusion.
- macular pucker, a wrinkle in the retina resulted by a build-up of fluid in the back of it.
- ocular melanoma, a type of cancer affecting the human eye.

4.3.3. Risk Factors of FA

Some side effects from fluorescein angiography:

- When looking at objects, it may seem dark or tinted. This side effect leaves off in a short time.
- Skin may look a bit yellow. This happens because the dye travels to all veins in the human body. skin will return to its usual colour in a short period.
- Urine may seem to be orange or dark yellow for up to 24 hours eventually. This is because kidneys will filter the dye from blood.
- It may feel a burn on skin if dye leaks during the injection. This side effect goes away in a short time.

Although it is hardly, there is a risk that could have an allergic response to the fluorescein dye. Person who are allergic to the dye may experience hives or itchy skin. Hardly ever, a person may have breathing or other serious problems. Physician can treat an allergic reaction with pills or shots.

4.4. Indocyanine Green Angiography

This technique uses a dye that lights up when presented to infrared light. The final images show retinal blood vessels and the deeper, harder-to-see blood vessels behind the retina in a tissue called the choroid.

Indocyanine Green Angiography (ICG) is a diagnostic technique that utilizes ICG dye to interrogate the bloodstream in the CHOROID – the layer of blood veins which lies beneath the retina. Indocyanine Green dye is infused into a blood vessel in the forelimb/hand. As the dye goes through the veins of the human eye, photos are taken to display the bloodstream [21].

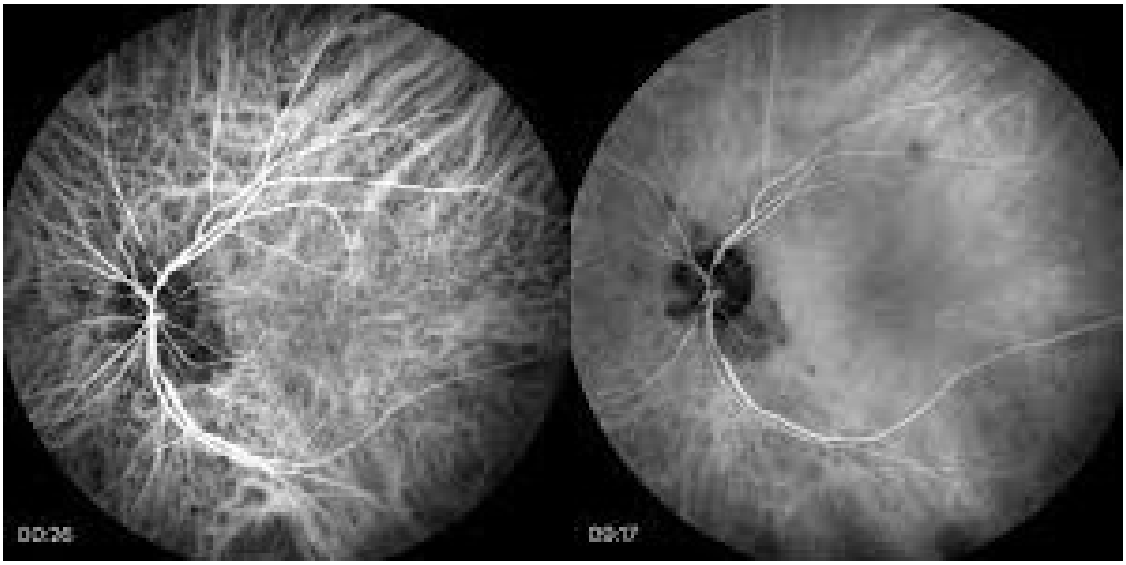


Figure 21: Indocyanine green angiography of retinal image [21].

The choroidal vessels are covered up underneath a layer of pigmented cells. Infrared light radiated by ICG dye can be recorded through the pigmented layer utilizing particular filters.

The most widely recognized use of indocyanine green angiography is the identification of choroidal neovascularization, a typical element of age-related macular degeneration. In different swelling or inflammatory conditions, just as with focal serous chorioretinopathy, unique ICG designs have developed that may encourage better comprehension of the disorder processes.

4.5. Ocular ultrasonography

This method uses high-frequency sound waves (ultrasonography) to help view the retina and other structures in the eye. It can also identify certain tissue characteristics that can help in the diagnosis and treatment of eye tumour.

An eye and orbit ultrasound are a test to view at the eye region. It also measures the size and structures of the eye. An ultrasound technician or an ophthalmologist who specializes in diagnosing and treating eye disorders and diseases usually performs the procedure called eye examination [22].

4.5.1. Technique of Ocular Ultrasonography

The test is most often done in the ophthalmologist's office or the ophthalmology department of a hospital or clinic. person eye is numbed with medicine anaesthetic drops. The ultrasound probe transducer is placed against the front surface of the eye. The ultrasound uses high-frequency sound waves that pass through the eye. Reflections echoes of the sound waves form an image of the structure of the eye. The test takes about 15 minutes [22].

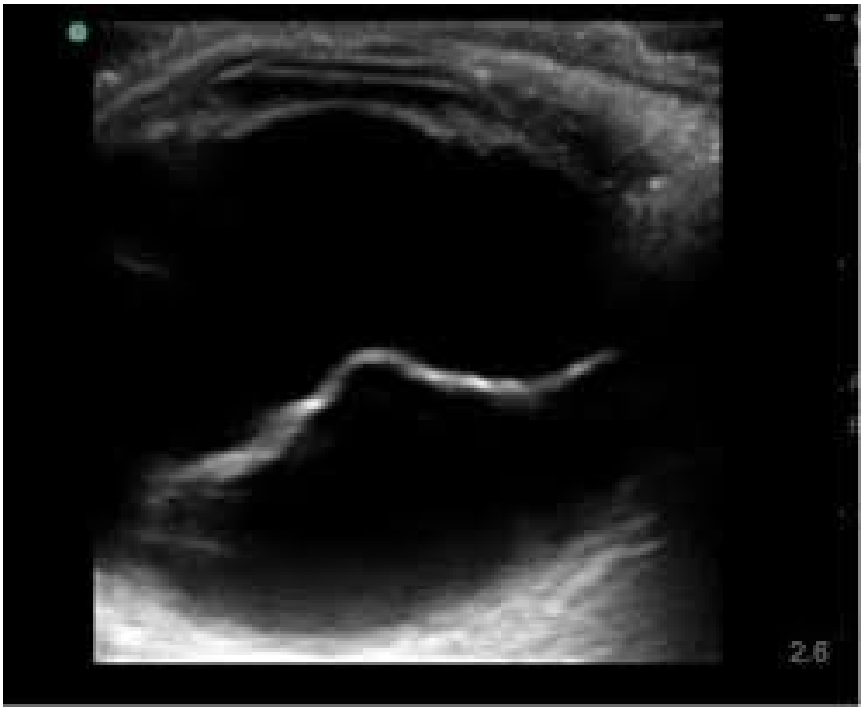


Figure 22: Ocular ultrasonography for retinal detachment [22].

There are 2 types of ultrasound scans: A-scan and B-scan.

For the A-scan:

person will most often sit in a chair and place your chin on a chin rest. person will look straight ahead. A small probe is placed in opposition to the front of your eye. The test may also be done with a person lying back. With this method, a fluid-filled cup is placed against a person eye to do the test.

For the B-scan:

person will be seated and may be asked to look in many directions. The test is most often done with person eyes closed. A gel is placed on the skin of persons eyelids. The B-scan probe is gently placed against person eyelids to perform the test [23].

4.5.2. Clinical Application of Orbit Ultrasound

Clinical conditions that might be revealed by the B-scan include:

- foreign bodies in the eye
- cysts
- swelling
- detachment of the retina
- destructive tissue or lesion to the human eye socket (orbit)
- vitreous hemorrhage bleeding into the clear gel, called the vitreous humor, that fills the rear of the human eye
- cancer of the retina, beneath the retina, or in another region of the eye

4.6. Orbit CT Scan

In rare instances, these imaging methods can be used to help evaluate eye injuries or tumour. A computed tomography (CT) scan of the orbit or eye socket is an imaging technique. It uses x-rays to create a detailed image of the eye sockets (orbits), eyes and surrounding bones.

4.6.1. Technique of Orbit CT Scan

person will be asked to lie on a narrow table that slides into the centre of the CT scanner. Only person head is placed inside the CT scanner. person may be allowed to rest his/her head on a pillow. Once person head is inside the scanner, the machine's x-ray beam rotates around the head but the person won't see the x-ray. A computer generates separate images of the body area, called slices. The images of CT can be stored, viewed on a monitor, or printed on film. The computer can generate three-dimensional models of the body area by stacking the slices together. person must lie still during the exam, because movement causes blurred images. person may be asked to hold the breath for short periods. The actual scan time takes about 30 seconds. The entire process takes about 15 minutes [27].

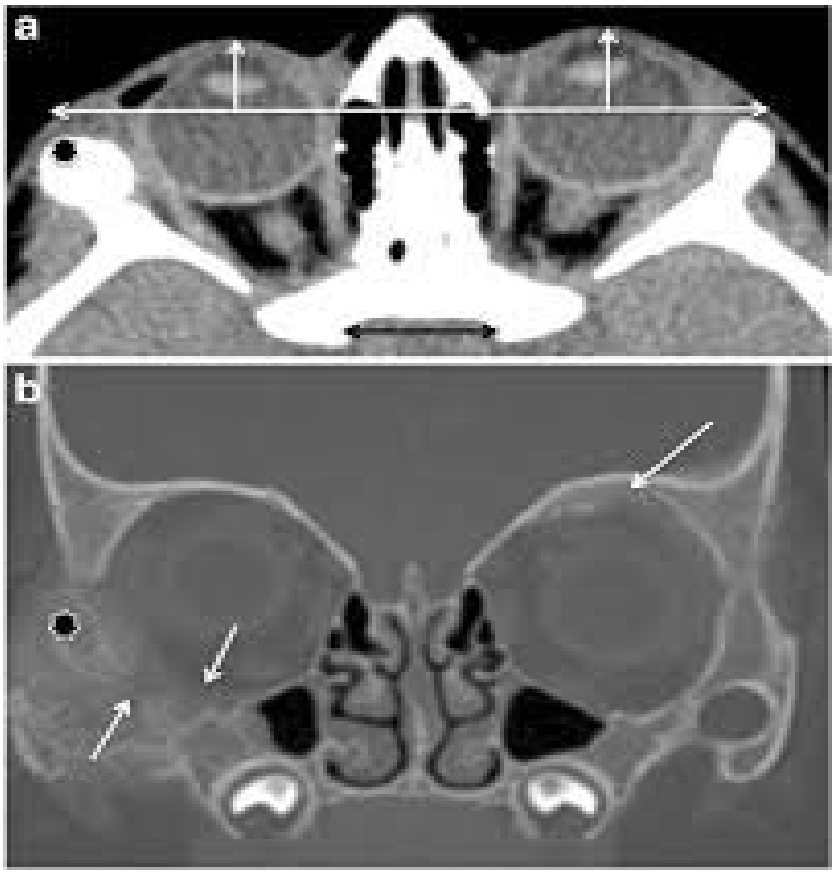


Figure 23: Orbit CT scan for eye tumour [27].

4.6.2. Clinical Application of CT Scan

CT test is helpful for diagnosing diseases that affect the following areas around the eyes:

- Blood vessels
- Eye muscles
- Nerves supplying the eyes, optic nerves
- Sinuses
- Abscess infection of the eye area
- Broken eye socket bone
- Foreign object in the eye socket

4.6.3. Risk Factors of Orbit CT Scan

CT scans and other x-rays are strictly examined and controlled to make sure they use the least quantity of radiation. The risk related to any individual scan is very low. The most common type of contrast injected into a vein contains iodine.

- If a person with an iodine allergy is injected this type of contrast, nausea, sneezing, vomiting, itching, or hives may occur.
- If a person has a known allergy to contrast but need it for a successful exam, person may receive antihistamines (such as Benadryl) or steroids prior to the test.
- The kidneys help filter the iodine out of the human body. If a person has kidney disease or diabetes, person should be closely monitored for kidney problems after contrast is injected. If a person has diabetes or have kidney disease, talk to provider prior to the test to know risks.
- Prior receiving the contrast, tell provider if the person takes the diabetes medicine metformin (Glucophage) because it may need to take extra precautions. A person may need to stop the medicine for 48 hours after the test.
- In rare cases, the contrast can cause a life-threatening allergic response called anaphylaxis. If a person has any trouble breathing during the test, tell the scanner operator right away. Scanners come with an intercom and speakers, so the operator can hear at all times.

4.7. RetCam

RetCam is a modern, state-of-the-art retinal mapping and evaluation system based on high-resolution digital photographic images that enables accurate diagnosis of various eye pathologies. Many infectious diseases contracted by mothers that can cause changes in the fundus of the baby's eye and affect vision in the future.

RetCam's high resolution camera captures images and magnifies them on a monitor, where it is possible to adjust brightness, contrast and colour balance, allowing the ophthalmologic diagnosis to be done quickly and with unparalleled accuracy [10].

It has FA (Fluorescein Angiography), as an option, which provides a high contrast for the detailed visualization of the fundus structures of the eye, which allows the physician to detect early and assertive cases of ROP and other ophthalmic anomalies in new-borns.

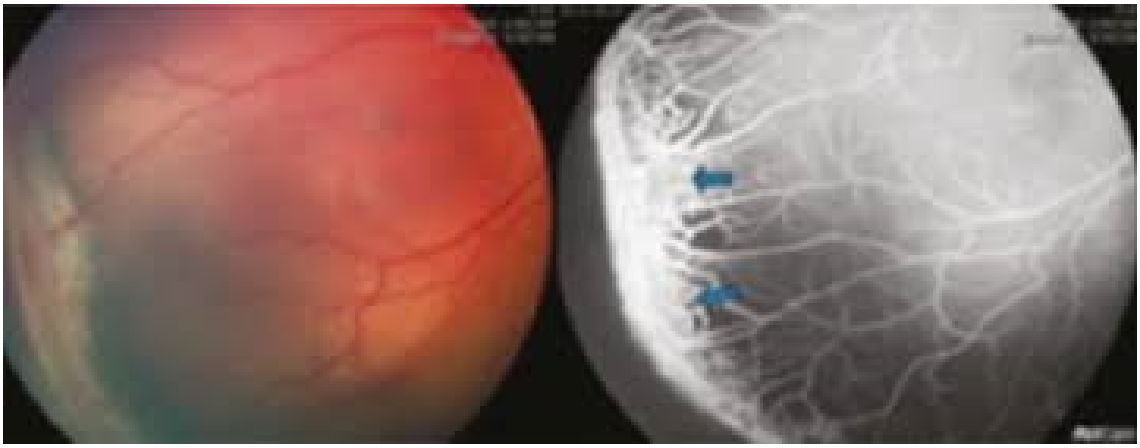


Figure 24: Retcam3 image of retina [10].

The equipment is more suitable for people who have some difficulty or sensitivity to perform examinations on the eye. With the equipment, there is an enlargement of the image record, which gives the clinical physician an analysis material that does not require the examination to be repeated with each new medical observation.

The images are stored on the device and can be recorded on CD, printed or sent electronically, if medical monitoring is done at a distance. This facilitates interaction with specialized canters and exchange of information among professionals in the field.

Another field of action of the equipment is for the diagnosis of Retinopathy of Prematurity and Retinoblastoma. These are eye problems that affect children and can lead to irreversible blindness if they are not detected for early treatment.

4.7.1. Clinical Benefits of Retcam 3

- Enables the capture of exceptional quality, full colour images that can be used for immediate assessment of the retina and anterior chamber
- Lightweight, ergonomic, easy to use handpiece
- Intuitive user interface for fast image capture and review
- Five interchangeable lenses: 130° ROP, 120° paediatric and young adult, 80° high contrast, 30° high magnification and portrait lens for exterior imaging
- Facilitates user review and patient follow up
- Effective educational tool for both staff and patients
- Provides reliable defensible medico legal documentation
- DICOM compatible
- Ease of portability for multiple sites
- Fluorescein Angiography module option with RetCam 3

5.IMAGE PROCESSING TECHNIQUES IN RETINAL IMAGING

5.1. Image Processing Algorithm

The retinal images are acquired through highly sensitive colour fundus camera and given as input to the pre-processing. After pre-processing, the features are extracted. The malformation in retinal images and classification of retinal exudates types is developed using Fuzzy 'C' Means (FCM) algorithm and K-Nearest Neighbour (KNN) classifier is used to classify these retinal images does contain exudates problem or not [4].

Pre-processing (uniform size, remove noise, enhance image)
Median filter
CLAHE Enhancement
Edge Detection
Blood Vessel Detection
Exudates detection
Fuzzy clustering Means
Feature Extraction
KNN Classifier
Performance measure
Specificity
Sensitivity

Accuracy exudates detection in retinal images that combined pixels clustering and elimination of false candidates. process have detected the exudates and abnormalities in the retinal images by using FCM and KNN classifier. FCM clustering and fine segmentation using morphological reconstruction. KNN classifier used to detect the type of disease.

A binary image is one resulting only black and white pixels. The retinal image consists of a binary array, typically of 0's and 1's. Images of any type may be converted to this design for processing or analysis.

5.2. Image Capture

The beginning of fundus digital image analysis is image capture. This is normally acquired by a fundus camera (mydriatic or non-mydriatic) that has a back-mounted digital camera. The digital camera operates in the same fashion as a conventional camera, but instead of having film, digital cameras use an image sensor. Direct digital sensors are a charge-coupled device (CCD) or complementary metal oxide semiconductor active pixel sensor (CMOS-APS). The CCD is an array of small light-sensitive diodes which convert the light signal photons into electrical charge electrons. This then converts the analogue light image into a digital pixelated image [4].

Figure 25: Image capture [25].

5.3. Image Processing

Image-processing action change the grey esteem of the pixels. There are three fundamental methods by which this is concluded. In its most basic structure, the pixels grey esteems are changed with no preparing of encompassing or 'neighbourhood' pixel esteems. Neighbourhood processing includes the estimations of pixels in a compact neighbourhood around every pixel being referred to. At last, changes are progressively mind-boggling and include control of the whole picture with the goal that the pixels values are spoken to in an alternate but identical structure. This may take into consideration progressively productive and amazing processing before the image is returned to its unique method of portrayal [27].

5.3.1. Image Enhancement

One of the troubles in picture capture of the ocular fundus is image quality which is influenced by factors, for example, average opacities, defocus or presence of noise. image enhancement includes the turn of events or improvement of an image with the goal that the outcome is progressively appropriate for consequent use. Enhancements may mean the image is increasingly satisfactory for review, handling or examination. This may include procedures, for example, improving contrast or brightening an image. The image histogram gives fundamental data about the presence of an image. It comprises of a graph demonstrating the occasions each grey level happens in the image [28].

Figure 26: Image enhancement [17].

5.3.2. Image Restoration

Procedure in this class object to reverse damage by known causes. Algorithms such as deblurring or removal of obstruction patterns belong to this category. Noise occurs due to errors in pixel values caused by external disturbance. There are many descriptions of noise, such as salt-and-pepper noise, Gaussian noise or periodic noise. Salt-and-pepper noise affect the appearance of randomly scattered white or black pixels over the image but it is possible to reduce this by using filters in which the mask evens out digression or ignores excessively high or low values [4].

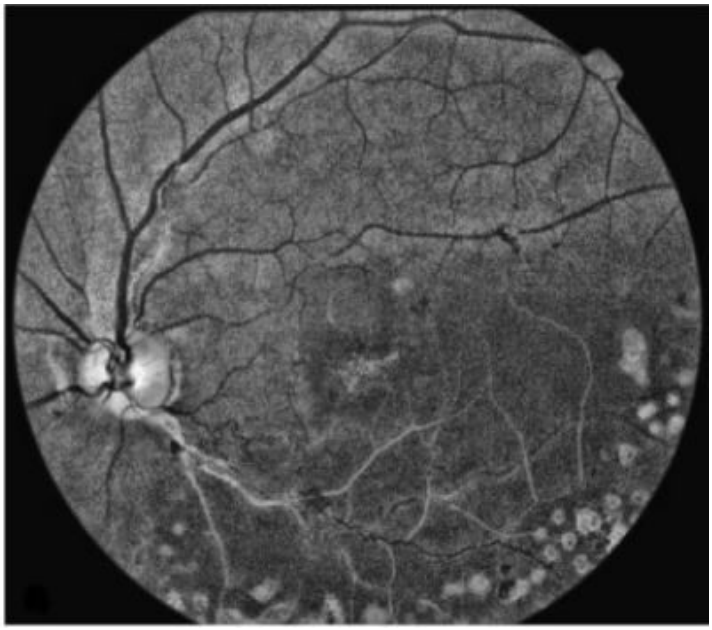


Figure 27: Image Restoration [17]

5.3.3. Image Segmentation

Segmentation requires dividing images into sub-sections that are of particular interest, such as explaining areas of an image that are appropriate to be subsequently analysed, or finding circles, lines or other shapes of interest. Segmentation can stop when such purpose of interest has been isolated. Segmentation algorithms for monochrome images are commonly based on the discontinuity of image intensities such as edges in an image, or on similarities examine by predefined criteria [5].

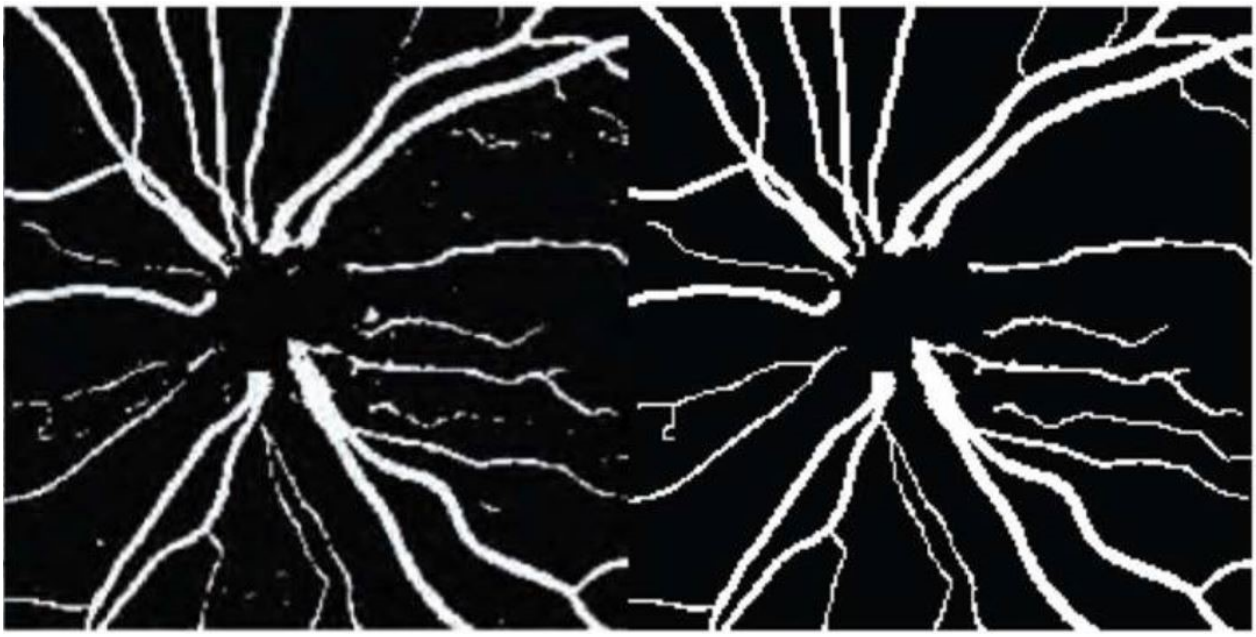


Figure 28: Result of segmented retinal image [5].

Thresholding:

Thresholding authorizes the separation of an image into discrete components by turning it into a binary image. This includes the image is separated into white or black pixels on the basis of whether their intensity value is greater or less than a certain threshold level. The method of thresholding may be particularly useful to remove unnecessary detail or variations and highlight feature that is of interest [1].

Edge detection:

Edges contain some of the most useful details of an image. They can be used, to measure the dimension of objects or to recognise and detach objects. An edge in a digital image involve of an observable difference in pixel values within a particular area. Most edge detection algorithms evaluate this alter by finding the magnitude of the gradient of the pixel intensity values. This can be accepted by the application of specialised filters of varying complexity and utility [3].

Filters:

Neighbourhood processing extends the capacity of processing algorithms by incorporating values of adjacent pixels in calculations. A user-defined matrix, or mask is defined with enough elements to cover not only a single-pixel but also some of its adjacent pixels. Each pixel covered by the components of the mask is subject to a corresponding function. The combination of mask and function is known as a filter. Thus, the result of applying a mask to a particular location is that the final result value is a function not only of the central pixel's values but also of its neighbouring pixel values [3].

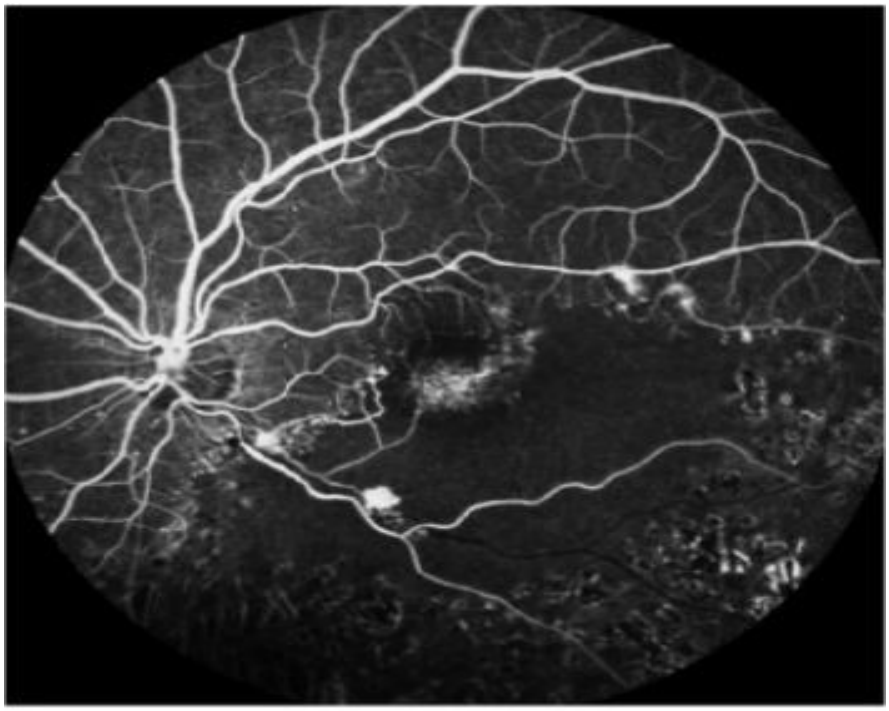


Figure 29: Filtered retinal image [28].

Morphological process:

Mathematical morphology in image processing is especially suitable for analysing shapes in images. The two main procedures are those of dilation and erosion. These procedures involve a special mechanism of combining two sets of pixels. Usually, one set includes of the image being processed and the other a smaller set of pixels known as a structuring element or kernel. In dilation, each point in the image is superimposed onto by the kernel, with its surrounding pixels [27]. The resultant effect of dilation is of increasing the size of the original object. Erosion is a reverse procedure in which an image is thinned through subtraction via a structuring element or kernel. The kernel is superimposed onto the original image and only at the region when it fits entirely within its boundaries will a resultant central pixel be accepted [4].

5.4. Image Registration

Image registration is a process of aligning two or more images of the same order. One image that is the base image compared with the other input images. The focus of registration is to execute spatial transformations to the input image to bring the input image into alignment with the base image. often, the input images may be misaligned due to discrete camera angles or different imaging modalities. The details of the correct alignment algorithm are calculated after the user identifies pairs of points that should exactly correspond in the two images [28]. Registration can be based on identified landmarks, on the alignment of segmented binary structures segmentation based, or directly onto measures computed from the image grey values. Comparisons are made with the transformed input image to the corresponding base image. Registration of images in this method is frequently used as a preliminary step in processing applications. This has been performed for sequential fluorescein angiography and colour fundal images [3].

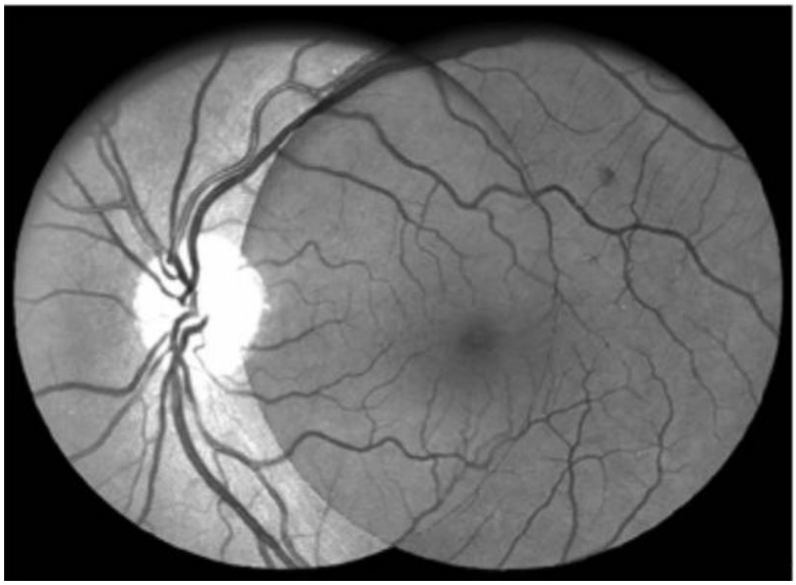


Figure 30: Image registration [28].

6. PROPOSAL OF SOFTWARE APPLICATION

The proposed system focuses on User and Retinal image archive management system. The proposed system is also aimed to achieve quick fetching of retinal records and basic analysis of retinal records.

6.1. Expectation of Software Application

1. Creation of a database containing the retinal records, associated clinical parameters of the retinal records.
2. Creation of user login form for authorizing users.
3. Create software application for visualizing and editing of the retinal image records from the RetCam 3.
4. To improve and standardize advanced searching and sorting functions of the retinal images in software application.
5. To include the statistical analysis of individual clinical parameters and technical aspects of the retinal records.

6.2. Justification of Software Application

My web application is mainly used in the hospital's ophthalmology department for patient diagnosis database management system. Usually, there will be multiple numbers of patients with an ocular disorder that requires several visits to the hospital, which involves at least an examination per visit and those examinations could have multiple numbers of retinal images to be stored under each patient's profile.

In the following scenario, the storage of records is heavy that results in a lag in fetching the documents. To overcome this issue my web application uses various links to fetch a specified retinal record which can be easily updated and maintained for a long period.

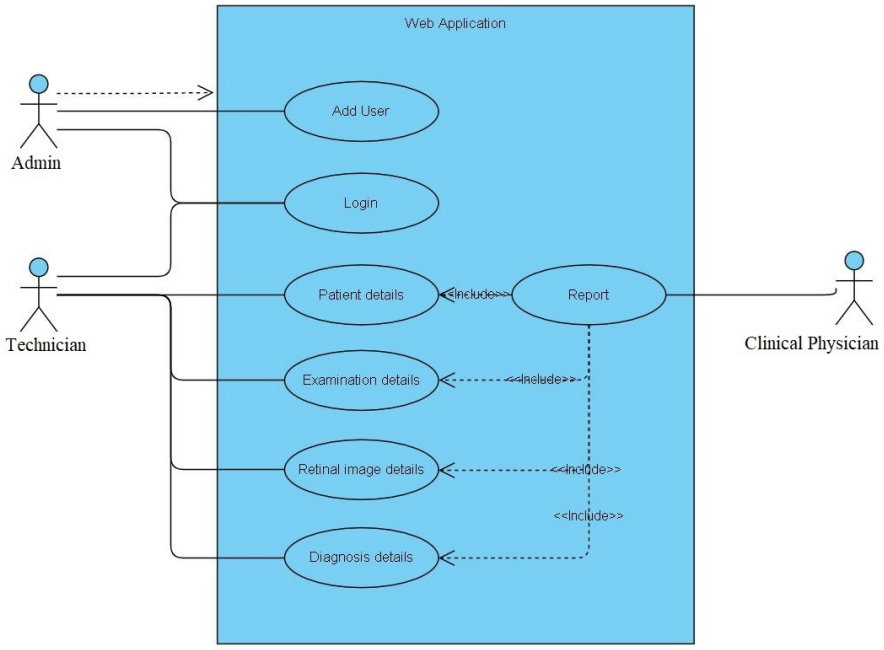


Figure 31: Use case diagram

In addition, with the information of retinal records this application helps to visualize basic statistical analysis of individual clinical parameters. Examined report can be exported to PDF for printing operation.

6.3. Advantage of Retinal Archive Application

- It offers the hospital on retinal record maintenance issues and provides a base for large database.
- Cost efficient
- Reliable
- Accuracy
- Secured
- Integrability
- Robust
- Time efficient
- User friendly
- Modularity

6.4. Outline of Software Application

This describes the retinal image Archiving and analysing application design. The Scope of this software application is to develop database to archive and analyse of retinal records. It includes all activities related to retinal records during the hospital visits of the ocular disorder patients. These records are also used for statistical visualization. If required examined document can be printed. Database created to stores retinal records.

The following modules are designed for the development of web application:

- Login module (validation)
- User module (Add)
- Diagnosis (Add, Counter, State)
- Patient (Add, Edit, Delete, Retrieve)
- Examination (Add, Edit, Delete, Retrieve)
- Retinal image (Add, Edit, Delete, Retrieve)
- Histogram module (View)
- Export module (Print)

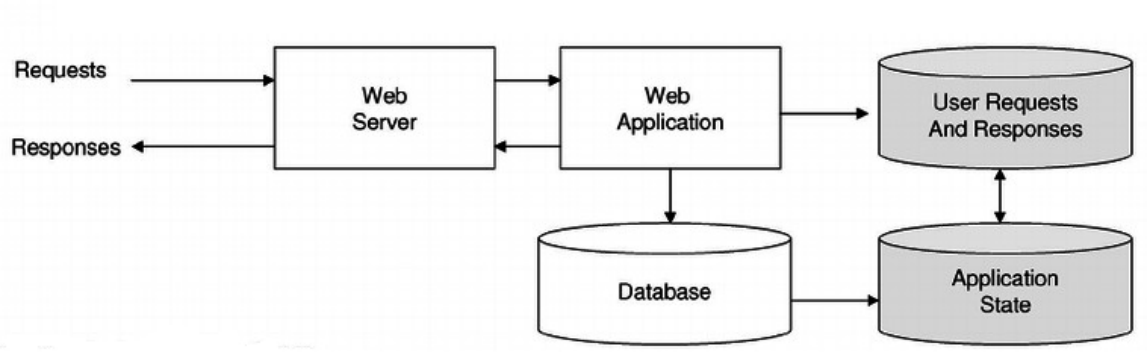


Figure 32: Design of the software application

7. SOFTWARE APPLICATION STRUCTURE

Retinal archive web application runs in a web browser. It is specially designed for ophthalmology department. This application welcomes user to introductory screen of the application with following information

1) The logo as “Retinal Archive”.
2) Login section at the center of the screen, which requests for the user name and password of the user in order to use application.

User name and password are necessary for one to use the web application. If user clicks on the login without providing the password, it will alert user to fill out this field. Then, if user provides wrong username or password, it will alert user “invalid credentials” and web application will not proceed further. It is designed to make use of employee id for username field. For successful login process, the application will enter user home page. From the home page user can interact with the application and make use of all developed modules in the retinal archive software application. This is described in the following flow chart - figure 33.

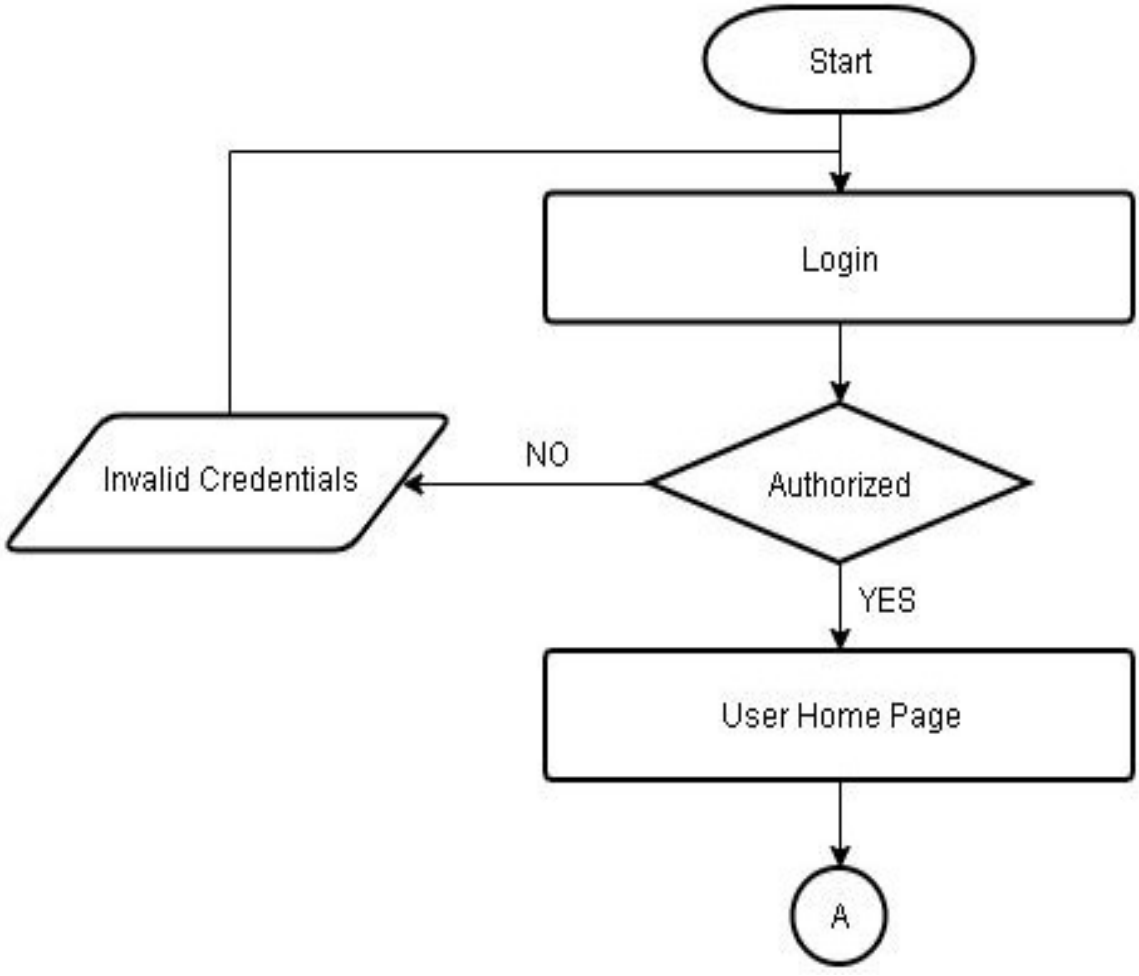


Figure 33: Flow chart of login section

7.1. Application Requirement

The retinal archive application requirement includes software as well as hardware using which the application is developed to run effectively. For further real time implementation local area network (LAN) is advisable.

7.1.1. Software Requirement

- operating system
- web browser
- Symfony local server
- SQLite Database
- Symfony frame work

7.1.2. Hardware Requirement

- Monitor
- HDD (120 gb min.)
- RAM (4 gb min.)
- Processor (2*1.6 GHz preferred)
- Printer

7.2. Software Application Input/output Design

The application contains a database with retinal records arranged and organized. Generally, it stores retinal images, patient details, examination details. In addition to this login credentials also added to the database.

Retinal records are the generated output through this application which can also be updated, added, deleted, edited and fetched as per the requirements.

The application database is a group of patient data which can be used to maintain and retrieve retinal records. This plays a major role in the retinal archive software application. It provides multiple functionalities such as ADD, UPDATE, RETRIEVE, DELETE retinal records as key components.

An authorised user can administer the Database Management System data which is efficiently integrated. Even when the software application crashes database file can be recovered safely which is a notable functionality of a database management system, where data is protected despite a system failure.

7.2.1. Database File Specification

There are several database management systems such as:

- Hierarchical databases
- Network databases
- Relational databases
- Object-oriented databases

For my application, relational DBMS is used because it is one of the easiest models. A relational database management system RDBMS comprises tables, rows, columns, keys, and indexes. Relational models are stored in fixed structures which is manipulated using SQL [30].

The basic requirements of a database include CPU, disk and controllers, memory, operating system, and network.

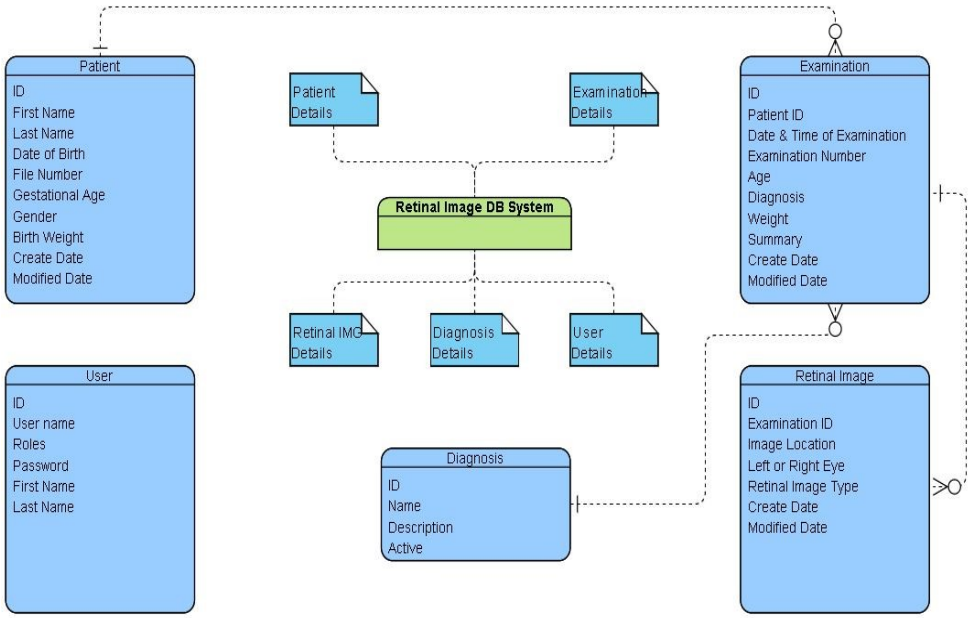


Figure 34: Description of Database table

Data access refers to the authorization to store, retrieve, and manipulate data. Usually, a relational database is accessed using Structured Query Language SQL, a computer language.

All relational databases such as SQLite, MySQL, Oracle uses SQL as their standard language. SQL allows users to describe, manipulate, and work with data. Basically, database tables can be created and dropped using SQL, these commands interpret using the SQL engine which is termed as Query Language Processor.

Interpretation process includes various components:

- Query Dispatcher
- Optimization Engines
- Classic Query Engine
- SQL Query Engine

The basic SQL commands in an RDBMS are CREATE, SELECT, INSERT, UPDATE, DELETE and DROP, which can be classified under 3 groups.

1. DDL - Data Definition Language
2. DML - Data Manipulation Language
3. DCL - Data Control Language

with the knowledge of this, the relational database is created with multiple tables for the software application. Entities created are as follows:

- User
- Patient
- Examination
- Retinal_image
- Diagnosis.

It is clearly explained in the above figure 34, with relationship details between each table.

It is one to many - relationship. For example, each patient has a multiple number of examinations, each examination has a multiple number of retinal images. User entity has no relationship to other entities since it contains login credentials and no other entities have access to the user entity.

7.3. Software Application Development

To connect to the created database a user interface is developed using PHP, html5 and CSS.
PHP- hypertext pre-processor

Php is basically used for server-side scripting, it's embedded with html. PHP is an open source scripting language which is compatible on various platforms and almost on all servers used today, this also supports wide range of databases. It is user-friendly.

Symfony is a PHP web application framework with a set of reusable PHP components. The entire Retinal archive web application was developed using symfony framework [12].

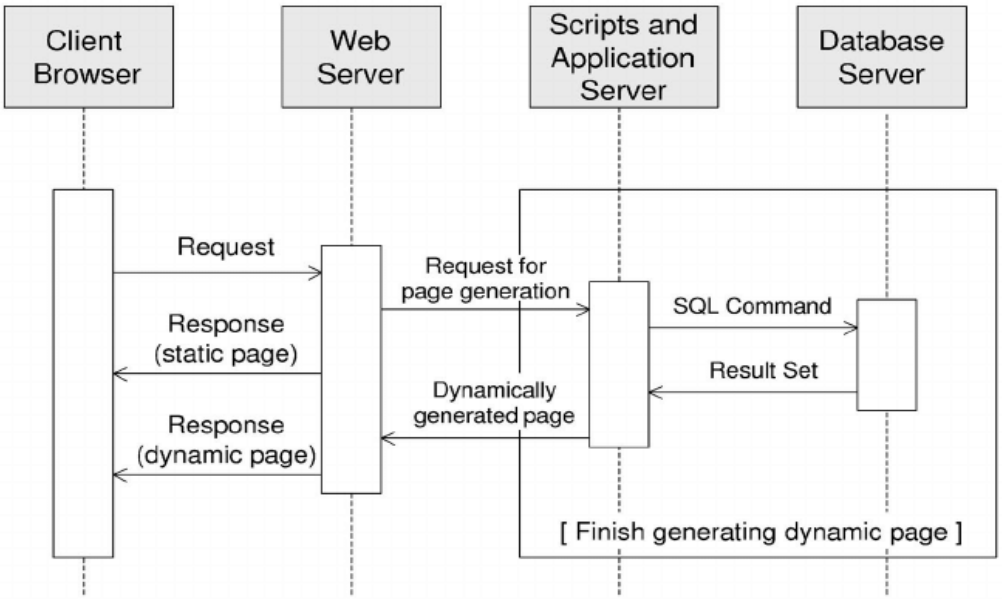


Figure 35: Sequence diagram

The application comprises of client-side and server-side scripting. A request is created from the client-side which reaches the database through web server and fetches the response (static or dynamic) related to the request and reaches the client-side.

7.4. Testing and Evaluation

Software testing is a process of evaluating the acquired results with the specified requirements. During the development phase of the software application a parallel testing has been carried out separately on each and every module.

Manual testing is the way toward testing programming by hand to become familiar with it, to discover what is and isn't working. This normally incorporates confirming all the highlights indicated in necessities records, manual testing incorporates the analysers attempting the product with the point of view of their end client's as a primary concern. Manual test plans shift from completely scripted experiments, evaluating detailed steps and anticipated outcomes, through high -level guides.

7.5. Application Maintenance

Maintenance work starts once the application is completely developed. This is the way toward modifying after the product has been delivered. This requires a comprehension of the program. This is accomplished by clearly reviewing the program code and related documentation. There are normally two sorts of maintenance. Upgrade maintenance has to do with the alteration of the product because of changes in the ever-dynamic condition and corrective maintenance is done because of a mistake found after delivering the product.

8. SOFTWARE APPLICATION IMPLEMENTATION

As we discussed in the above chapters, Retinal Archive web application is designed with a login section at the center of the web browser, it requests user name and password to enter the application home page this was elaborated in figure 33. After successful login it enters home page. All input fields in the application has constraints which displays an alert-based error message when constraints aren't fulfilled.

If retinal image stored in the database retrieving process will be delayed so to overcome this delay, retinal images are stored in folder in the application.

8.1. Web Application Description

On the header tab of the web application, the top right corner of home page contains "User Name" who logged in and also displays the settings option next to it. In settings, user can change the password as well as sign out from the application.

Top left corner contains application logo "Retinal Archive" and next to it is the "Home" button, which is used reach home page from other web pages linked from the home page.

8.1.1. Application functionalities

- New patient
- New user
- Administration
- Diagnosis
- Patient search
- New Examination
- Examination search
- New Retinal Image
- Image search
- Histogram

In addition to this functional button in each module are

- Add
- Save
- Cancel
- Delete
- Edit
- update
- Print
- Generate

These buttons have specific function to access the created database and modify the database accordance to the assigned process. Now, I will explain each functionality in the application.

8.2. Description of Functionality in the Application

Next to "home" button the "New Patient" button appears that's used to add new patient details through the patient form by filling the required details in it and "Save" button will save the form in the created database. Wrong entries can be deleted with "Cancel" button before performing save operation.

Next to "New Patient" button the "New User" button can be utilized by the admin to authorise a person and the user information gets saved to the created database.

Next to it lies the “Administration” button which leads to “Diagnosis” button that’s used to add disease name, description, active/inactive state, and a counter for specifying the number count of the diagnosis usage. “Add” button is used to add a new diagnosis detail which is user definable which gets added automatically into the database.

The side bar contains Patient search, Examination search, Image search and Histogram.

Number of found search results and pagination informs on which page the user stays, this is common in all three search flow processes.

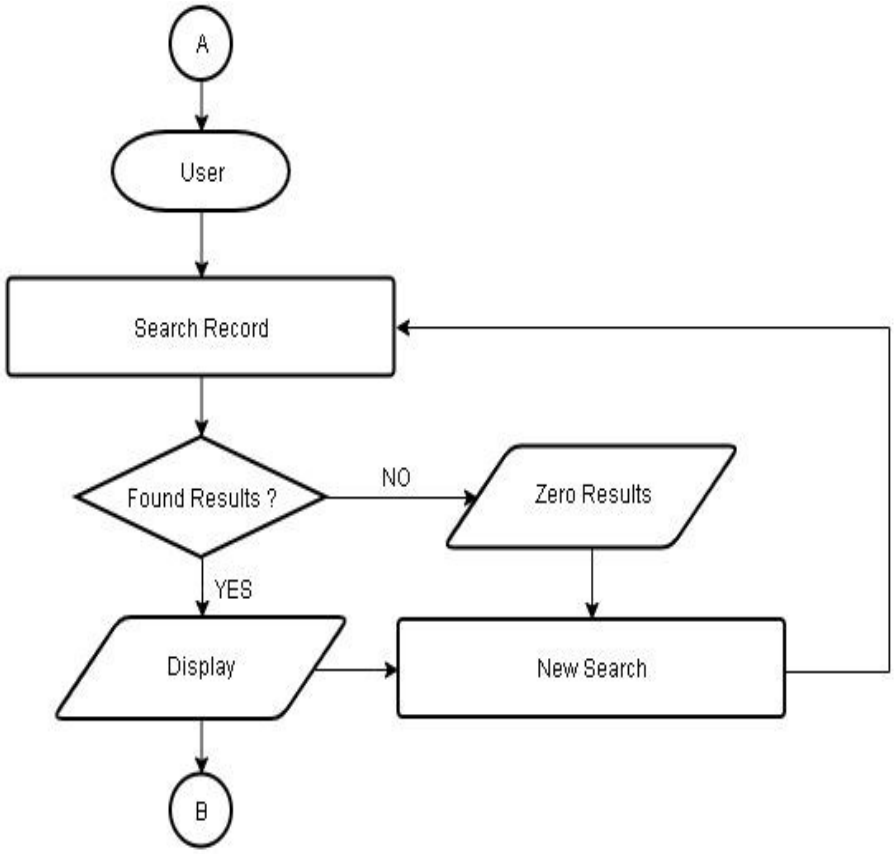


Figure 36: Flow chart for search module

8.2.1. Search Module Description

“Patient search” button is used to fetch the file from the database based on the requirements. By default, the Patient search page shows 5 last added records. Interacting with the fetched file user can add new examination details which directly gets added to the created database. The new retinal image gets added to the image folder created by the application and the path of the folder is added to the created database. User can edit or delete the fetched retinal record.

“Examination search” button navigates to a new web page that loads on the same tab and opens the examination search page; this fetches the examination records according to the specified requirement. Same as patient search it show default last 5 added records. From the fetched file user can edit, delete, view the records, from this page user can add new retinal images. In addition, examination can be exported along with clinical notes as pdf for printing.

“Retinal search” button is similar to Examination search. It is used to fetch the image-based records as per the requirements. Deleted image files are stored in the trash folder created by the

application so the user can retrieve the deleted image file with all details whenever necessary. The search process and the application process flow are showed in the following flow charts figure 36 & figure 37.

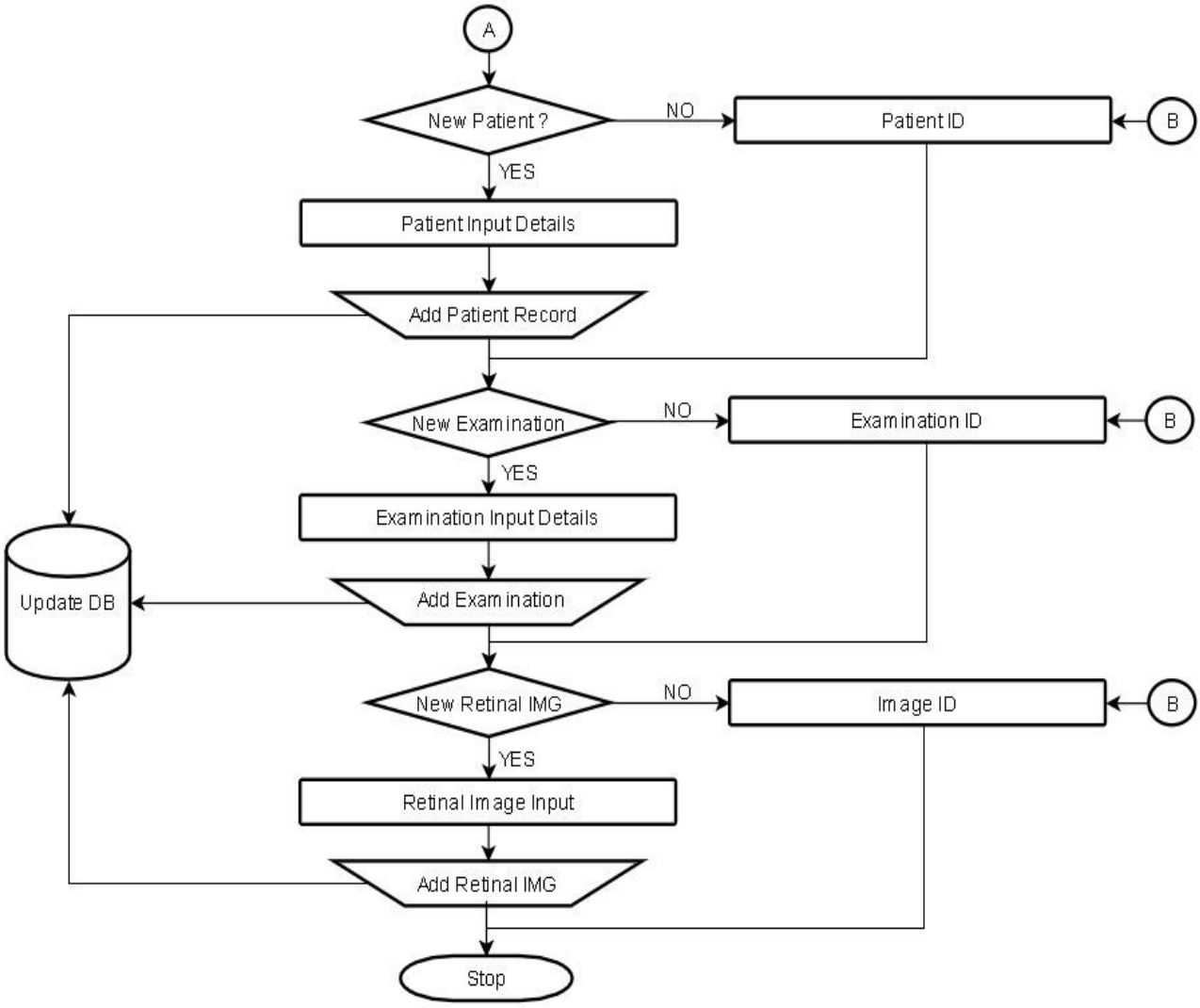


Figure 37: Flow chart of application process

8.2.2. Statistical Module Description

"Histogram" button leads to the visualisation of basic statistical details. The displayed results include a statistical analysed data in text format on the right side of the histogram page. Charts are plotted based on three categories: Patient count, Age and Gender.

By selecting the category from dropdown menu user can visualize the statistical results.

- Patient – This category is used to visualize the number of patients per diagnosis from the retinal records.
- Age – A sub drop down menu is displayed to select the specified diagnosis to visualize the number of patients in accordance to age for selected diagnosis.
- Gender- Similar to age category a drop down appears with a list of diagnosis. This visualises the number of patients in accordance to gender for selected diagnosis.

9. RESULTS AND DISCUSSIONS

Retinal Archive web application is designed and developed for interacting with retinal records which are saved in database. Web application runs in a web browser. Database created with multiple tables for easy processing of retinal image. It will reduce the irrelevant data fetch from the data base.

Above chapters I have discussed about the application design, development, functionalities of the web application. In this chapter, I am presenting the outcomes of the developed application.

First three images in this chapter displays about the login section of the Retinal Archive application. Designed for multiple users.

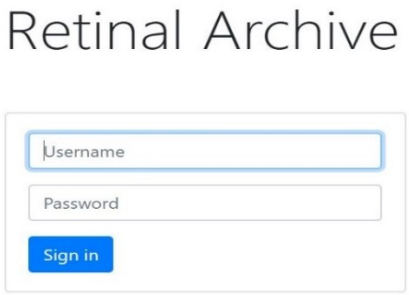


Figure 38: Software application Login page.

Figure 38 shows the introductory page that contains login credentials that is username, password and "sign in" button of the Retinal Archive application.

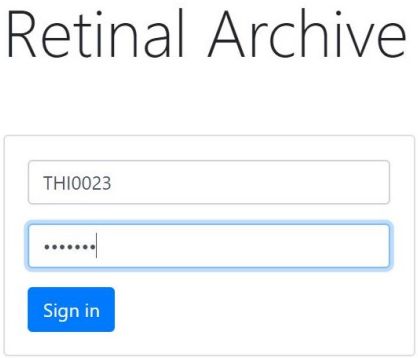


Figure 39: Login page with user entry.

Figure 39 shows the login page with user entry. This should meet the constrains which allows user to enter the home page of the application.

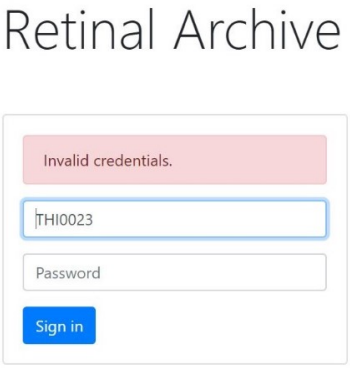


Figure 40: Login page with error message.

Figure 40 shows the failed login credentials and the error message. Application login only for authorized users.

After getting access to the application, user will be in home page of the application. Figure 41 shows how the home page look like and the functionalities in it.

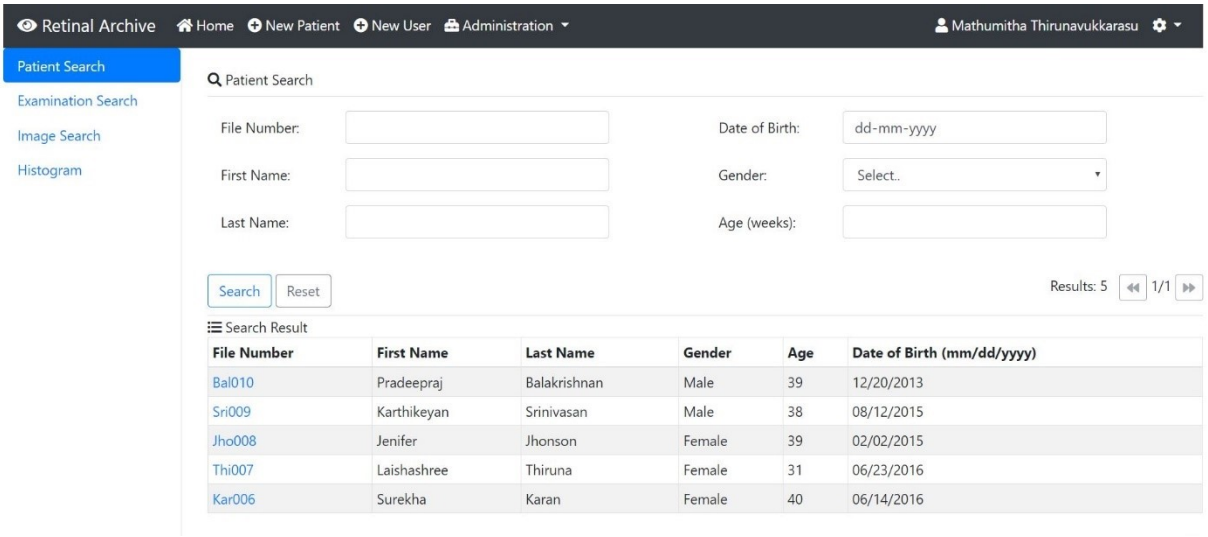


Figure 41: Home page of web application

As already known, Retinal Archive web application is connected to SQL Database to add, to edit, to save, to delete, to retrieve, to analysis, to plot statistics, to export for patient retinal records to evaluate pathology conditions of human eye. New user can be added after login. User can change their password using setting button in the top right corner. Each function in the application has specified functions to it. From home page user can add diagnosis details, patient details, user detail and can navigate to search operation. Plot statistical value from the records. Each module outcomes are listed below in detail.

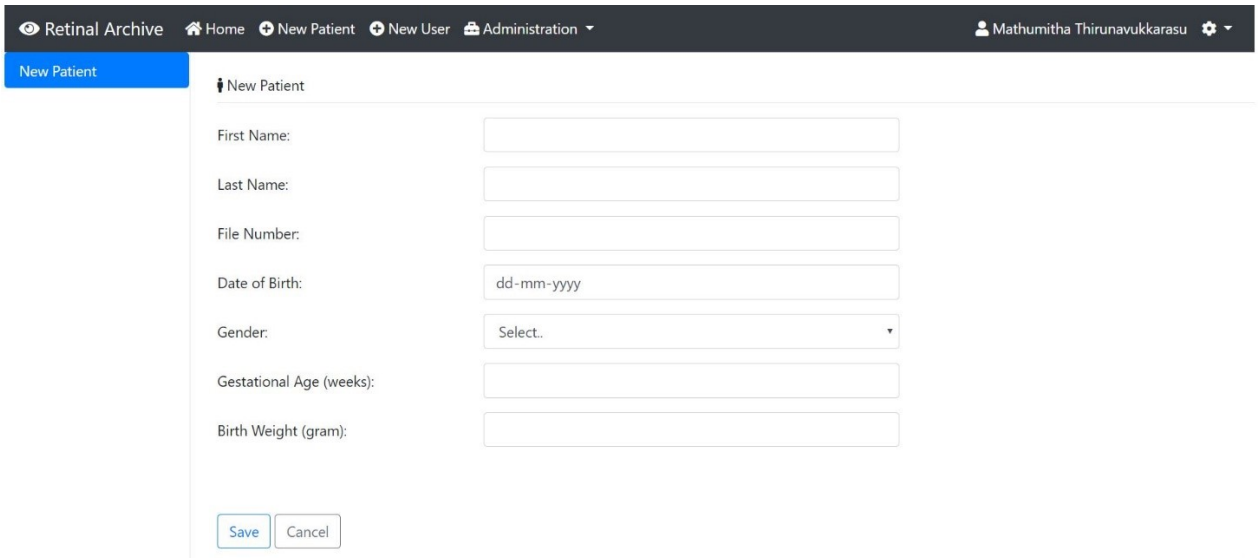


Figure 42: Adding new retinal data.

Adding new patient details. Patient form requires Name, Age, Gender, DOB, Weight, File Number to save in the database using Save button. Cancel button perform reset the details before performing the save function. Figure 42 show the result page of the application for add “New Patient” button.

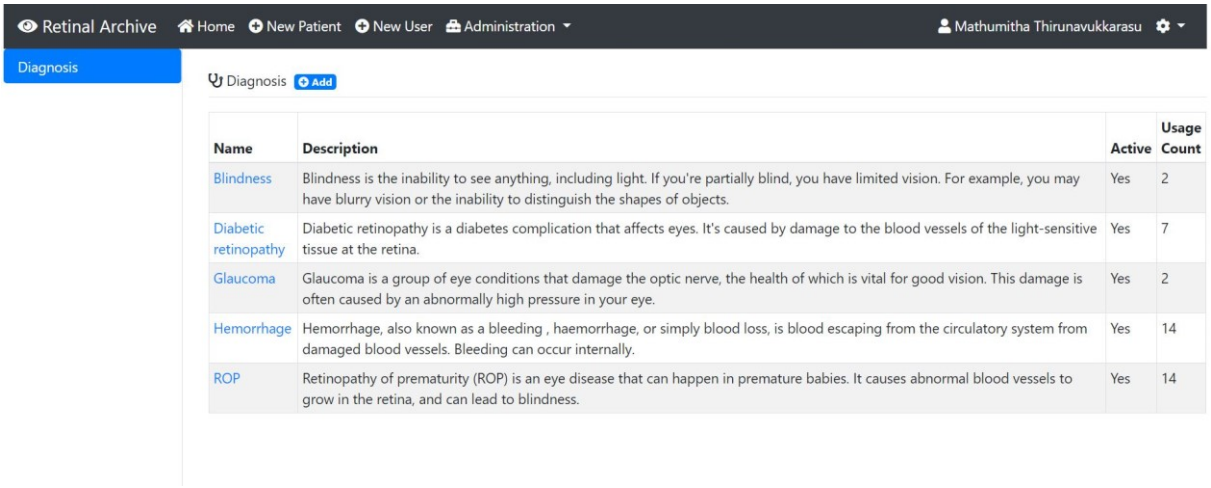


Figure 43: Adding Diagnosis

Figure 43 show Diagnosis page outline. This is used to add diagnosis name with description of the diagnosis. It can be stated activate/inactivate. Active diagnosis can use in the required fields, inactive diagnosis will show the warning message and can't added to examinations. This page shows an information about number of times specific diagnosis used.

Now I will discuss about the search module in the application, it plays a major role in my application because of fetching the saved records accordance to the requirement. It will retrieve records based on patient search, examination search, image search. Results can be viewed in below pictures.

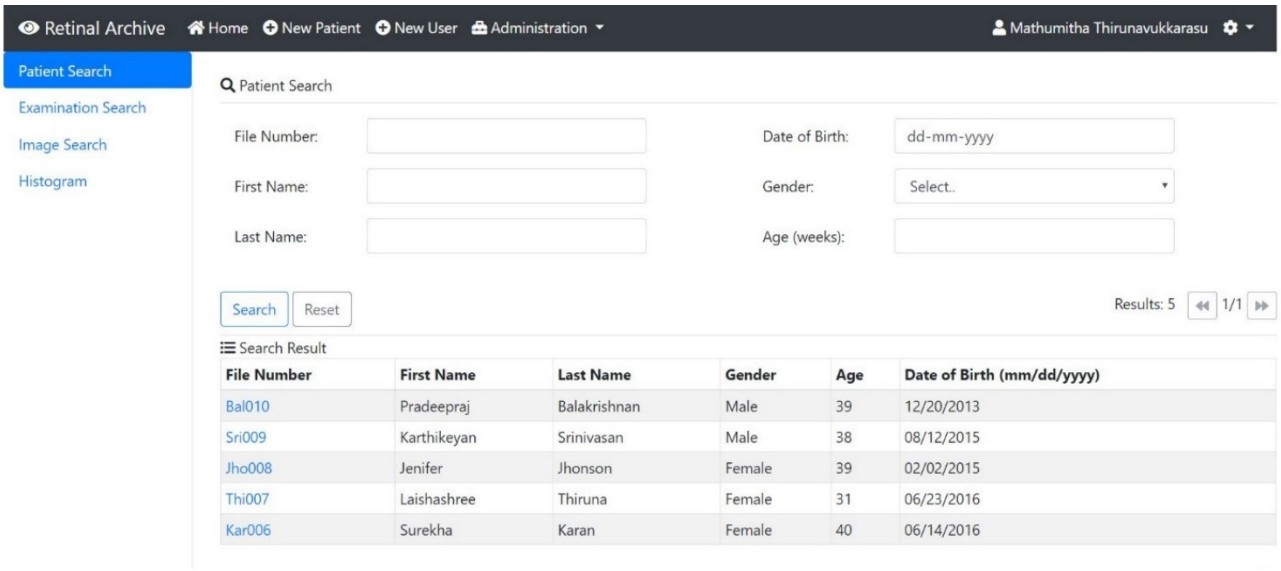


Figure 44: Patient search.

Figure 44 provides information about the searching function based on patient details. Last added 5 records display as default. By selecting the fetched record user can add new examination which will updated in database, and it can edit or delete according to user requirement.

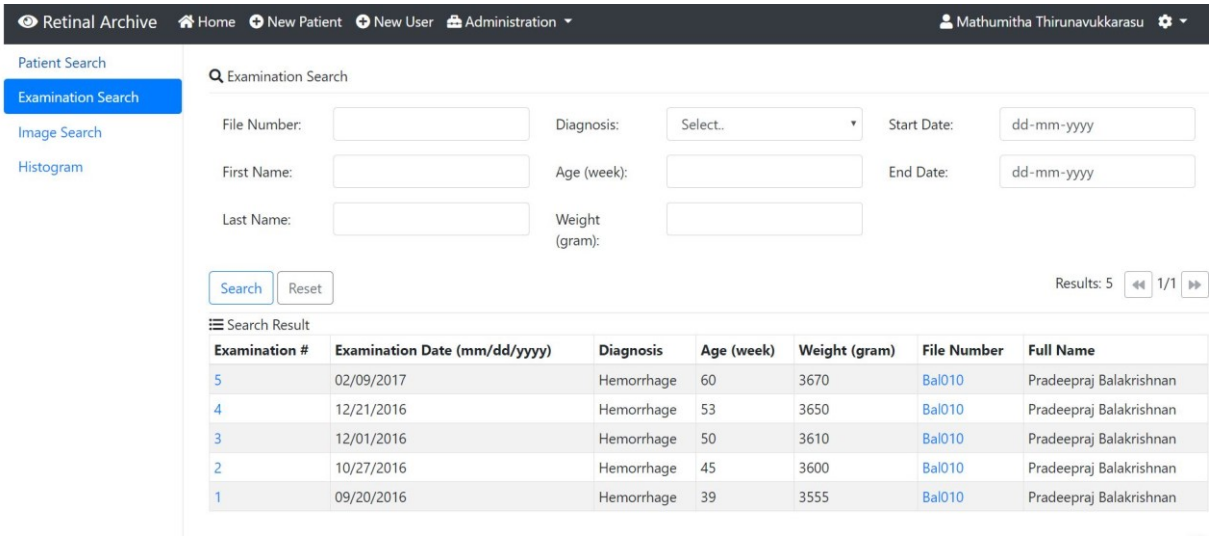


Figure 45: Examination search.

Figure 45 provides information about the searching function based on examination details. Similar to patient search, last added 5 records display as default. By selecting the fetched record user can add new retinal image, and it can edit or delete according to user requirement. Image search is similar to examination search.

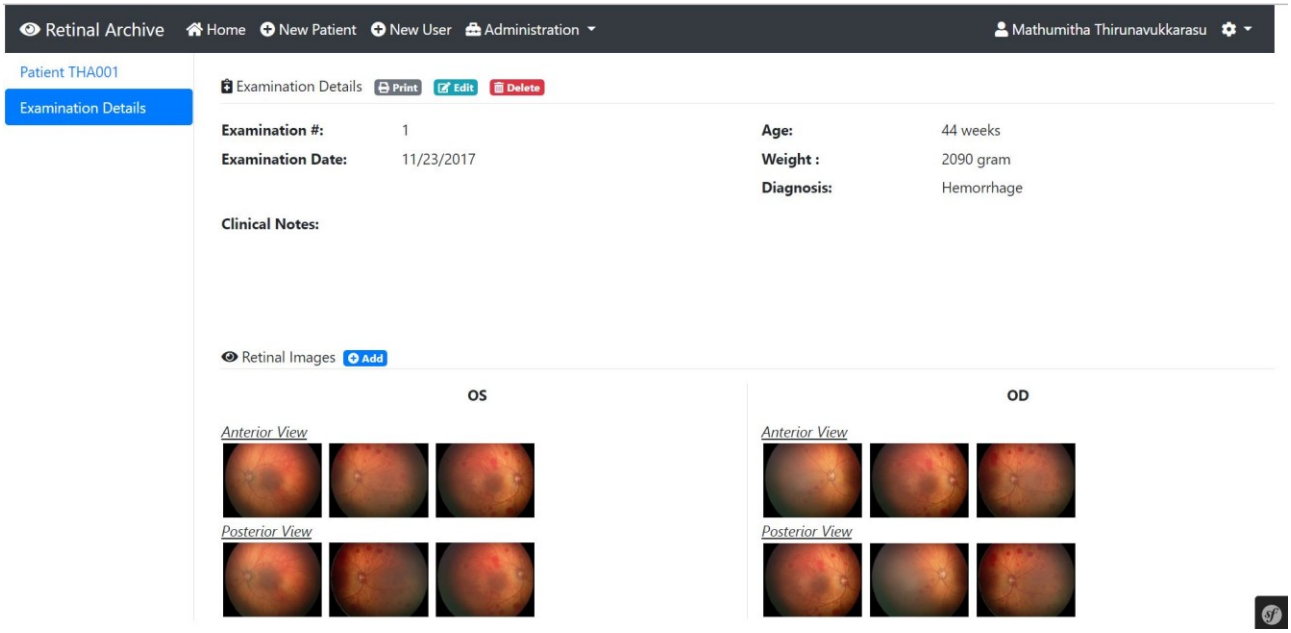
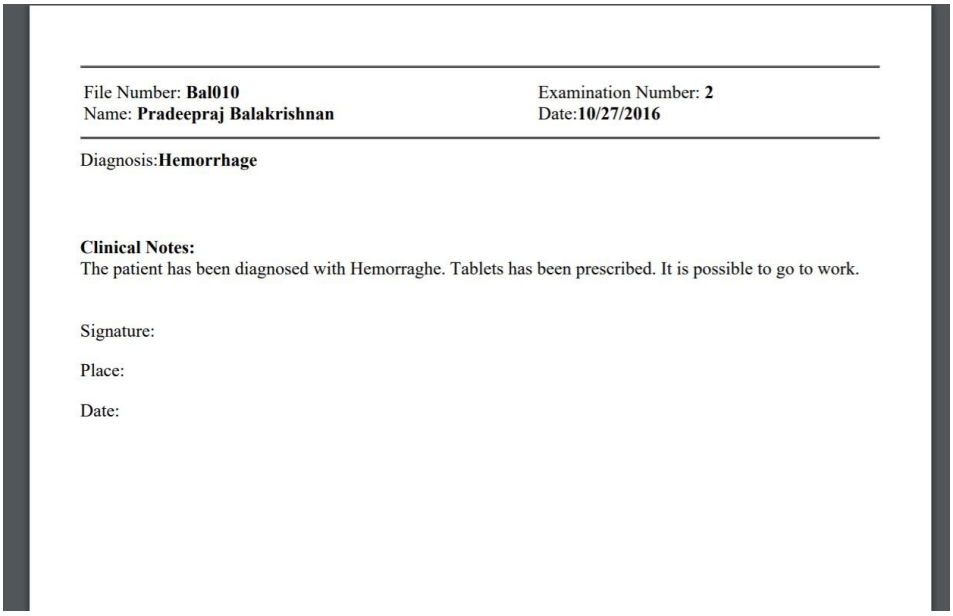


Figure 46: Retinal image search.

As already told retinal images are saved in separate folder and the path is given to database for easy fetching of the records. “Images” is the parent folder inside this RetinalArchive and Trash folder.

This folder has details of file number, left or right eye image, date. If the records are deleted, it will be in trash folder, from folder these images are retrieved whenever needed.

Figure 46 show the outline of the examination adding page with previous visit image details. Once patient diagnosed with ocular disorder, user will add clinical notes. This information can export as pdf for printing or sharing via email for referring out. Below figure 47 is the result of exported document with clinical notes.



File Number: **Bal010**
Name: **Pradeepraj Balakrishnan**

Examination Number: **2**
Date:**10/27/2016**

Diagnosis:**Hemorrhage**

Clinical Notes:
The patient has been diagnosed with Hemorraghe. Tablets has been prescribed. It is possible to go to work.

Signature:

Place:

Date:

Figure 47: Exporting file for printing.

Finally, discussion about the statistical analyse of retinal records in the web application. As mentioned in previous chapter histogram function is used to visualize statistical representation based on categories.

Figure 48 is result of histogram, for sample I have displayed the number of patients per diagnosis visualization. Like this histogram function can per for other two category as I mention earlier.

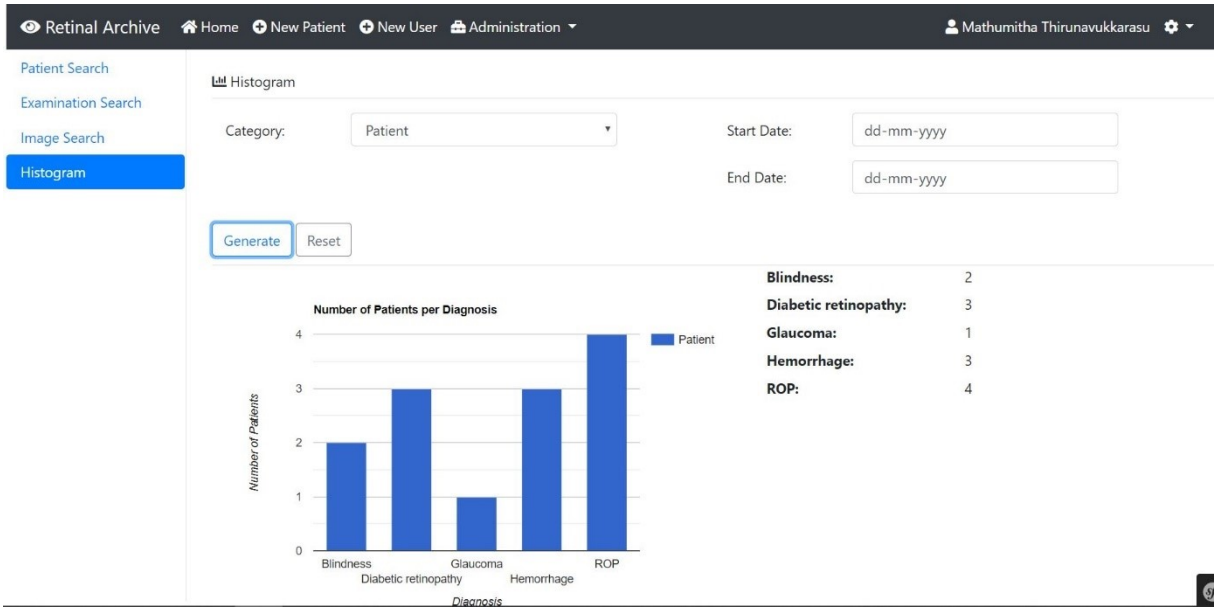


Figure 48: Histogram and Statistics.

Web application is developed and the results of the functionalities are explained in this chapter. It met the all requirements of the software development proposal.

10. CONCLUSION

As I discussed above study of literature dealing with the retinal imaging methods and technical specification, principle and analysis of digital imaging system RetCam 3 for diagnostic of the retinal diseases are explained.

Theoretical proposal of Software application for archiving of the retinal records from the RetCam 3. Information about the proposal and realization of a database containing the retinal records, associated clinical parameters and technical aspects of the retinal records from the RetCam 3 are explained.

Design and realization of the software application for visualization and editing of the retinal records from the RetCam 3. Results of proposed and realization of advanced searching and sorting functions of the retinal images in the proposed software application, including the statistical analysis of individual clinical parameters and technical aspects of the retinal records are visualized

My Patient database software application which I developed is used to save the retinal records in the system or specified network. and the retinal records given to the database are easily retrieved. Retinal images from the retcam are stored. This software application is created to save, retrieve, edit, update, delete, export, statistical analysis of retinal images of patients. Usage and the results about the patient database software application are explained and discussed about the practical result of the patient database software application.

After that the testing of retinal records in the clinical practice. For testing retinal records with ROP and other data from the patient data are utilized. Practical results of software application with all user definable functions are successfully accomplished with real time retinal records.

I would conclude that web application was developed and tested with fulfilment of proposed requirements. All modules developed in the application are functioning properly.

11. FUTURE WORK

As I am discussed in above topic, retinal images are captured from the patient are stored in database. With the multiple table formation in the database, retinal images are retrieved with relevant details of the patient. Compare the retinal images of the patients taken at different dates. Analyse the retinal image for identification of disease or problem in the retinal image of the patient. This can be developed further with:

- User deletes.
- Password can be reset if user forgot password by email authentication.
- By clicking Diagnosis, it can fetch all patient records, who examined with it.
- Can resize the retinal image according to the space, by click on retinal image it will enlarge.
- Export file with selected retinal image.
- Export file for statistical representation.
- Can be hosted as a web application in a private/local network.
- The security feature can also be added to a database in order to protect data.
- Retinal image report can be internally shared within respective doctors via email.

REFERENCES

[1] DENG WENXIANG., 2013, Cuda K-Nn: application to the segmentation of the retinal vasculature within SD-OCT volumes of mice. MS (Master of Science) thesis, University of Iowa,

[2] AIELLO LLOYD PAUL, BECK ROY W., BRESSLER NEIL M., BROWNING DAVID J., CHALAM K.V., DAVIS MATTHEW, FERRIS FREDERICK L., GLASSMAN ADAM R., MATURI RAJ K., STOCKDALE CYNTHIA R. and TOPPING TREXLER M., 2011, Rationale for the Diabetic Retinopathy Clinical Research Network Treatment Protocol for Center-Involved Diabetic Macular Edema. *Ophthalmology*. 2011. Vol. 118, no. 12, p. e5-e14. DOI 10.1016/j.ophtha.2011.09.058. Elsevier BV

[3] SIM DAWN A., KEANE PEARSE A., TUFAIL ADNAN, EGAN CATHERINE A., AIELLO LLOYD PAUL and SILVA PAOLO S., 2015, Automated Retinal Image Analysis for Diabetic Retinopathy in Telemedicine. *Current Diabetes Reports*. 2015. Vol. 15, no. 3. DOI 10.1007/s11892-015-0577-6. Springer Science and Business Media LLC

[4] JANNEY.J, B., DIVAKARAN, S., ABRAHAM, S., G, M. AND G, U., 2015, Detection and classification of exudates in retinal image using image processing techniques. [online]. 2015. Availablefrom:https://www.researchgate.net/publication/283751285_Detection_and_classification_of_exudates_in_retinal_image_using_image_processing_techniques

[5] online: available https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4512601/

[6] Hageman, G. S., Gehrs, K., Johnson, L. V. & Anderson, D. in Webvision: The Organization of the Retina and Visual System (Univ. Utah Health Sciences Center, 1995).

[7] Ogden TE. Retina: basic science and inherited retinal disease. Vol. 1. St. Louis: The CV Mosby Co.; 1989

[8] Kolb H, Fernandez E, Nelson R, Jones BW. Webvision: Organization of the retina and visual system. 2005

[9] online: available www.natus.com/ RetCam3 brochure_EU_low.pdf

[10] online: available https://www.retina-labs.com/understanding-diabetic-retinopathy/

[11] online: available https://www.stackoverflow.com/

[12] online: available https://www.symfony.com/

[13] online: available https://www.developers.google.com/chart

[14] online: available https://www.fontawesome.com/icons

[15] online: available https://www.w3schools.com/

[16] online: available https://ourcodeworld.com/articles/read/799/how-to-create-a-pdf-from-html-in-symfony-4-using-dompdf

[17] Huang D, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W, et al. Optical coherence tomography. Science 1991.

[18] Krebs, I. Noemi Lois and John V. Forrester: Fundus Autofluorescence. Graefes Arch Clin Exp Ophthalmol. 249, 309 (2011). https://doi.org/10.1007/s00417-010-1330-0

[19] SCHMITZ-VALCKENBERG, STEFFEN, HOLZ, FRANK G., BIRD, ALAN C. and SPAIDE, RICHARD F., 2008, FUNDUS AUTOFLUORESCENCE IMAGING. *Retina*. 2008. Vol. 28, no. 3, p. 385-409. DOI 10.1097/iae.0b013e318164a907. Ovid Technologies (Wolters Kluwer Health)

[20]ZAHRAN, YAZAN, 2015, How to Read Fluorescein Angiography. *Advances in Ophthalmology & Visual System*. 2015. Vol. 2, no. 4. DOI 10.15406/aovs.2015.02.00054. MedCrave Group, LLC

[21]GIBSON, J M, 2006, The Sankara Nethralaya atlas of fundus fluorescein angiography. *Eye*. 2006. Vol. 20, no. 12, p. 1492-1492. DOI 10.1038/sj.eye.6702135. Springer Science and Business Media LLC

[22]GARG., DR.RAJVEER, 2016, Role of computed tomography and magnetic resonance imaging in evaluation of orbital lesions. *International Journal of Advanced Research*. 2016. Vol. 4, no. 6, p. 1812-1822. DOI 10.21474/ijar01/646. International Journal Of Advanced Research

[23]BYRNE, SANDRA FRAZIER and GREEN, RONALD L, 2002, *Ultrasound of the eye and orbit*. 2. New Delhi, India : Jaypee Brothers Medical Publishers.

[24]HICKMAN S.J., TOOSY A.T., MISZKIEL K.A., JONES S.J., ALTMANN D.R., MACMANUS D.G., PLANT G.T., THOMPSON A.J. and MILLER D.H., 2004, Visual recovery following acute optic neuritis. *Journal of Neurology*. 2004. Vol. 251, no. 8. DOI 10.1007/s00415-004-0477-1. Springer Science and Business Media LLC

[25]MARX, JM, HOCKBERGER, RS and WALLS, RM, 2003, Rosen's Emergency Medicine: Concepts and Clinical Practice, Fifth Edition. *Annals of Emergency Medicine*. 2003. Vol. 41, no. 5, p. 769-770. DOI 10.1016/s0196-0644(03)90209-4. Elsevier BV

[26]BOWLING, BRAD and KANSKI, JACK J, 2016, *Kanski's clinical ophthalmology*. 8. Philadelphia : Elsevier.

[27]AKITA, KOICHIRO and KUGA, HIDEKI, 1982, A computer method of understanding ocular fundus images. *Pattern Recognition*. 1982. Vol. 15, no. 6, p. 431-443. DOI 10.1016/0031-3203(82)90022-x. Elsevier BV

[28]SONKA, MILAN, HLAVAC, VACLAV and BOYLE, ROGER, 1997, *Image processing, analysis, and machine vision*. 2. pacific grove.

[29]LEE, RYAN, WONG, TIEN Y. and SABANAYAGAM, CHARUMATHI, 2015, Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye and Vision*. 2015. Vol. 2, no. 1. DOI 10.1186/s40662-015-0026-2. Springer Science and Business Media LLC

[30]] DATE, C. J. An introduction to database systems. 8th ed. Boston: Pearson/Addison Wesley, 2004. ISBN 0-321-19784-4

[31]GARCIA-MOLINA, Hector, Jeffrey D ULLMAN a Jennifer WIDOM. Database systems: the complete book. 2nd ed. Upper Saddle River, N.J.: Pearson Prentice Hall, c2009. ISBN 978-0-13-187325-4.

[32]RYAN, Stephen, et al. Retina. 5th ed. London: Saunders/Elsevier, 2013. eISBN 978-1455737802.

[33]SONKA, MILAN, HLAVAC, VACLAV and BOYLE, ROGER, 2008, *Image processing, analysis, and machine vision*. 8. toronto canada : thomas enginering.