DIAGNOSTIC PERFORMANCE OF DRY EYE TESTS IN PRIMARY SJOGREN'S SYNDROME PATIENTS IN INDIAN SETTING

DISSERTATION SUBMITTED TOWARDS FULFILLMENT OF

THE RULES AND REGULATIONS FOR THE M.S. BRANCH III

OPHTHALMOLOGY EXAMINATION OF

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

TO BE HELD IN APRIL, 2015

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SUBMITTED BY

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BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled **"Diagnostic performance of dry eye tests in primary Sjogren's syndrome patients in an Indian setting"** done towards fulfillment of the requirements of the Tamil Nadu Dr MGR Medical University**,** Chennai for MS Branch III Ophthalmology examination to be conducted in April 2015, is the bonafide original work of Dr. Roma Johri, Post Graduate student in Ophthalmology, Christian Medical College, Vellore.

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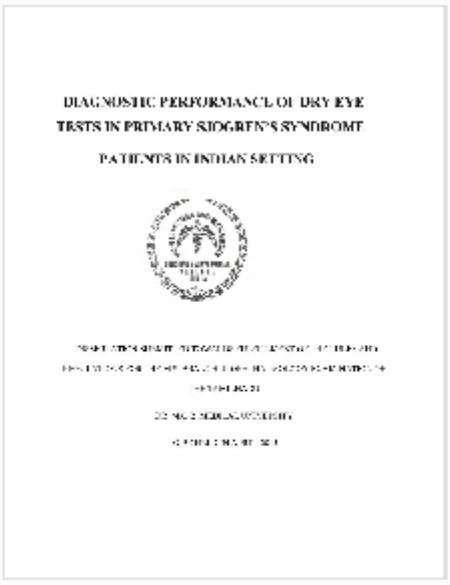

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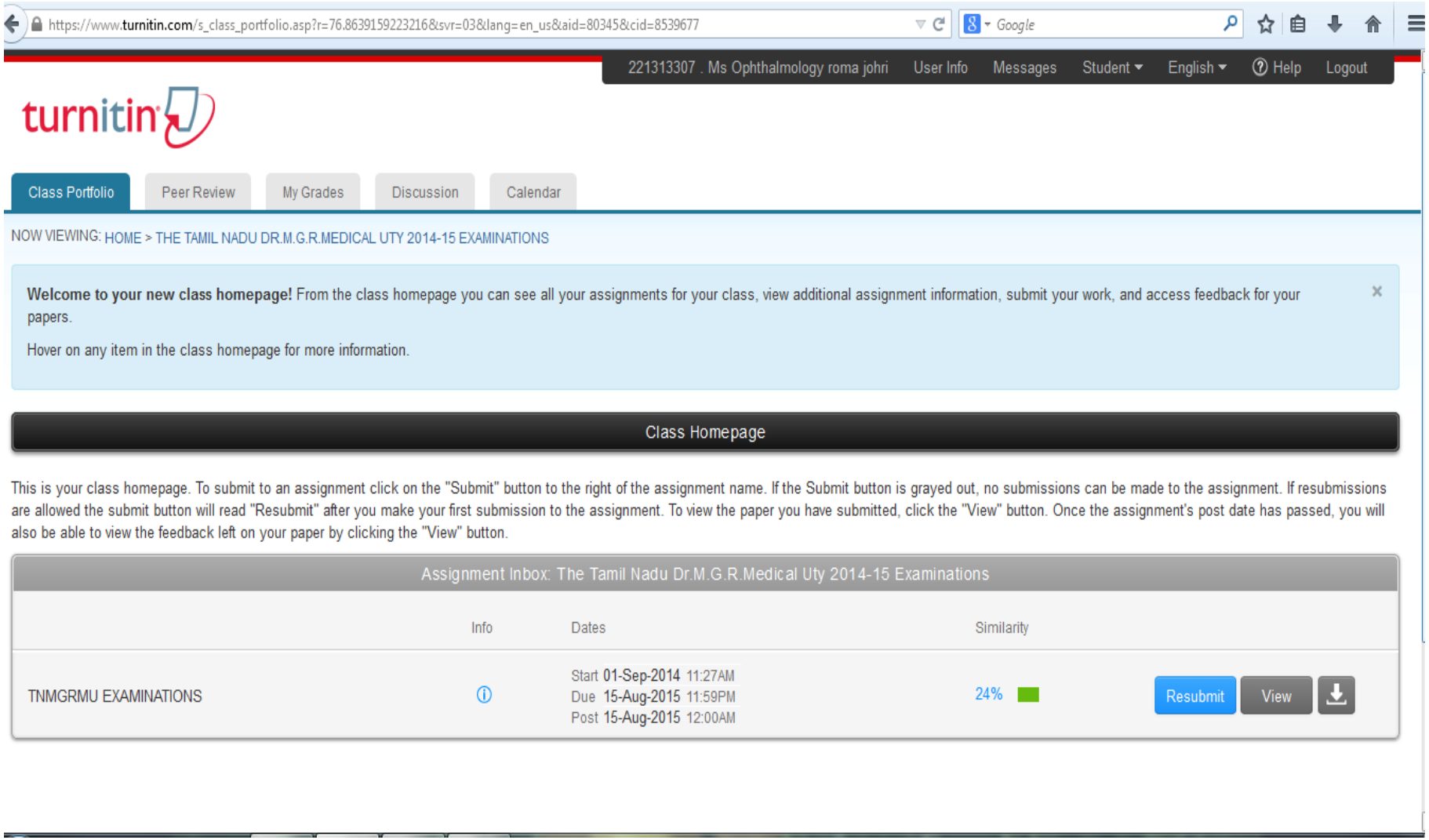
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INTRODUCTION

INTRODUCTION

Sjøgren syndrome (SS) is a chronic autoimmune disease of unknown etiology, that affects exocrine glands, mainly salivary and lacrimal with marked mononuclear cell infiltrate leading to progressive impairment of gland function(1)(2). It commonly presents as xerostomia and xerophthalmia.

According to American- European Consensus Group (AECG), the prevalence of primary Sjogren's syndrome (pSS) is about 0.2%. It mainly affects women, with male to female ratio of 1:9 (3).The peak incidence is seen in fourth to fifth decade. The pathogenesis is multifactorial including environmental, viral and genetic association with HLA DR haplotype.

Systematic multidisciplinary approach is required in proper evaluation of Sjogren's syndrome, which includes assessment of the oral, ocular and systemic components of the disease. Numerous criteria have been proposed till now to facilitate the diagnosis of SS and no consensus has yet been reached, even though the need for a definitive set of diagnostic criteria is widely recognized.

Its diagnosis is with help of clinical signs and symptoms of dry mouth and dry eyes along with positive test for antibodies to anti-SS-A and anti- SS-B antigen or positive salivary gland biopsy, which characteristically shows focal lymphocytic infiltration. Labial biopsy which form major diagnostic tool is a painful procedure with small but significant proportion of unreliable results.

Ocular surface is considered as an integrated unit and any dysfunction results in scarce or unstablity of the preocular tear film. Various criteria have been proposed to diagnose SS, but none has reached a general consensus. Modified AECG (American

European Consensus Group) criteria(4) includes dry eye tests like Schirmer I test and vital dye staining (Rose Bengal, fluorescein)(5). The ocular staining score (OSS) which uses lissamine green dye to grade the conjunctiva and fluorescein dye to grade the cornea is included in ACR (American college of Rheumatology association) classification criteria(6). Lissamine stain causes less ocular irritation than Rose Bengal(7).

In our study subjective symptoms of patients suspected of pSS will be assessed by validated of OSDI (Ocular Surface Disease Index) questionnaire(8)(9). The purpose of this study is to evaluate the diagnostic performance of Schirmer I test, TBUT and OSS test in pSS patients by assessing the sensitivity, specificity and likelihood ratio of each test performed. This study also aims to correlate between ocular symptoms, signs, immunological variables and labial salivary gland biopsy. Schirmer I of 5mm or less in 5 mins, TBUT of less than 10 secs and OSS score of 3 or above will be considered as abnormal.

AIMS AND OBJECTIVE

AIMS AND OBJECTIVE

1. To evaluate the diagnostic performance of Schirmer I test, Tear film break-up time (TBUT) and Ocular staining score (OSS) test in Primary Sjogren's syndrome patients in an Indian setting.

2. To analyze the correlation between ocular symptoms, signs, immunological variables and labial salivary gland biopsy.

MATERIALS AND METHODS

MATERIALS AND METHODS

Study design: Cross sectional, observational study

Study settings: Department of Ophthalmology, Christian Medical College, Vellore

Study population:

This study was conducted over a period of 7 months (February 2014 – August 2014) in Department of Ophthalmology, Christian Medical College, Vellore. Patients diagnosed of Primary Sjogren's syndrome or clinically suspected of Primary Sjogren's syndrome (pSS) with their pathology and immunology reports awaited for confirmatory diagnosis as per ACR criteria, were referred from Rheumatology outpatient clinic to Department of Ophthalmology. All patients with established diagnosis of pSS who satisfied the inclusion criteria were included in the study.

Inclusion Criteria:

- Patients diagnosed as Primary Sjogren's syndrome (pSS) with age above 18 years.
- Patient who are willing to participate in the study and sign the informed consent.

Exclusion Criteria:

- Patient in whom diagnosis of primary Sjogren's syndrome (pSS) has been excluded.
- Patient with other connective tissue disorders.
- Past head and neck radiation treatment.
- Current treatment with daily eye drops for glaucoma.

- Corneal surgery in last 5 years to correct vision.
- Cosmetic eyelid surgery in last 5 years.
- Contact lens wearer
- Physical or mental condition interfering with successful participation in the study.
- Pregnancy

Informed consent

Informed consent was obtained from all patients included in the study. The consent form attached as Appendix 2. Institutional Research Board (IRB) approval was obtained from the institution for the conduct of the study **(IRB Min .No. 8671 dated 19.2.14)**

Methods

All patients diagnosed of Primary Sjogren's syndrome or clinically suspected of Primary Sjogren's syndrome (pSS) with their pathology and immunology reports awaited for confirmatory diagnosis as per ACR criteria, were referred from Rheumatology outpatient clinic to Department of Ophthalmology

All patients were asked to stop artificial tear eye drops for 1 day prior to ophthalmology examination. Patient presenting to Schell Eye Hospital were recruited, explained about the nature and intent of the study and informed consent were taken.

Patient were asked to fill a validated questionnaire (Ocular surface disease index) OSDI including 12 questions, related to their subjective symptom felt the week before. Total score was noted. Schirmer I was done by using sterile Schirmer strips without anaesthesia and amount of wetting after 5min was noted in each eye tested.

Fluorescein dye was instilled to determine TBUT and time between last blink and the first appearance of randomly appearing dry spot was noted for each eye. Grading of the corneal flourescein staining pattern (Step 1 of Ocular SICCA grading) was done.

Anterior segment evaluation was conducted with slit lamp bio microscope. Grading of conjunctival lissamine green staining pattern (Step 2 of Ocular SICCA) was done. Total OSS for each eye was calculated after summation of corneal fluorescein score and conjunctival lissamine green score for the nasal and temporal bulbar conjunctiva.

Schirmer I Test (without anaesthesia):

It was done before any drops are instilled in the eye. By using sterile Schirmer strip (ContaCare Ophthalmic) bent at the notch and placed carefully at the junction of outer and middle one-third of inferior fornix of both eyes. Patient was instructed to keep both eyes open. Wetting of strip was measured in millimeter after 5mins. A value of less than 5mm was considered as abnormal.

Tear break-up time (TBUT):

It was done after 2 minutes of placing fluorescein dye strip moistened with a drop of saline in inferior fornix. With 10x magnification, high illumination and using cobalt blue filter over the light source. The patient was asked to blink and then keep his/her eyes open.

The TBUT, defined as the time in seconds between patient's last blink and first appearance of random dry spot on the corneal surface, is measured 3 times and mean value was recorded. TBUT of less than 10 seconds was considered as abnormal.

Corneal Fluorescein Staining Pattern (Step 1 of ocular SICCA grading):

Each cornea was examined at slit lamp by using cobalt blue filter. It was a time sensitive and dynamic process therefore to ensure reproducibility grading was initiated between 4-8 minutes following instillation of fluorescein.

PEEs that stain cornea are counted and scored

Grading was done as below:

No PEEs means score 0

1-5 PEEs means score 1

6-30 PEEs means score 2

>30 PEEs means score 3

Additional point were added if

1. PEE occurred in the central part of 4mm diameter portion of the cornea.
2. 1 or more filaments are seen anywhere on the surface of the cornea.
3. 1 or more patches of confluent staining, including linear staining pattern are found anywhere on the cornea.

The total fluorescein score for the cornea was noted in OSS 1. (Maximum score-6)

External eye examination at Slit Lamp:

It was performed before application of lissamine green. The slit amp with same magnification but decreased illumination using a neutral density filter abnormalities of lids, conjunctiva and cornea were noted.

Conjunctival lissamine green staining pattern (step 2 of the ocular SICCA grading):

Lissamine green strip moistened with a drop of saline was applied to the inferior conjunctival fornix of each eye. Make the patient blink several times to prevent dye from pooling in the conjunctival folds. The conjunctiva was examined immediately with the slit lamp using 10x magnification and neutral density filter. Grading

0-9 dots of staining with lissamine in the interpalpebral bulbar conjunctiva –> score 0

10-32 dots –> score 1

33-100 dots –> score 2

>100 dots –> score 3

Because of difficulty in counting individual dots in the moving eye on the slit lamp, any area of confluent staining of more than 4mm sq or more is considered to be more than 100 dots.

Nasal and temporal areas of the conjunctiva were graded separately. (OSS 2)

Maximum score will be 3 for each area. Total maximum score of 6 for each eye.

The total OSS for each eye was summation of corneal and conjunctival staining. Therefore, the maximum possible score for each eye was 12. The eyes were graded separately and recorded. OSS score more than 3 was considered as abnormal.

Detailed diagrammatic Algorithm of the study

Patients diagnosed of Primary Sjogren's syndrome or clinically suspected of Primary Sjogren's syndrome (pSS) with their pathology and immunology reports awaited for confirmatory diagnosis as per ACR criteria, were referred from Rheumatology outpatient clinic to Department of Ophthalmology

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Result of the test were analysed and correlated with labial biopsy report and immunological variables. Data was evaluated for diagnostic performance of each test with appropriate statistical analysis

Statistical method used:

Formula: $$n = \frac{Z^2_{\alpha/2} * P * Q}{d^2}$$

where, P = sensitivity of test = 72%

Q = 100 – P

d = precision = 10%

= 95% confidence interval

77 subjects with Sjogren's syndrome and 77 normals with

10% precision and 95% confidence limits

Analysis:

All the data contained in the proforma were entered into an epidata format. For non parametric data the descriptive statistic applied were analysed by Interquartile range (IQR), that is by analysis of median and 25-75 percentiles. Data were statistically evaluated by applying the Statistical Package for the Social Science (SPSS) for windows 17.0 for the independent sample t-test, Mann-Whitney U-test for comparison of Schirmer's I test, Tear-breakup time (TBUT), OSS (ocular surface staining) in Primary Sjogren's syndrome (pSS) and Non Sjogren syndrome group(Non SS). Significant results values for less than 0.05 were considered as statistically significant. Patients were grouped as follows after analysis:

SS group: Patients diagnosed of Primary Sjogren's syndrome as per ACR criteria

Non SS group: Patients clinically suspected of Primary Sjogren's syndrome, but who did not fulfill ACR criteria.

The prevalence of pSS (the proportion of the patients who have disease in the population under testing) was calculated by using population included in our study as a reference. Each of dry eye test performed were analysed for sensitivity (the percentage of those symptomatic patients who are positive for the test, a high sensitivity means that a negative test can rule out the disease) and specificity (the percentage of normal subjects who were test negative, a large specificity means that a positive test can rule in the disease). Specificity and sensitivity were calculated comparing pSS and Non SS patients. All data were processed in order to calculate Receiver-Operating characteristics curves (ROC). This curve will give the diagnostic exactness of a particular test variable by plotting the sensitivity of test against the specificity at all possible thresholds.

Assessment of Cutoff Values with the ROC Procedure

According to the ROC procedure, optimal cutoff value is usually chosen as the hinge point of the curve between sensitivity and specificity for each of the observed values in the study population.

In the description of box plot summary of the medium ± SD of the values resulted from the study, collected from each group of patients. Data shown in separate figures corresponds to the range min-max values (bounded with lines), results values ranging from 25% to 75% and median is shown as black lines, from each group of patients.

We also calculated the likelihood ratio, a measure that combines information about sensitivity and specificity, and gives a direct valuation of how much a positive or negative result can change the likelihood that a patient would have the disease, to summarize data about diagnostic tests. Positive likelihood ratio (LR+) suggests the increase chances of having a disease if the test is positive and is given by sensitivity divided by 1- specificity.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Sjøgren syndrome (SS) is a chronic autoimmune disease of unknown etiology, which affects exocrine glands, mainly salivary and lacrimal with marked mononuclear cell infiltrate leading to progressive impairment of gland function(1)(2). It is named after a Swedish ophthalmologist Sir Henrik Sjogren (1899-1986) who described it first. It commonly presents as xerostomia and xerophthalmia.It can either present alone as primary Sjogren's syndrome (pSS) or as secondary Sjogren's syndrome (sSS) when associated with an other underlying connective tissue disorder like Rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE).

Prevalence:

Out of the two to four million persons in United States having SS, one million have an established diagnosis (10). The disease remains undiagnosed in most of the cases because of the nonspecific nature and heterogeneity of its clinical manifestations.

According to AECG, the prevalence of primary Sjogren's syndrome (pSS) is approximately 0.2%. It mainly affects women, with male to female ratio of 1:9 (3). This can be due to effect of sex hormones. Oestrogen has immune stimulating role whereas androgens acts as immune suppressor. It can present in any age group but the peak incidence is seen in fourth to fifth decade of life. Approximately 60% of SS patients have disease secondary to an underlying accompanying with autoimmune disorder such as rheumatoid arthritis (RA), systemic sclerosis or systemic lupus erythematosus (SLE). In some studies from Rheumatology clinics, it is shown that about 25% of the patients with SLE or RA have the histologic evidence of the SS(11) .

In India Primary Sjogren's syndrome is rarely reported as studied by Misra et al (12)in tertiary care rheumatology clinic even though the clinical and immunological profiles were similar to those seen in Western countries.

Genetics:

Familial clustering of various autoimmune diseases and the co-association of other autoimmune diseases in individuals has been frequently reported. Relatives of SS patient are commonly found to have other autoimmune diseases (30%)(13). The polymorphicity of gene like major histocompatibility complex (MHC) are one of the major genetic risk factors for development of autoimmune diseases(14). In SS, DRB1*0301-DQB1*0201-DQA1*0501 haplotypes are the major risk factors for formation of an anti-SSA/SSB response and to the development of the disease. The protective factors were DQA1*02:01, DQA1*03:01 and DQB1*05:01 alleles(15).

Pathogenesis:

The pathogenesis is multifactorial including environmental, viral and genetic association with HLA DR haplotype.

The chronic immune system stimulation play a central role in pathogenesis as demonstrated by several indices of immunological hyper-activity, including various autoantibodies, like anti-Ro/SS-A (anti-Ro) and anti-La/SS-B (anti-La). The exact mechanism of the underlying humoral and cellular autoimmune reactions is unknown. Both T and B lymphocytes play a role in its pathogenesis. Increased activity of B cell is depicted as hypergammaglobulinemia and the circulating auto antibodies. Organ specific auto antibodies are produced against the cellular antigens seen in the salivary ducts, nerve cells, thyroid gland, erythrocytes, gastric mucosa, pancreas and the prostate. In approximately 60% of the patients with SS non organ specific auto antibodies are seen.

These auto antibodies include antibodies to the small RNA protein complexes, which include SS-A and SS-B, rheumatoid factor and antinuclear antibodies. These auto antibodies contribute to tissue dysfunction before the inflammation is evident(16).

The histopathological picture of Sjogren's syndrome reflects periductal sialoadenitis characterized by focal lymphocytic aggregate around the glandular ducts including the salivary glands, lacrimal glands and exocrine glands of the respiratory and the gastrointestinal tracts and the vagina. Infiltrate consists of T cells, B cells and the plasma cells, with predominant activated $CD4^+$ helper T cells. T cells produces interleukin (IL)-2, 4, 6, 1, and the tumor necrosis factor (TNF) (17). This suggests that there is immune mediated destruction of the exocrine glands in patients with pSS.

Nearly 20% of the infiltrates consists of B cells. These locally produce immunoglobulins. These immunoglobulin have auto antibody reactivity(18). Ultimately, these infiltrate will extend to occupy entire acinar epithelium, leading to dysfunction of glands and manifesting as dry eye and dry mouth and major salivary gland enlargement(19).

'Benign lymphoepithelial lesions' are defined as absence of clinical and serological features of SS, with association of some morphological alteration such as 'epimyoepithelial sialoadenitis'.

The infiltrate in the acinar epithelium, leads to abnormal function of the glands which presents as sicca features and enlarged major salivary gland(19). The inflammatory processes of pSS occur mainly through glandular epithelial cells. These cells presents antigen presenting proteins. These cells can promote adhesion, and co-stimulate T lymphocytes. Antigen-presenting function of epithelial cells is increased by cytokines like interferon IFN -γ and TNF-α may help in the function of antigen presentation of epithelial cell. IFN-γ induces apoptosis of the salivary gland epithelial

cells (SGECs). This is by increased-regulation of the Fas protein. Fas protein is a cell surface receptor. Its activation leads to apoptosis(20), a programmed cell death. The expression of the CD40 protein is high in cells of patients with SS than in normal control group. CD40 can also be induced in SGECs by IFN-γ and IL-1B(21). SGECs have important role in induction and the maintenance of the lymphocytic infiltrates in patients with SS(10).

According to a study(22), the sera of SS patients have the impaired capacity to degrade secondary necrotic cell remnants (SNEC) and deficiency of endonuclease DNase 1 activity. Their study concluded that after cell necrosis, immune system of SS patients may be extremely exposed to necrotic debris and play a major role in autoimmune and inflammatory reactions seen in this disease.

Apart from anti SSA and anti SSB, the newer antibody, anti-salivary gland protein (SP1) has been identified in Sjogren's syndrome patients(23).

Autoimmune antibodies:

Anti SS-A and Anti SS-B antibodies

Auto antibodies in the pSS are mainly against the Sjogrens autoantigens SS-A and SS-B and against IgG rheumatoid factor. The SS-A and SS-B autoantigens consist of many antigenic proteins which are coupled to small RNA molecules. These RNA-protein molecules are seen in all human cells. These autoantibodies can be detected using counter-immunoelectrophoresis, immunoblotting technique, ELISA or RNA precipitation assays. Counter-immunoelectrophoresis is mainly used for anti SSA antibodies and immunoblotting technique is used for anti SSB. 60-70 percentage of

patients with SS have anti SSA but they are not specific indicator of the disease. 40-50 percentage of patients with pSS have anti SSB which are more specific than anti SSA. The auto antibodies may be the product of an oligoclonal B-cell proliferation and its pathogenic role and origin in pSS is still controversial.

In patients with the multisystem autoimmune disease like pSS auto antibodies are classified into 2 major groups; auto antibodies to DNA and non DNA antigens. The non DNA antigens include antinuclear antibodies to the extractable or soluble nuclear antigens (which has small ribonucleic acid that is (RNA) connected to non histone proteins). Three main categories includes: the U group including U1–U6 small nuclear RNAs, the Ro group and the La group.

The Ro/SSA antigen consist of a 60kDa protein and has small nucleocytoplasmic RNA protein complex (hY1, hY3, hY4, hY5)(24). The La/SSB antigen acts as termination factor for RNA formation and is of 48kDa protein(25).

The finding of serum antibodies which are directed against the muscarinic M3 receptor gives advance understanding in the pathogenesis of not only glandular dysfunction but also related features of autonomic dysfunction in some patients(26).

The presence of Ro or SSA and La or SSB auto antibodies in serum is suggestive of early onset , longer disease duration and extra glandular disease manifestations like splenomegaly or lymphadenopathy, vasculitis, purpura, lymphocytic infiltration of the labial salivary glands and recurrent parotid gland enlargement(27)(28)(29)(30).

Pourmand *et al*(31) had reported a poor correlation between the serum titres of IgA antibodies and SS-A and SS-B antigens and the oral and ocular sicca symptoms.

Hammi et al (32) conducted a study on 40 patients and 20 healthy controls who met the 1993 criteria ofEuropean community and who were age and sex matched with no sign or symptom of the disease. The sample of their serum as well as saliva was measured with the help of AffiniTech SSA or Ro and SSB or La antibodies kit. They also compared the result with serological value of SS-A and SSB done by an independent clinical laboratory. In their study it was found that serum detection of SSA/Ro and SSB/La was more significant than saliva ($p=0.001$). They found good agreement among the results with AffiniTech Kit and independent laboratory ($p<0.001$) but poor agreement between serum and saliva results ($p=0.168$).

Hansen et al(33) conducted a study for detection of serum antibodies against SSA/Ro and SSB/La in 103 blood donor. They found that in patients with the primary Sjogren's syndrome who were verified by Copenhagen criteria, 67% were found to have Ig G anti SSB antibodies and 71% were found to have anti SSA antibodies. They also noticed that all patients who had anti SSB antibodies also showed the presence of anti SSA antibodies. The clinical manifestations of pseudolymphoma, Raynaud's phenomenon, fatigue and arthralgia, were more common in patients with anti-SS-B/La and/or -SS-A/Ro antibodies.

Toker et al(34) investigated the presence of the anti SSA and anti SSB antibodies in the tears of patients with Sjogren's syndrome and association of these antibodies with worsening of keratoconjunctivitis sicca. He included 28 patients with Sjogren's syndrome with 17 normal controls and evaluated tear fluid and sera level with the help of enzyme linked with immunosorbent assay kit designed for the quantification of IgG class autoantibodies directed against highly purified SSA and SSB antigens. They found that 57.1% of SS patients showed increased level of anti SSA, whereas 50% of

patients were found to have anti SSB in sera. 6 patients have anti SSA in tear fluid, out of which 1 was negative for serum antibodies. 10 patients have anti SSB in tear fluid.

The positive correlation was found between serum and in tear fluid anti SSA and also also between serum antibodies and dry eye symptoms score. He suggested the possible contribution of these autoantibodies (anti Ro level and anti La) in serum or tear fluid to the pathogenesis and severity of the disease.

Kessel et al (35)investigated and found that anti Ro or La antibodies are good substitute to invasive salivary gland biopsy in the patients suspected of suffering from Sjogren's syndrome.

Minor salivary gland biopsy:

Labial biopsy is very specific test for assessment of the salivary component of pSS. After the procedure patient may have temporary soreness, but there will be fast healing without much scarring. Focal lymphocytic sialadenitis is characteristic histopathologic feature of SS. It is defined as multiple, dense aggregates of more than 1 focus (50 lymphocytes) in the perivascular area or periductal area in the most of sample of glands. In patients who are suspected to have persistant swelling of parotid gland due to lymphoma, parotid biopsy can be done.

Nakamura et al(36) did a retrospective study by selecting 112 minor salivary gland biopsy(MSGB) cases who fulfilled AECG criteria .He classified the subject into 63 primary SS with 49 non SS group. With the help of multiple logistic regression analysis the diagnosis of the primary Sjogren's syndrome was associated with positive.

Minor salivary gland (MSGB) biopsy (odds ratio (OR) of 105; 95% CI 13, 849), positive anti-SSA or Ro antibody (OR 96; 95% CI 10, 923) and the existence of dry eye

(OR 8, 95% CI 2, 43). Among the components of the AECG criteria, the major contributors are MSGB and anti-SSA/Ro antibody.

The abnormal finding seen is positive rate in sialography significantly correlated with the MSGB grading (P-value for trend = 0.0006), whereas other subjective and the objective components were not found to be associated with MSGB grading.

Guellec et al (37) did systematic review of studies from Pubmed and Embase and analysed the sensitivity and specificity of MSGB in pSS. The sensitivity ranges from 63.5% to 93.7% and specificity ranges from 61.2% to 100%.They failed to find the information about the diagnostic role of biopsy as some studies used a set of criteria which include MSGB to diagnose pSS.

Clinical Features:

It typically manifest as dry eyes (xerophthalmia or keratoconjunctivitis sicca (KCS)) and with dry mouth (xerostomia). KCS presents insidiously over a period of several years.

30-70% of patients presents with systemic involvement before or after the diagnosis of this autoimmune disease and mostly associated with increased level of anti-Ro/La antibodies compared to sicca-limited group.

Most extraglandular manifestations are presumed to be due to ‘autoimmune epithelitis’ as autoimmune system mainly affects the epithelial cells. Its pathogenesis can also be due to vasculitis and/or immune complex deposition, complement activation as in skin vasculitis, glomerulonephritis and peripheral neuropathy.

Oral manifestation:

Most of the patients with pSS may not complain of oral dryness, despite xerostomia being the most common presentation. Patient may have cracks, soreness, difficulty in eating, problem with denture or unpleasant taste. Xerostomia can give rise to difficulties to swallow very dry foods without fluid, and need for frequent sips of liquid or water, especially at night.

Antimicrobial properties of saliva are lost which may increase dental caries and make the patient prone to oral candidiasis, tooth decay and periodontal infections. Swelling of parotids and other xeroses, such as dryness of the nose, throat, skin, and vaginal area, can often occur. In SS patients, salivary dysfunction leads to increase in number of *Lactobacillus* and *Candida* organisms.

With the progression of the disease oral mucosa become glazed, wrinkles formation start and tongue become depapillated and lobulated, taste buds become abnormal and there is plaque formation.

Change in quality of speech (clicking) is noted as because of dryness tongue get stuck to hard palate while speaking(38).Oral dryness can severly affects the quality of life, affecting the daily activities of living such as eating, sleeping and speaking.

Chronic or episodic salivary gland swelling which manifest as unilateral presentation in the beginning and later becoming bilateral, presents as tender swelling and sometimes trismus. This can lead to reduced salivary flow rates and increase risk of dental caries.

Ocular manifestation:

Most common ocular presentation of pSS is dry eye. Keratoconjunctivitis(KCS) presents insidiously over a period of several years. Patients of SS describe a 'gritty' feeling or 'sandy' feeling in eyes. It can also manifest as gritty sensation, itching, redness, soreness, photophobia, eye fatigue, discharge, decreased visual acuity and sticky lids.

Abnormal mucus component of the tear film and decreased secretion of tears cause collection of thick mucus secretion along inner canthus. Conjunctivitis, superficial corneal erosion and filamentary keratitis are the other presentation. Ocular complications includes opacification, vascularization, corneal ulceration and perforation (39).

Fatigue:

Main symptoms observed is severe debilitating fatigue seen in 50 % of patients with pSS. Patients do not feel refresh after sleep and it take a long time for them to get sleep. Cause of fatigue is unknown but can be due to subclinical hypothyroidism. 22% of patient with SS will have fibromyalgia but myositis is rarely seen(40)(41).

Pulmonary involvement:

Muciod secretions present in the upper and lower respiratory tract will decrease in patients with the SS, leading to dryness of the nasal tract, throat, and trachea; which may result in symptoms of chronic dry cough.

It is significant in 10% of the patients and presents as xerosis of nose, xerotrachea, interstitial pneumonitis, pseudolymphoma and fibrosis. Subclinical

pulmonary disease is seen in 30% of patients (42) as was seen on high resolution computerized tomography of chest. Even though disease may have component of small airway obstruction, the role of corticosteroid and beta agonist is still controversial.

Renal involvement:

Renal involvement mainly in the form of interstitial nephritis, which can appear earlier than sicca symptoms. Type I and II distal renal acidosis is most commonly observed manifestation. Patients may have glomerular lesion, proteinuria, hematuria and nephritic syndrome. The development of hypertension and renal insufficiency is due to renal vasculitis (10).

Skin involvement:

More than 50% of patients presents with dermatological manifestations as dry skin, angular chelitis, violaceous discolouration of digits, erythema annulare, chilblain lupus, palpable purpura and urticarial vasculitis.in a study 9 to 70% patients with pSS had vasculitis of small or medium sized vessels. Only 30% of pSS had mild Raynaud's phenomenon(39).

Patients of SS may presents with symptoms of dryness of skin, pruritis, hypersensitivity rashes and irritation.

Musculoskeletal involvement:

Intermittent asymmetrical joint pain of small joints is one of commonly reported symptoms in (53%) pSS . Joint deformity and erosion are not the usual manifestion but typical non erosive arthritis is commonly seen(43).

Gastrointestinal involvement:

Lymphocytic infiltration of intestine leads to malabsorption. Nausea, epigastric pains, dysphagia, esophageal dysmotility and gastritis are other manifestation of the disease. Hepatitis mainly autoimmune is found in 1.7% to 4% of pSS patients while autoimmune cholangitis is seen in 5 to 10% of patients(44). In patients with Hepatitis C infection, xerostomia is common manifestation but there is absence of dry eyes and autonatibodies (anti Ro/SSA).

Endocrine involvement:

Hashimoto thyroiditis is seen in approximately 20% of the patients and half of them have the subclinical hypothyroidism. Antibodies to thyroid peroxidase and level of thyroglobulin suggest the possibility of future development of thyroid disease.

Haematological involvement:

Malignanat lymphoproliferation is one of the initial or later manifestation of primary Sjogren's syndrome and pathogenesis behind this the expansion of monoclonal B cells. Localized low to intermediate grade lymphoma of B cell lineage is common malignancy seen in SS, and need to managed by combination of chemotherapy.

Neurological involvement:

Sensory polyneuropathies in form of sensory ataxia and small fibres sensory painful neuropathy, is one of the major neurological manifestation in pSS. Trigeminal and other cranial neuropathy, mononeuritis multiplexa and polyradiculopathy are the other neurological presentations. The cause for neuropathy van be due changesin the endoneurium microvessel.

Treatment:

Ocular involvement, manifested in the form of keratoconjunctivitis sicca, is treated with use of local and the systemic stimulators of tear secretion, tear moisture replacement like lubricant, methylcelluse inserts and supportive surgical procedures. Punctal occlusion either by temporary method (collagen or silicon plugs) or permanent method (electrocautery). Supportive measures include use of goggles or glasses with side chambers to prevent the existing moisture.

Treatment of the oral manifestations is done by intense oral hygiene, to prevent and treat oral infections, liberal use of saliva substitutes, and by local and systematic stimulation of salivary secretion. Cholinergic agents or secretogogues like, pilocarpine and use of cevimeline, will be helpful in patients with residual salivary function, and ocular drops like cyclosporin seems to be of use in some patients. Systemic therapy with immunosuppressives are used for the treatment of the severe extraglandular manifestations in Sjögren's syndrome.

Newer Anti-B-cell therapy is upcoming potential therapy for glandular and the extraglandular features, such as vasculitis or glomerulonephritis, in addition to the management of the lymphoma which are associated with Sjögren's syndrome. Induction

of the oral tolerance and newer gene transfer modalities are recently attempted in some animal models, with good results but their utility in humans is still debatable.

Prognosis:

The lymphoproliferative disease, primarily non-Hodgkin lymphoma is one of the most life threatening complication associated with the primary Sjögren syndrome. The risk of lymphoma is 40 times more in patients with the primary Sjögren syndrome than that in the general population. Various studies have shown lymphoma as a cause of death in pSS on long follow up(45)(46).

In some patients of Sjogren's syndrome who has few adverse prognostic factors like purpura, mixed monoclonal cryoglobulinemia and low level of C4 complement, will have more rate of mortality.

Tear Film and its role in Dry eye

As the importance of the objective tests for estimating ocular dryness has been proposed by 2012 criteria(47). So, correct evaluation of 'dry eye' becomes important in the investigation of the patients who are suspected case of the disease,SS.

Dry eye syndrome is a complex disorder usually referred as a qualitative and quantitative alteration of the tear film and patients report subjective symptoms of foreign body sensation, burning, itching, redness and photophobia(48). Over many years, research has been made in finding out the structural elements of tear film and integrity of ocular surface and ultimately to forming the updated concepts about the way in which tear film is formed, spread and maintained, and the physiological events leading to the development of dry eye.

The tear film is subdivided structurally into an anterior most lipid layer, a middle thick aqueous layer and an inner one mucin layer. Meibomian glands, goblet cells, lacrimal glands, and epithelial cells of the ocular surface help in formation of these layers. In the 1980s, the ocular surface was defined to be a functional unit of tear (lacrimal functional unit (LFU), whose components are then represented by the lacrimal gland, corneal and conjunctival epithelium and goblet cells, tear film and border of eyelid with meibomian glands.

Ocular surface is important for functioning of visual system and act like an interface between the outer environment and host. To maintain its functionality hydrodynamic factors like eyelid blinking and closure are essential. In 1995, 'dry eye syndrome' was described by the Dry Eye Study group (49) as a tear film pathology that occurs either due to decreased tear formation or increased evaporation. This leads to damage to interpalpebral ocular surface thereby causing various symptoms showing ocular discomfort.

According to DEWS study(Dry Eye Workshop) 2007 ,the dry eye syndrome is described as multifactorial disease of tear and the ocular surface that leads to symptoms like discomfort, visual disturbance, and tear film instability associated with potential damage to ocular surface itself. It can also lead to increase in osmolarity and inflammation of the tear film.

Tear film is an integrated dynamic system which shows response to pathologic events by change in quality and quantity of tear production, increasing proliferation and migration of the epithelial cells and by increasing conjunctival vessel permeability.

Dry eye is known to be a multifactorial disorder that involves various interacting mechanisms. Therefore dysfunction of any component can cause dry eye disease by alterations in the volume, its composition, the distribution, stability and also the

clearance of the tear film. Decreased tear production and epithelial damage along with increased osmolarity and instability plays major role. These events start itself as self-perpetuating and mutually reinforcing the complex global mechanisms, therefore leading to ocular surface inflammation and dry eye. These can be associated with abnormality in mucus part of tear film leading to ropy discharge. Small erosions on the surface of the cornea can be due to dessication. Infections by *Staphylococcus aureus* can cause conjunctivitis.

According to DEWS report (50), dry eye disease consists of two major part of etiopathogenic groups including evaporative dry eye and also the aqueous tear deficiency dry eye. Hyperevaporative dry eye can be caused due to intrinsic and extrinsic ocular causes. Among the evaporative causes, changes are seen in tear film composition, eyelid dysfunction, incomplete blinking or decreased blinking rate, ocular surface irregularities and drug action. Extrinsic cause includes vitamin A deficiency, topical drug preservatives, contact lens wear and ocular surface disease.

Among the aqueous tear deficient group dry eye can be subclassified as SS and non-SS syndrome groups. The latter group has various primary causes, includes absence of a lacrimal gland (congenital or acquired), impairment or dysfunction of the lacrimal gland, reflex block and drug action. Non-SS dry eye can be due to various conditions. SS dry eye is mostly due to the autoimmune inflammation in the lacrimal glands.

In majority of cases, instances of hyperevaporative and aqueous tear deficient dry eye are not so well described clinically but there exist some degree of overlap among the two groups. Therefore accurate classification becomes difficult. Subjective assessment and objective tests are the diagnostic tool which have clinical utility in tear film disorder(51).

The disease needs a multidisciplinary approach by an ophthalmologist including detailed clinical history about the symptomatology, accurate examination of the patient including eyelid anatomy and morphology, blink rate and laboratory tests to lead to a conclusive diagnosis. Since there is no perfect test to diagnose dry eyes, variety of tests singly as well as in combination are tried. The one which hold major weightage are Schirmer's test, Tear Break up time test (TBUT) and ocular surface staining score (OSS) test as these tests are easy to perform, sensitive and easily reproducible.

Dye used for staining the ocular surface includes fluorescein dye, Rose Bengal and lissamine green. Staining with Rose Bengal causes lot of irritation and discomfort to patient leading to its rare use. Lissamine green stain damaged epithelial cells and is very sensitive with an added advantage of less discomfort and irritation. Double staining with the 1% fluorescein and 1% lissamine can be a useful tool for diagnosis of the dry eye and for evaluating the therapeutic effect in patients with the dry eye syndrome.

Kashkouli et al (52) conducted a study to find out the result of Schirmer I test done in 5 minutes and in 1 min and proposed that 1 min Schirmer I is faster, comfortable and more reliable. He also concluded that Schirmer I test done with open eyes is much more reliable than done with eyes closed in patients with dry eyes in Sjogren's syndrome patient.

Management of dry eye after diagnosis depends on the cause and grading of severity for the condition. Treatment approach should be guided in normalizing tear film, decreasing inflammation of ocular surface, stimulating healing of epithelium, with improvement in neural feedback system.

Treatment should be directed in relieving the sign and symptoms of dry eye, protection of tear film and stopping the vicious cycle of inflammation.

Ocular surface disease Index (OSDI)

It is the one of the best validated questionnaire for dry eye. It consists of 12 questions for rapid assessment of symptoms of dry eyes and their impact on the vision related functioning system. OSDI is assessed on scale ranging from 0 to 100 with larger score representing the severity of disability.

It has 3 subscales which includes vision related function include 6 questions, ocular symptoms including 3 questions and environmental triggers including 3 questions. 12 items were graded on scale of 0 to 4, where 0 means none of the time, 1 means some of the time, 2 means half of the time, score of 3 means most of the time and 4 means all of the time. Total scores were calculated using this formula as described OSDI= [(sum of score for all questions answered) * 100]/ [(total number of questions answered)*4].

Schiffman et al (9)study includes 109 patients with symptoms dry eye and 30 normal controls who filled OSDI questionnaire and National Eye Institute Visual Functioning Questionnairre (NEI VFQ 25) health status questionnaire. They also did detailed ophthalmic examination like TBUT, Schirmer and fluorescein and lissamine green staining test on these participants. The objective of this study was to determine the usefulness as an end point in the clinical trials testing for efficacy of newer treatment for dry eyes. The mean OSDI scores were 36 in severe dry eye group, 18 in mild to moderate group and 5 in control group. They concluded that OSDI has good sensitivity

and specificity which is effective in discriminating normal and various grades of dry eyes as defined by physician's evaluation of severity and composite disease for severity score.

Vitale et al (53)examined the association between vision targeted health related quality of life i.e (VT-HRQ) and tear surface parameters which are seen in patients with Sjogren's syndrome. He included 42 patients selected by AECG criteria and assessed results of Schirmer I, vital dye staining tests and questionnaire (OSDI and NEI-VFQ). They concluded that there is modest association between objective measures of dry eye and questionnaire of VT-HRQ, whereas NEI-VFQ and OSDI was found to have similar impact of SS-related dry eye on VT-HRQ.

Differential Diagnosis:

The condition which can present with xerostomia includes diabetes mellitus, sarcoidosis, amyloidosis, viral infection, psychogenic, trauma or irradiation.

Dry eye may be seen as a manifestation of amyloidosis, sarcoidosis, inflammation due to conjunctivitis, blepharitis, pemphigoid, Stevens-Johnson syndrome, drugs, trauma, burns, neurological dysfunction of lacrimal gland, vitamin A deficiency, blink abnormality and decreased corneal sensation.

Parotid gland enlargement (bilateral) may be seen in endocrine dysfunction (like acromegaly and gonadal dysfunction), viral infection (like human immunodeficiency virus, hepatitis C, mumps), metabolic diseases like diabetes mellitus, pancreatitis, cirrhosis and hyperlipoproteinemia.

The differential diagnosis plays a major role in treatment for systemic manifestation of Sjogren's syndrome. As most of the autoimmune diseases like SS, SLE, RA,

scleroderma has a similar presentation of joint pain, myalgia, low grade fever and Raynaud's phenomenon, the differentiation can be difficult. The aim of the workup for Sjogren's syndrome is to eliminate possibility of above mentioned disease and to document salient features of SS. This process includes coordination of the multi speciality like assessment of eyes, oral cavity and head and neck in addition to rheumatologist.

Diagnosis of disease:

Diagnosing this disease is often difficult. Symptoms are non specific as it presents in older age group due to senile atrophy of secreting tissue or due to some other cause like use of some drugs. In addition, symptoms of this disease do not presents concurrently, thereby denstists, physician and ophthalmologist will treat each symptom individually, unknown of the fact that it can be an association of systemic disease. The wide diversity of symptoms expression also adds to difficulty in initially diagnosing the disease.

In the past, patients with Sjogren' syndrome were commonly misdiagnosed as their symptoms were considered to be minor or vague or they may mimic those of the other diseases.

With the help of refined criteria for diagnosis, specialists like rheumatologists, dentists, ophthalmologists, physician, who would have only focused only on the symptoms of their area of expertise, will be able to get a patient's comprehensive image, leading to early detection and treatment of the disease.

None of the laboratory test holds the definitive diagnosis. But, a combination of some abnormal test reports is commonly noticed: elevated level of erythrocyte sedimentation rate (ESR), anemia, leucopenia and the hypergammaglobulinemia and

antibodies like Anti-nuclear antibodies (ANA), anti-Ro or anti-La and the rheumatoid factor (RF).

Systematic multidisciplinary approach is required in proper evaluation of SS, that includes assessment of the oral, ocular and systemic components of the disease.

The widely used criteria include those revised in 2002 by the joint effort by research groups in the Europe and in the USA (AECG-American European Consensus Group).

AECG- (American European Consensus Group) 2002 criteria(4)

I. Ocular symptoms includes a positive response to at least one of following questions:

1. Have you had daily, troublesome, persistent, dry eyes for the duration of more than 3 months?
2. Do you get a recurrent sensation of sand like or gravel in the eyes?
3. Do you put tear substitutes for more than 3 times a day?

II. Oral symptoms includes a positive response to at least one of the following questions:

1. Have you had a daily feeling of dryness of mouth for the duration of more than 3 months?
2. Have you noticed recurrently or persistently swelling of the salivary glands as an adult?
3. Do you frequently drink liquids to help in swallowing dry food?

III. Ocular signs- that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:

1. Schirmer's I test when performed without anaesthesia (≤5 mm in 5 minutes)

2. Rose Bengal score or other ocular dye score (a score of 4 or more according to van Bijsterveld's scoring system)

IV. Histopathology: In minor salivary glands biopsy (obtained through normal-appearing mucosa) presence of focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) which are present in r 4 mm^2 of glandular tissue

V. Salivary gland involvement: objective evidence of the salivary gland involvement is defined by a positive result for at least one of the following diagnostic tests:

1. Unstimulated whole salivary flow (≤1.5 ml in 15 minutes)

2. Parotid sialography showing the presence of the diffuse sialectasias (punctate, cavitary or destructive pattern), without any evidence of obstruction in the major ducts

3. Salivary scintigraphy which is showing delayed uptake, reduced concentration and/or delayed excretion of tracer

VI. Autoantibodies: presence in the serum of the patients, the following autoantibodies:

1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

Revised rules for classification

For primary SS

In patients without any potentially associated disease, pSS may be defined as follows:

a. The presence of any 4 of the 6 items is indicative of pSS, as long as either item IV (Histopathology) or VI (Serology) is positive

b. The presence of any three of the four objective criteria items (that is, items III, IV, V, VI)

Secondary SS:

In the presence of some another connective tissue disease, presence of the item I or item II, with addition of any two from items III,item IV and V

Exclusion criteria:

Previous history of head and neck radiation therapy, hepatitis C infection, infection like AIDS, pre existing lymphoma, and sarcoidosis, graft versus host disease, use of anti-cholinergic drugs ,since time shorter than fourfold of the half-life of drug.

Recently, the SICCA (Sjögren's International Collaborative Clinical Alliance) presented a new expert consensus approach in which classification criteria based entirely on objective measures(47). In this criteria, not only ocular symptoms and oral symptoms have been excluded, but also the study of minor salivary gland involvement has been removed from the criteria.

SICCA criteria(47)

(I) Ocular signs

Keratoconjunctivitis sicca with ocular staining score ≥ 3, according to the Whitcher et al i.e preferential use of the fluorescein staining or lissamine green staining, but tear break-up time; and non anesthetized Schirmer I test can also be used. It is presumed that individual is not currently using some daily eye drops for glaucoma and who has not had corneal surgery or any cosmetic eyelid surgery in the last 5 years).

(II) Histopathology of biopsy of minor salivary gland :

Focal lymphocytic sialoadenitis, with focus score ≥ 1 i.e a focus is defined as the presence of 50 or more lymphocytes per 4 mm^2 of glandular tissue adjacent to the normal appearing mucous acini)

(III) Autoantibodies:

Positive serum anti-SS-A or Ro and/or anti-SS-B or La or (positive rheumatoid factor and anti-nuclear antibody (ANA) titer ≥ 1:320)

Classification criteria includes:

At least two of the three items in order to classify a patient as SS

Exclusion Criteria:

History of head and neck radiation treatment, hepatitis C infection, AIDS, sarcoidosis, amyloidosis, graft versus host disease, IgG4-related disease.

Literature suggests various criteria to diagnose the disease based on clinical, pathological and laboratory finding. Modified AECG criteria(54) appear to the most widely used as it takes into their consideration the multisystem nature of this disease; the criteria includes the ocular and the oral signs and symptoms, antibodies to SSA and SSB

and labial salivary gland biopsy. Patient should meet 4 out of 6 proposed items including a positive lip biopsy or positive serology for antibodies.

AECG criteria have the disadvantage of inclusion of the subjective tests (symptoms), kind of physiologic measures which lacks specificity and alternative objective tests which are not diagnostically equivalent. Further the inclusion of these symptoms of dry mouth and /or dry eyes can lead to misclassification of the asymptomatic patients. Alonwith it, physiologic measures, such as unstimulated whole salivary flow (UWS), anaesthetized Schirmer test and the salivary scintigraphy, are very useful for assessment of salivary or tear function, but lack the specificity for SS.

Measurement of unstimulated salivary flow is done with help of sialometry that is by collection of saliva in a calibrated tube for duration of 15mins. Normal flow defined is 1.5ml. It is a simple and a noninvasive procedure, but doesnot help to distinguish between various causes of xerostomia. Other tests include salivary gland schintigraphy and parotid sialography.

ACR criteria(6) require two out of 3 components – including labial biopsy, anti Ro/anti La antibodies and OSS. It does not include subjective symptoms of dry eye/dry mouth. A diagnosis of SS when in its early stages has potential clinical relevance, but it is difficult and cannot be made alone on the clinical grounds.

Hay et al (1)conducted a population based study on 341 patients, out of which 44.6% were male and 55.4% were female with a median age for male was 46 years and for female it was 49 years. 96% of the patients had ocular symptoms. Overall the commonest ocular symptom was “smoke irritates the eyes”, reported by 58% followed by “sand or gravel sensation” in 22%.

Schirmer test was found to have sensitivity of 0.77 and specificity of 0.72 in hospital setting against the clinician “gold standard ” diagnosis of Sjogren’s syndrome but in other study it was found to have poor reproducibility (55) making it less valuable clinically. For Schirmer test with wetting of 5 mm or less when measured over five minutes under the basal conditions with the eyes slightly closed was considered to be abnormal. Tear Break up time (TBUT), which was found to be a simpler test to measures tear film stability but need slit lamp for evaluation. Measurement of antibodies to the Ro and La was done by ELISA in blood sample (Shield Diagnostics), and anti-Ro and anti-La > 2 U/ml were defined as abnormal.

No association was seen between presence of autoantibody and either symptoms or signs of dry eyes or dry mouth. Strongest association was found in subjects with both the ocular and oral symptoms and objective results. He found a weak association between the presence of oral symptoms or ocular symptoms and the test results of USF (unstimulated salivary flow) or Schirmer I. They examined the association separately for the subjects less than and over 55 years of age and reported higher frequencies of the abnormal findings in the elderly. This was thought to be due to age related changes causing dysfunction of lacrimal and salivary glands. Ocular symptom in elderly was assumed to be probably due to other causes like blepharitis thereby not giving an abnormal Schirmer test.

The limitation of this study was selection bias as only 55% subjects agreed to participate in the study, low prevalence of the affected subjects in that community compared with hospital sample with decreased frequency of dry eye and dry mouth complaints. This study also lack standardisation, leading to high false positive result and low predictive value.

Jacobsson et al (56) studied 705 subjects of age group 52 to 72 years and randomly did serologic testing and other exocrine gland function measuring tests on symptomatic (n=77) and asymptomatic subjects (n==32). He has found that the high levels of antibodies to Ro and La antibodies, in a population with symptoms of dry eyes or dry mouth and impaired exocrine gland function on the objective testing but the difference was very small and may not be clinically significant.

Tsuboi et al (2) studied 694 subjects with Sjogren's syndrome(SS) or suspected SS from 10 hospitals to validate their revised Japanese Ministry of Health criteria (JPN) (1999), AECG (2002), ACR (2012). Out of 476, 302 were pSS and 218 was non SS. The sensitivity of JPN criteria to all forms of SS (79.6%) and secondary SS (75.3%) was highest. The sensitivity for primary SS (83.1%) was highest with AECG. The specificities of JPN and AECG criteria for all forms of SS, primary SS, and secondary SS were highest in the diagnosis of SS in Japanese patients. The gold standard was clinical diagnosis by physician. The JPN criteria (1999) were intended to help in diagnosis, whereas the AECG (2002) criteria and the ACR criteria (2012) were useful in classification used in clinical studies and trials. Moreover, ACR criteria may not identify patients who have negative result for labial biopsy as it does not include analysis of salivary secretion and imaging results. AECG includes oral and ocular symptoms and can give false positive results in non Sjogren subjects due to aging or visual display terminal syndrome.

Their study suggested JPN criteria to be superior to other two criteria in diagnosis of Sjogren's syndrome in Japanese patients. But JPN criteria are not validated by ACR and EULAR, so it is only used in Japan.

Vitali et al (57) conducted a study on 447 European patients with Sjogren's syndrome and 246 controls, to establish a diagnostic criteria by performing a series of oral and ocular tests, parotid sialography and minor salivary gland biopsy. The most common ocular symptom found in this study was feeling of dry eye or 'sand in the eye' and most common oral symptom was feeling of dry mouth while eating or breathing. Among the ocular test, Schirmer test showed best balance between the sensitivity and specificity (76.9% and 72.4% respectively). Staining with Rose Bengal was found to be most specific (81.7 %). Tear film lactoferrin level and break up time showed unreliable results especially in Primary Sjogren's syndrome. The results of these tests vary with the age and type of Sjogren's syndrome. However the study concluded the positivity of these tests along with presence of the subjective symptoms and the serological abnormalities forms the accurate diagnosis.

Martin and Martin et al (58) developed a simple mathematical score which uses clinical and the laboratory variables for diagnosing the SS, thereby reducing need of the minor salivary gland. The following variables were used in their model: ANA antibody, SS-A/SS-B antibody, Schirmer test/TBUT, C3/C4, serum gammaglobulin level. Then, one hundred consecutive individuals who were reporting clinical syndromes consistent with sicca syndrome were included in their study. The application of these multifactorial and mathematical model was shown to have the high predictive value for SS versus the controls or versus the patients with other autoimmune disorders (Sensitivity 93%, Specificity 100%), with an estimated minor salivary gland reduction of 77%. They proposed that mathematical model can be considered as useful non-invasive approach in diagnosing Sjogren's syndrome and recommended that its validation to be done on a larger scale.

Akpek et al (59) conducted a retrospective study on 220 patients of dry eye syndrome, out of which 10.9% were found to have pSS .Only 33.33% carried diagnosis of pSS at initial presentation. On initial evaluation 66.66% were positive for anti SSA/anti SSB and those who were serology negative (16.7%) showed positivity with minor salivary gland biopsy. He concluded to focus on diagnostic evaluation of pSS which remain underdiagnosed in many patients of dry eye syndrome.

Galvez et al (60)did study on 88 patients who underwent labial biopsy with clinical suspicion of Sjogren's syndrome and analysed that the preliminary European criteria has higher sensitivity but lesser specificity than AECG criteria.

Brun et al (61) investigated 203 patients with a clinical diagnosis of Sjogren's syndrome. 88.8% had MSGB done and 99.5% had information about autoantibodes. He used cut off for Schirmer as 5 in 5 minutes and also took salivary gland tests into account. Mean age group found was 55 years and 96.4% was female. He concluded that only 40.9% patients satisfied the proposed modified European criteria that include the presence of either antibody or salivary gland biopsy positive. This study concluded that approximately one-third of patient who have an established diagnosis by preliminary European criteria, will lose the diagnosis according to modified criteria and the use of immunological variables and histopathology of salivary gland will be premise for diagnosis. But the proposed modified criteria, if used by scientific community and research will lead to comparable population SS patients and prove it to be an autoimmune related systemic disease.

Versura et al(62) collected clinical and the cytological data from 177 patients who need to be evaluated for diagnostic performance of the test that are included in Sjogren's syndrome diagnostic criteria. Out of the 62 patients with Sjogren's syndrome,

5patients were male with mean age group of 56.1±10.2 years and 57 were females with mean age group of 61.6±10.8 years. This study revealed poor diagnostic accuracy of Schirmer I test (sensitivity=0.42; specificity= 0.76; LR +1.11; area under the curve in ROC analysis < 0.412), TBUT though showed poor performance (with sensitivity of 0.92 but specificity of 0.17; LR +1.11 and area under ROC curve 0.59) can exclude diagnosis of pSS but with low specificity. Validated subjective symptoms questionnaire (sensitivity 0.89 and specificity 0.72; LR+3.18; area under curve 0.896), Jones test, measurement of corneal sensitivity with corneal aesthesiometry and the tear clearance test showed high diagnostic performance. Lissamine green showed best performance (sensitivity of 0.63 and specificity of 0.89; LR of +5.72) with statistically significant difference between pSS and other groups. But the limitation of this study was incorporation bias for Schirmer test.

Barboza et al (63) studied 17 patients with Sjogren syndrome and 25 normal controls. Ocular surface disease index (OSDI) questionnaire was used for symptom assessment and ocular signs were tested using Schirmer I and II, ocular surface staining with Rose Bengal dye, pachymeter and aesthesiometer. This study showed a weak correlation between the symptoms of patients with Sjögren's syndrome and ocular signs that indicate disease severity concluding that all symptomatic patients did not showed positivity for corresponding tests. This weak correlation was attributed to variation in corneal sensitivity. All other parameters studied in the disease group showed statistically significant (< 0.05) difference in comparison to control group.

Markusse et al (64)did a study on 44 (40 men and 4 women with a mean age group of 55 years) randomly selected primary Sjogren’s syndrome subjects and found that ocular involvement was present in 42 patients. 21 patients were clinically suspected as pSS but on the basis of ophthalmology evaluation, diagnosis was excluded .He

concluded that there is limited role of Schirmer, Rose Bengal staining and tear film break up time in diagnosis the disease.

Nichols et al (65) conducted a study on 75 patients with dry eye disease selected with non specific criteria by clinician. Patients were interviewed regarding symptoms of dry eyes and underwent ophthalmological examination like tear meniscus height, TBUT, Schirmer test, Rose Bengal staining, fluorescein and phenol red test. They found a poor correlation between symptoms of dry eyes and their tests after adjustment for age and use of lubricants.

Bjerrum et al (66) compared results of the dry eye test and symptoms in patients with the primary Sjogren's syndrome ,secondary SS and normal controls. Schirmer value and TBUT below10mm/5mins and 10 secs respectively , had high sensitivity and low specificity, but Rose Bengal and Schirmer less than 5mm/5mins showed reverse results. There was variability in test on repeated visits. They concluded that in case of test negative but with symptoms of pSS, examination of Keratoconjunctivitis sicca should be repeated.

Yoon et al (67) concluded that nasal conjunctiva has more staining compared to the temporal conjunctiva and staining of cornea ($p = 0.04$). And this staining pattern of the nasal conjunctiva showed a significant correlation with the OSDI score ($p < 0.01$) and TBUT ($p = 0.03$). Staining of temporal conjunctiva showed significant corelation with ocular symptoms (p of 0.01), and the staining of cornea correlated with TBUT (P of 0.02). This study proposed the strong correlation of double vital staining (1% lissamine and 1% fluorescein) with symptoms and the ocular surface parameters in those patients with dry eye, thereby helping us to identify ocular surface changes easily.

Whitcher et al (68) studied SICCA cohort of 1208 patients and promotes the use of two different vital dyes for grading different areas of ocular surface as the key diagnostic parameter in KCS. Patients were divided into two KCS subgroups: KCS only and SS-KCS group.

Among participant with KCS only, the median OSS (Ocular staining score) was 5 compared to 9 among those with the SS-KCS with statistically significant difference between 2 subgroups ($p<0.0001$). This study also showed significant difference in Schirmer I and TBUT among 2 subgroups with no difference in symptoms of dry eye or dry mouth. He also introduced OSS score which include (stepI) fluorescein staining pattern of the cornea to count for punctuate epithelial erosions(PEE) and lissamine green staining pattern of the conjuctiva(Step 2).It was considered to be a diagnostic tool as well as to monitor the response to treatment. The total OSS is the summation of staining of corneal fluorescein score and the staining of lissamine green scores for nasal and temporal bulbar conjunctiva. Hence, the maximum score possible for each eye is 12. An OSS score higher than 0 is supposed to be an abnormal and can be a sign of KCS. And the scores of 1 or 2 can also represent the late staining artifact if there is delay in interpretation of fluorescein corneal staining pattern. Because it can lead to a significant high level of misclassification, an abnormal OSS score is defined as being score of 3 or above.

Paschides et al (69) conducted a study on 81 primary Sjogren's syndrome and 276 normal control. Mean value of TBUT in pSS group was found to be 7± 3 and in control group 13±6.Schirmer I test showed a mean value of 10±9 in normal group and 4±7 in pSS group. Rose Bengal was found to be the best test in their study with a mean of 5±2 in pSS and 1±1 in normal group with statistically significant difference in 2 groups.

Adatia et al(70) examined the hypothesis that the reduction in corneal sensitivity is associated with the increased ocular surface disease and reduction of symptoms in patients with Sjogren's syndrome. He assessed 18 subjects who are diagnosed to have Sjogren's syndrome with OSDI questainnaire and Symptom Severity of Discomfort(SSD) scale along with ophthalmological examination including corneal esthesiometer, fluorescein stain and lissamine green staining, Schirmer I and TBUT. Both lissamine green and fluorescein showed negative correlation with the central corneal sensation (r of -0.3542, p value of 0.034) indicating the reduction of corneal sensation with increased ocular surface disorder. He also concluded that patients with pSS have less symptoms with increased corneal disease as depicted by advanced corneal staining.

Liew et al (71) conducted study on 327 patients and concluded that patients with SS had the worse corneal and the conjunctival staining and Schirmer I test compared to patients with Non Sjogren's syndrome.

Numerous criteria have been described to facilitate the diagnosis of SS and no consensus has been reached yet, even though there is requirement for the definitive set of a diagnostic criteria.

In **our study** subjective symptoms of patients suspected of SS-I will be assessed by validated of OSDI (Ocular Surface Disease Index) questionnaire(8)(9).The purpose of this study is to evaluate the diagnostic performance of Schirmer I test, TBUT and OSS test in SS-I patients by assessing the sensitivity, specificity and likelihood ratio of each test performed. This study will also aim to correlate between ocular symptoms, signs, immunological variables and labial salivary gland biopsy. Schirmer I of 5mm or less in 5 mins, TBUT of less than 10 secs and OSS score of 3 or above will be considered as abnormal.

In this study we will evaluate diagnostic accuracy of dry eye tests in Primary Sjogren's syndrome in the Indian setting which can be endorsed by clinician across the world to increase their credibility and also to maximize standardization when enrolling patients into the clinical trial. This study will also help in early suspicion of the disease and its timely management.

RESULT AND ANALYSIS

RESULT AND ANALYSIS

There were 95 patients who were recruited for the study after applying the inclusion and exclusion criteria.

Sex distribution of patients

Out of 95 patients; 5 were males and 90 were females.

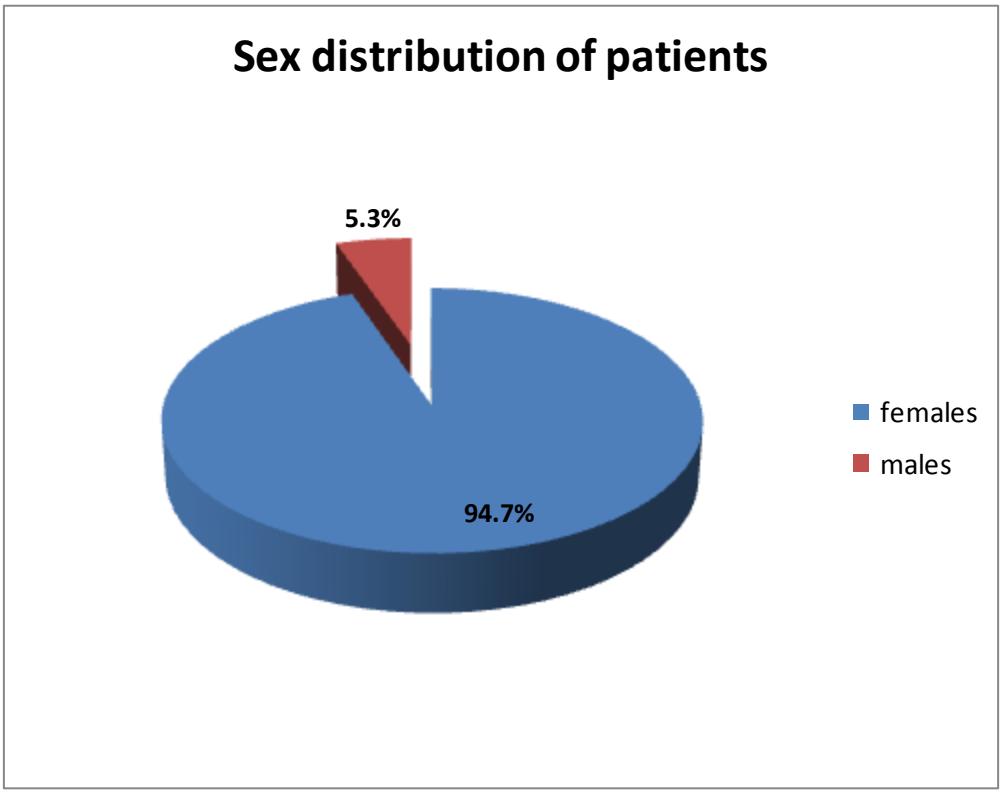

Fig.1 Sex distribution of patients

Age distribution of patients

The patients were in age group of 18 to 71 years;

3 patients were less than 20 years, 31 patients were between 21-40 years, 54 were between 41-60 years and 7 were between 61-80 years.

Mean age group of the patients was 43.74 years. Mean age group among female patients was calculated to be 43.54 years and mean age group among male patients was found to be 47.20 years.

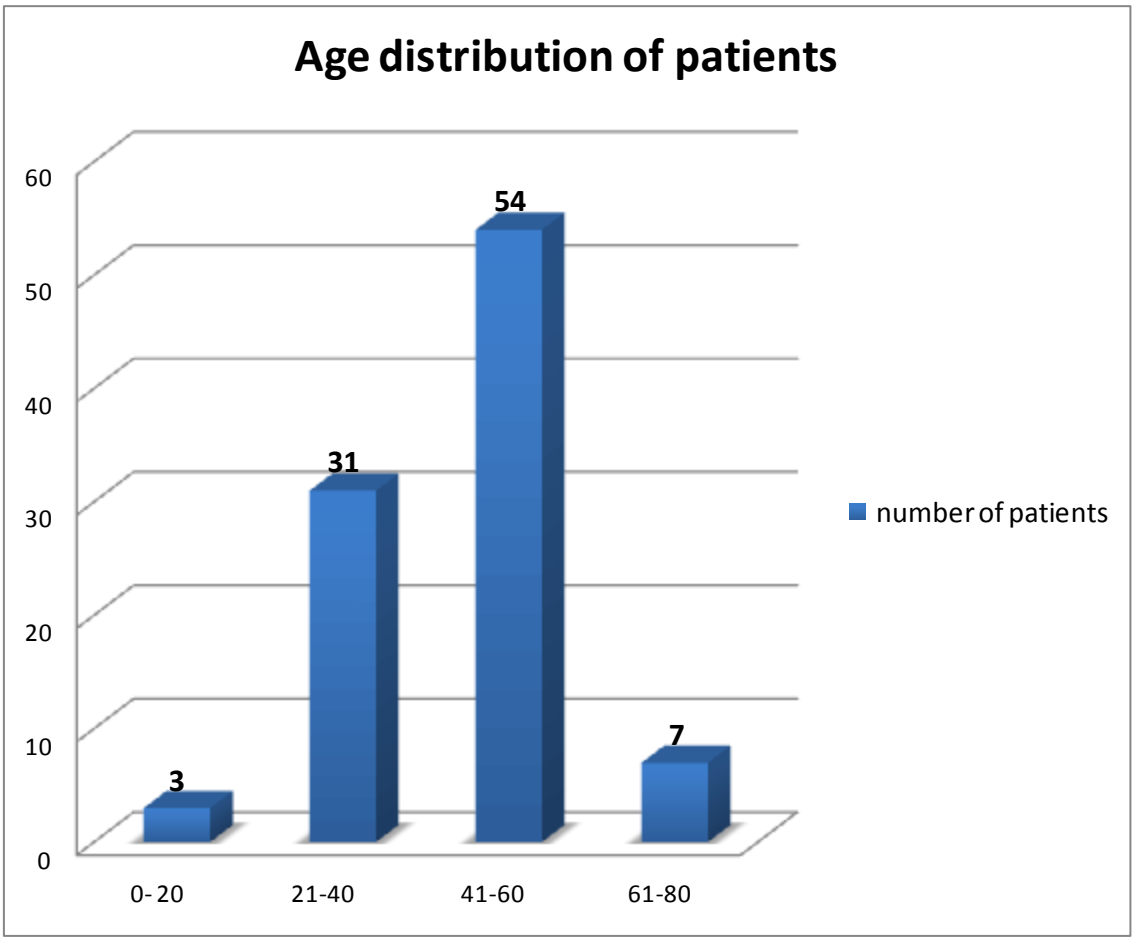

Fig2. Age distribution of patients

Occupation of the patient:

Out of total patients recruited in the study, 69.5% were housewives, 18.9% were students, 7.4% were working in an office without air conditioner (AC) and 3.2% were working in office with an AC.

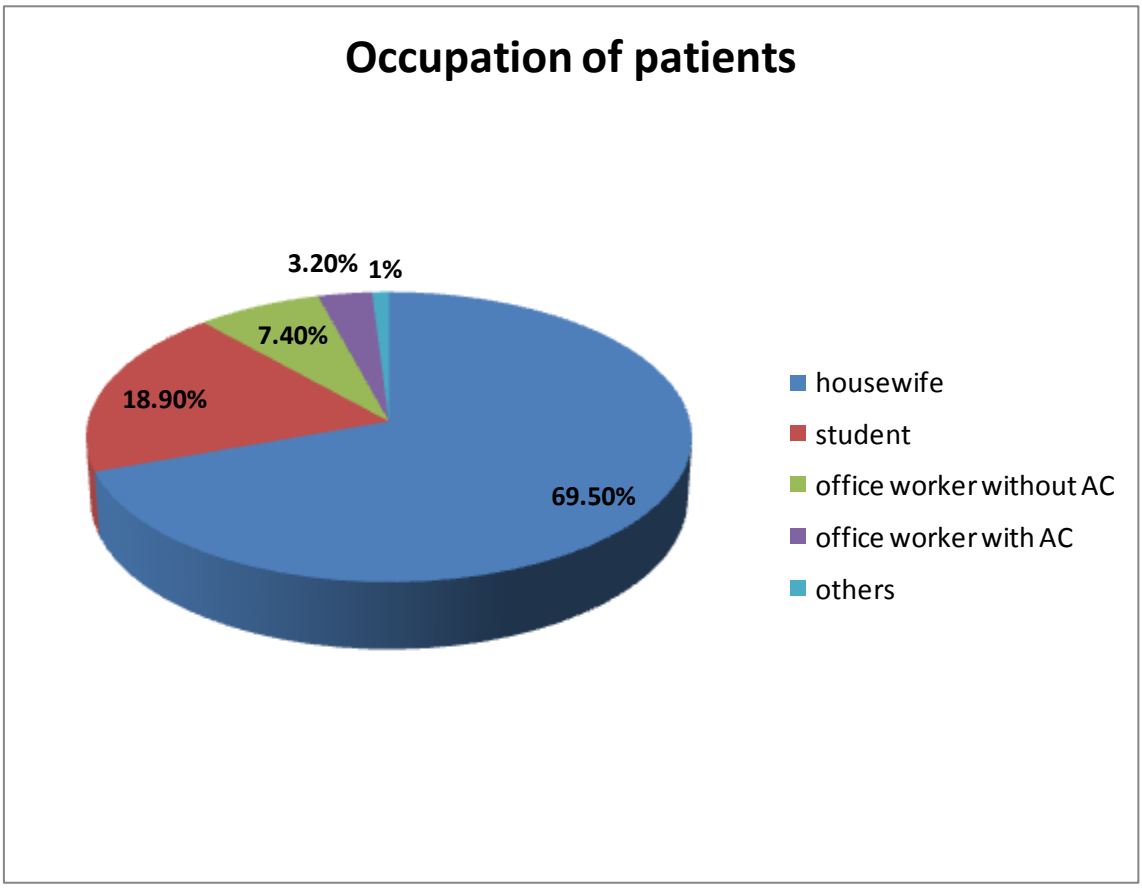

Fig.3 Occupation of patients

Chief complaints:

Of the 95 patients, 86 (90.5%) patients had ocular complaints. The mean duration of symptoms was 2.15 years with a minimum of 1 month and maximum of 96 months. There was no difference in the duration of symptoms between male and female patients.

Patients presented a range of symptoms that included sandy eyes, gritty sensation, itching, redness, stickiness, photophobia, vision disturbance and cheek swelling (parotid enlargement). The most common symptoms were itching and foreign body sensation.

56.8% patients complaints of itching and foreign body sensation in their eyes, 49.5% complaints of burning eyes, 33.7% have feeling of dryness in eyes, 22.1% complaints of sticky sensation, 10.5% have vision disturbance, 6.3% have complaints of redness in their eyes. Most of the symptomatic patients have more than 1 complaint.

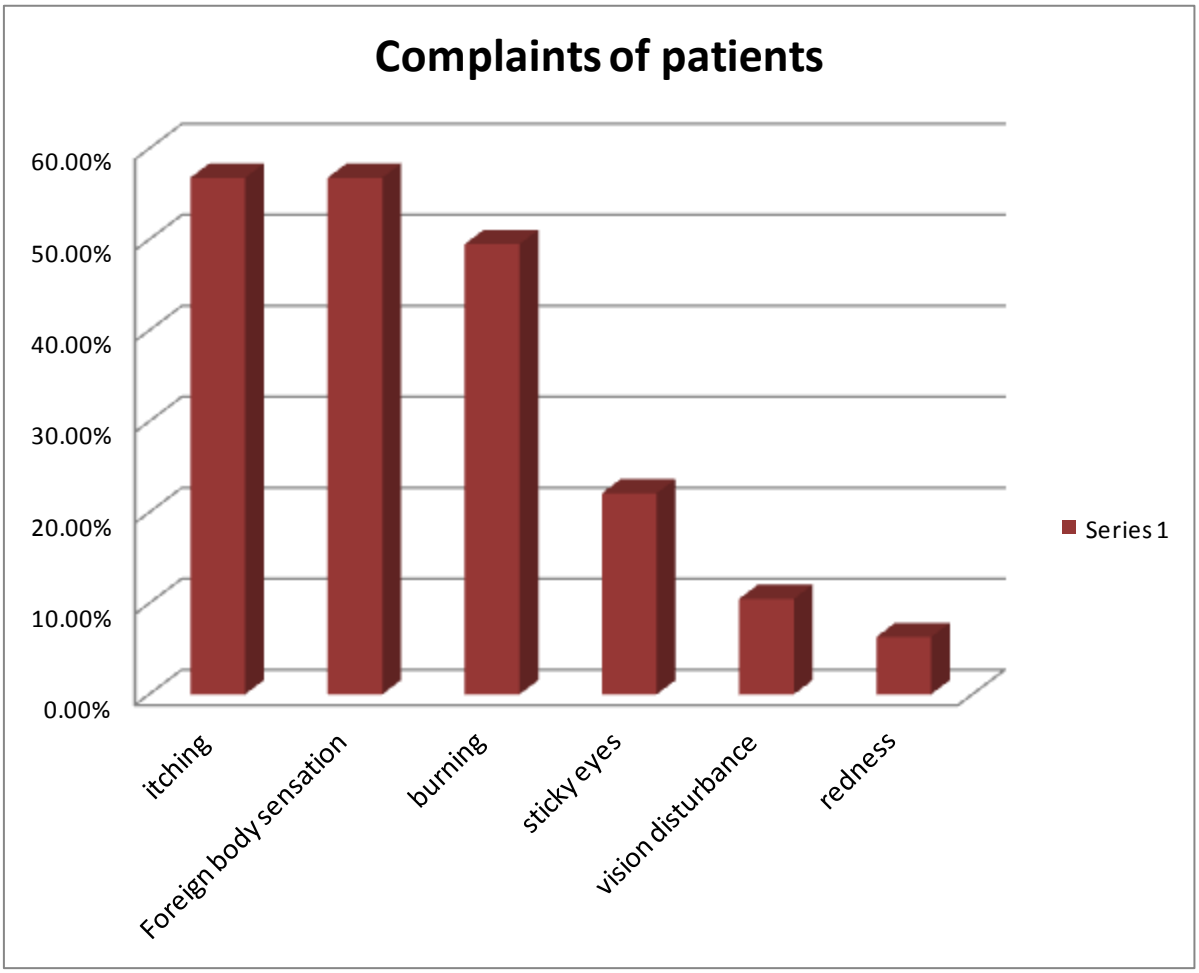

Fig.4 Complaints of patients

Visual disturbance was seen in 10 patients who were in the age group of 50 to 65 years. 57% of symptomatic patients were using lubricant eye drops.

3% patients give history of use of systemic anticholinergic drugs, 72 % patients denied use of anti cholinergic drug and the remaining 25% did not have the complete details of systemic medication used.

Blood tests results of the patients.

Anti SS- A antibodies tests was done in ninety two patients and anti SS-B was done in fourty nine patients out of total study population of ninety five

Table 1. Blood tests results of the patients

Tests	Positive	Negative	Total	Not done
Anti SS-A	30(32.60%)	62(67.39%)	92(100%)	3(3.15%)
Anti SS-B	11(22.44%)	38(77.55%)	49(100%)	46(48.42%)
Labial Biopsy	37(39.36%)	57(60.63%)	94(100%)	1(1.05%)

Anti SSA antibody:

Of the 92 patients, 30 (32.60%) patients had positive anti SS-A titre (>20Ru/ml) and 62 had negative titre.

Out of the 30 patients who were positive for anti SSA, 23 patients (76.70%) were finally diagnosed to have primary Sjogren's syndrome.

The sensitivity and specificity was 76.7% and 88.7% respectively. The positive predictive value of anti SSA is 76.7%.

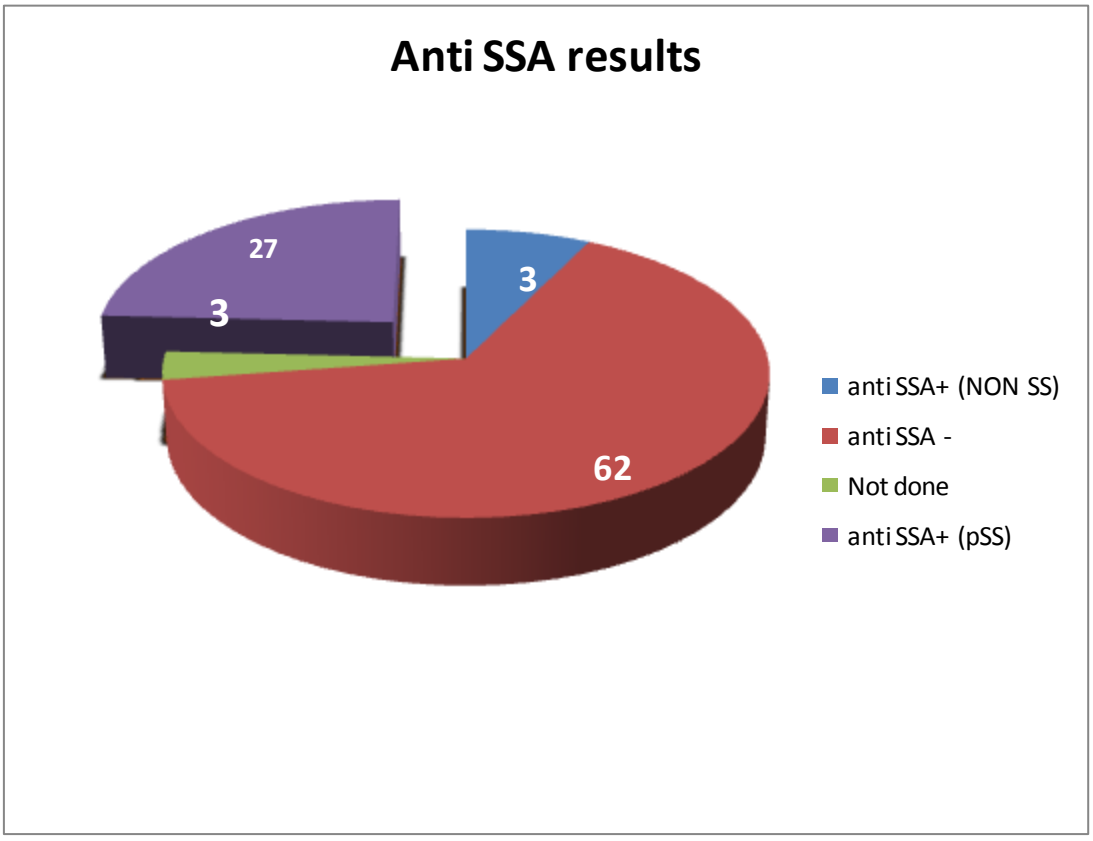

Fig. 5 Anti SSA results

Anti- SSB antibody:

Out of 49 patients who got the test done, 11 (22.44%) patients were found to be positive for anti SS-B titre (>20Ru/ml) and 38 patients were found to have a negative titre.

All the 11(100%) patients who were having anti SSB positive titre were diagnosed to have pSS.

The sensitivity and specificity was found to be 52.4% and 73.7% respectively. The likehood ratio and positive predictive value could not be calculated as it represents very small part of the sample population.

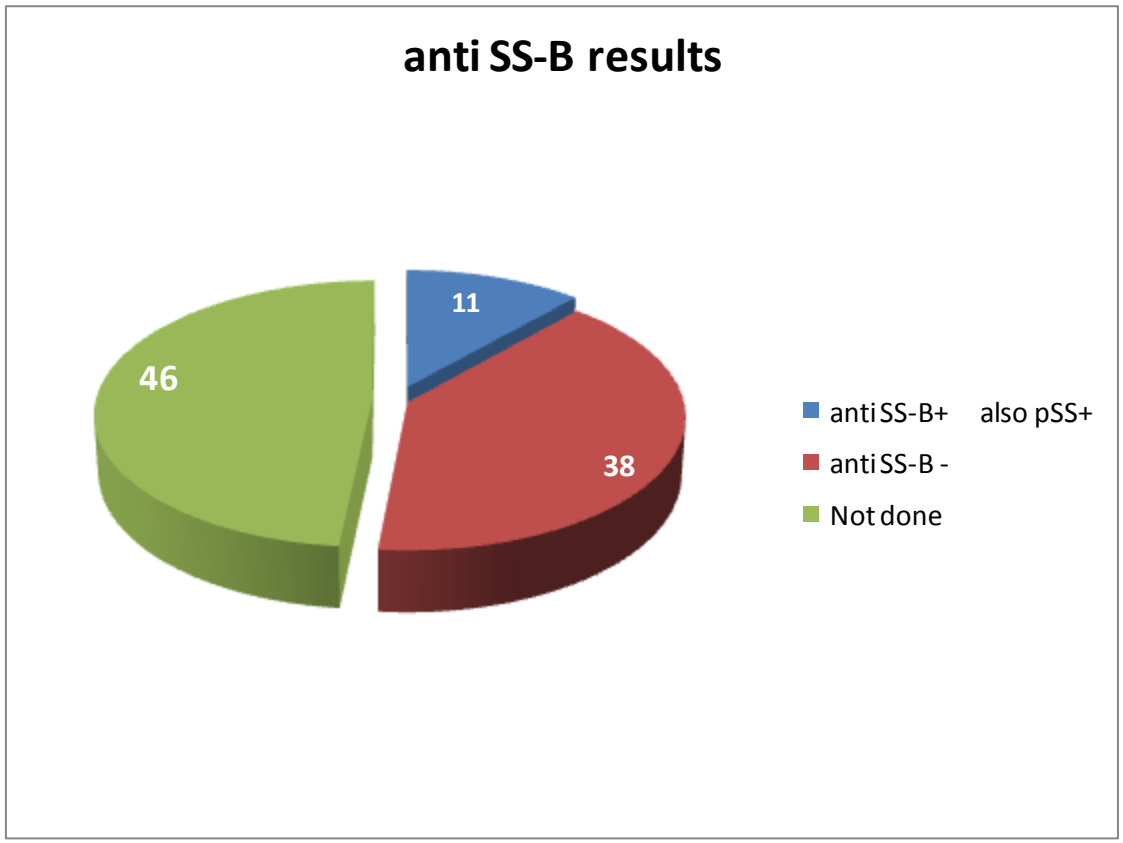

Fig.6 Anti SSB results

Labial Biopsy:

Out of 95 patients who were included in the study, 94 patients had labial biopsy done. 37(39.36%) patients were found to be positive for labial biopsy (grade IV inflammation) and 57 (60.63%) patients showed negative result.

Out of the 37 biopsy positive patients, 30 (81.08%) of them were diagnosed to have primary Sjogren's syndrome.

The sensitivity and specificity of MSGB was found to be 96.8% and 88.9% respectively. The positive predictive value of biopsy was found to be 81.1%.

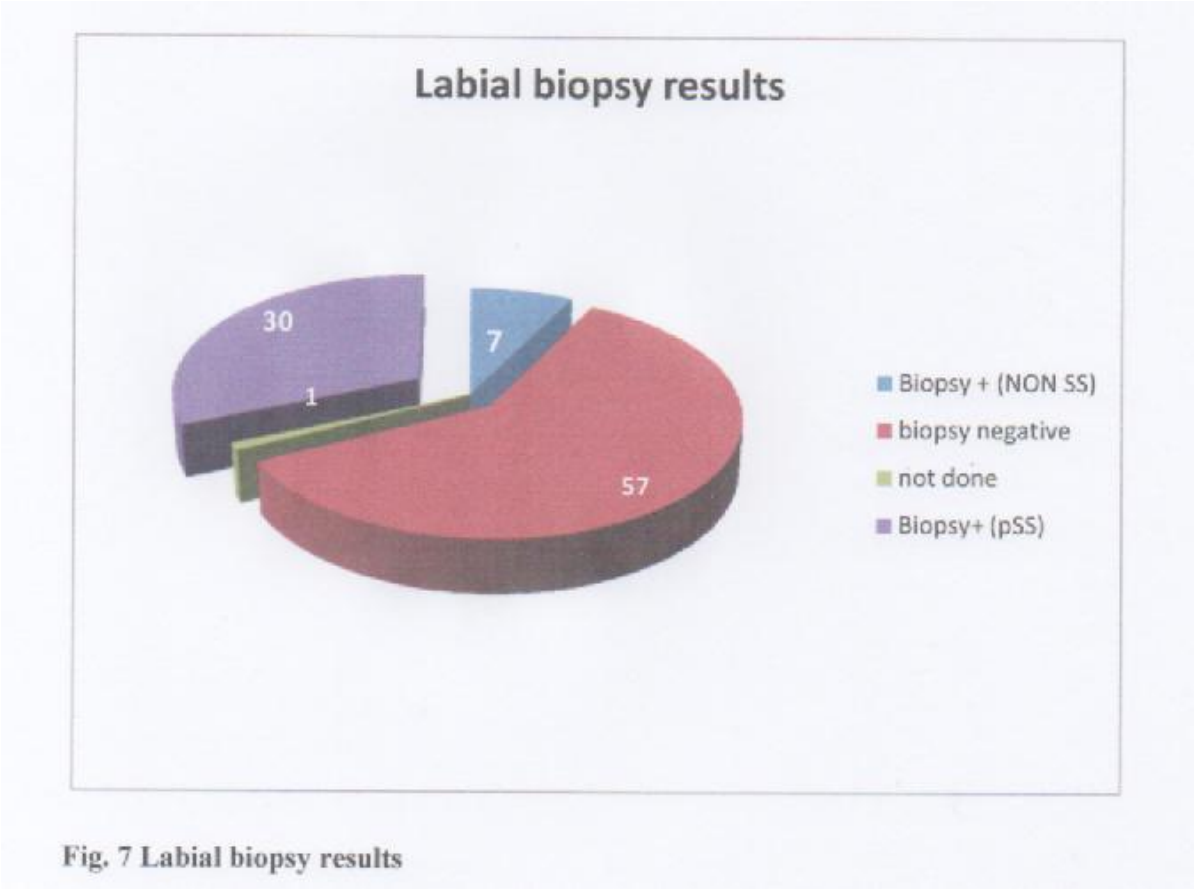

Fig. 7 Labial biopsy results

ACR criteria for diagnosis of Sjogren's syndrome:

Out of 95 study patients, 31 patients were diagnosed to have primary Sjogren's disease (pSS) as per ACR criteria.

According to this criteria, 14 patients were included as they have anti SSA titre and labial biopsy positive test result, 8 patients have all 3 (anti SSA, anti SSB and labial biopsy) positive, 2 patients had anti SSB titre and labial biopsy positive and 1 patient had anti SSA titre and anti SSB titre positive, 6 patients were included as they have labial biopsy positive result and OSS ≥3.

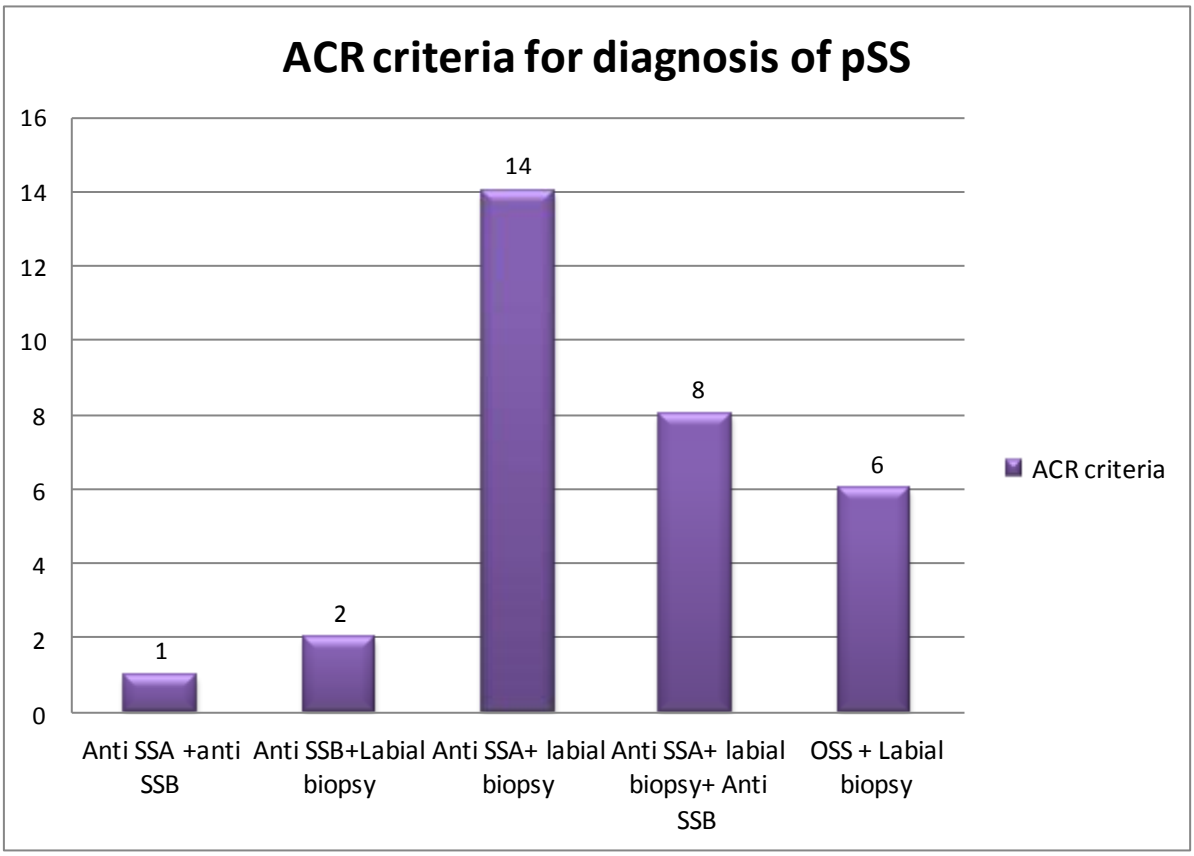

Fig.8 ACR criteria for diagnosis of PSS

NUMBER AND PERCENTAGE OF POSITIVE TEST RESULTS OF OSDI, SCHIRMER TEST, TBUT and OSS (in patients with pSS and Non SS group)

Ocular surface disease index (OSDI):

43 patients have an OSDI score below 18, 49 patients were having the score in the range of 18-36 and 3 patients were having score of more than 36. The number of primary Sjogren syndrome patient found in the range of normal, mild to moderate and severe were 8, 20 and 3 respectively.

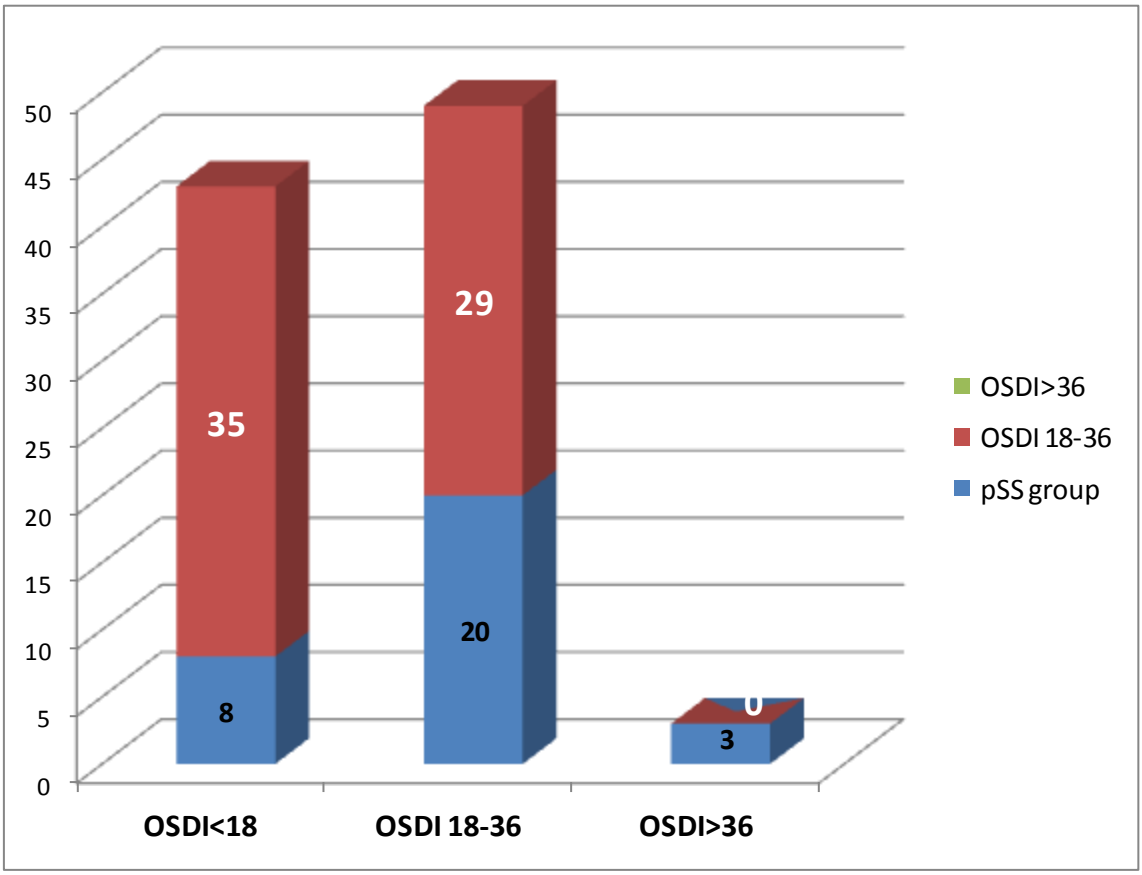

Fig.9 Distribution of OSDI

Schirmer I (Sch-I) tests:

8 patients of pSS group were found to have Schirmer value 11-15mm compared to 13 patients of Non SS group. Schirmer value of 6- 10mm were seen only in 12 patients of pSS group and only 4 patients of the Non SS group, but Schirmer value of ≤ 5mm was seen only in 3 patients of pSS and was not seen in any patient of the control group.

Table 2 Distribution of Schirmer test

	Schirmer 11-15mm (total=21)	Schirmer 6-10mm (total=16)	Schirmer ≤5mm (total=3)
pSS	8/31= 25.8 %	12/31= 38.70%	3/31= 9.67%
Non SS	13/64= 20.31 %	4/64= 6.25%	0/64= 0%

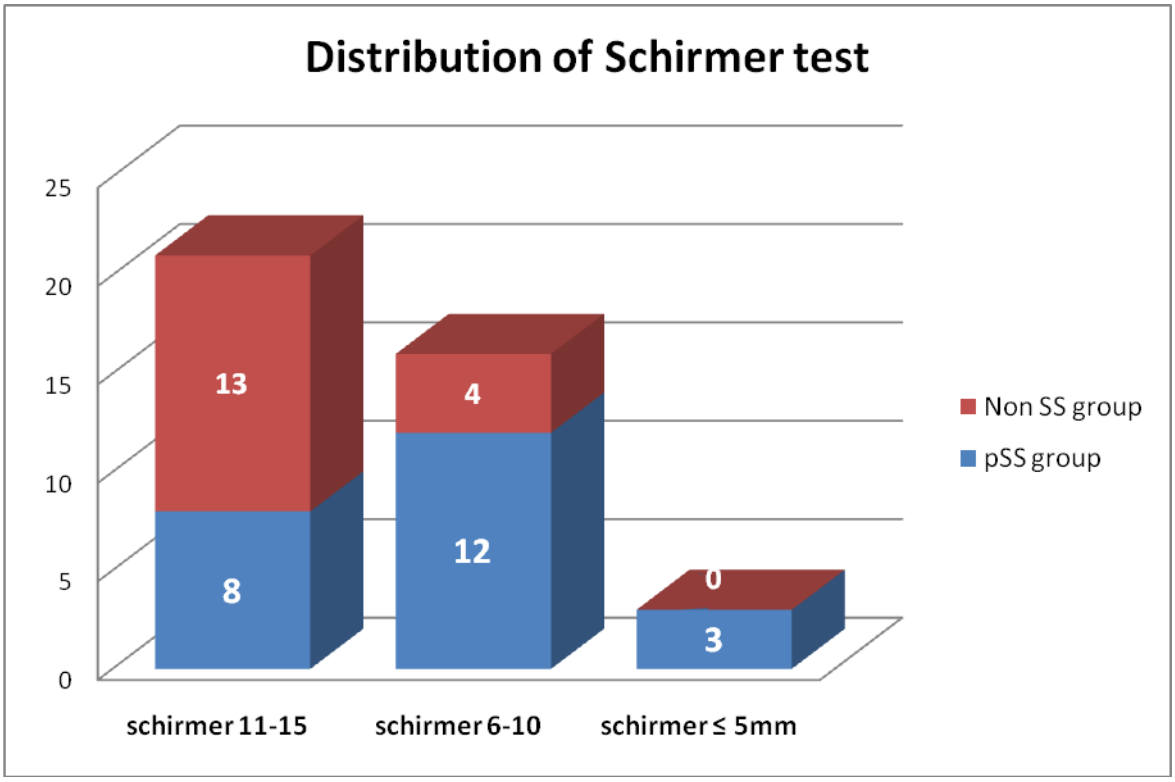

Fig.10 Distribution of Schirmer test

TBUT tests

TBUT value of 8-10 secs was seen in 6 patients of pSS group and in 38 patients of the Non SS group. TBUT value of 6-7secs was seen in 23 patients of pSS group and 24 of control (Non SS) group. TBUT ≤ 5secs was seen only in 2 of the patients of pSS group and was seen in 1 patient of the control group (Non SS).

Table 3, Distribution of TBUT

	TBUT 8-10 secs (total=44)	TBUT 6-7 secs (total=47)	TBUT ≤ 5 secs (total=3)
pSS	6/31=19.35%	23/31=74.19%	2/31=6.45%
Non SS	38/64=59.37%	24/64=37.5%	1/64=1.56%

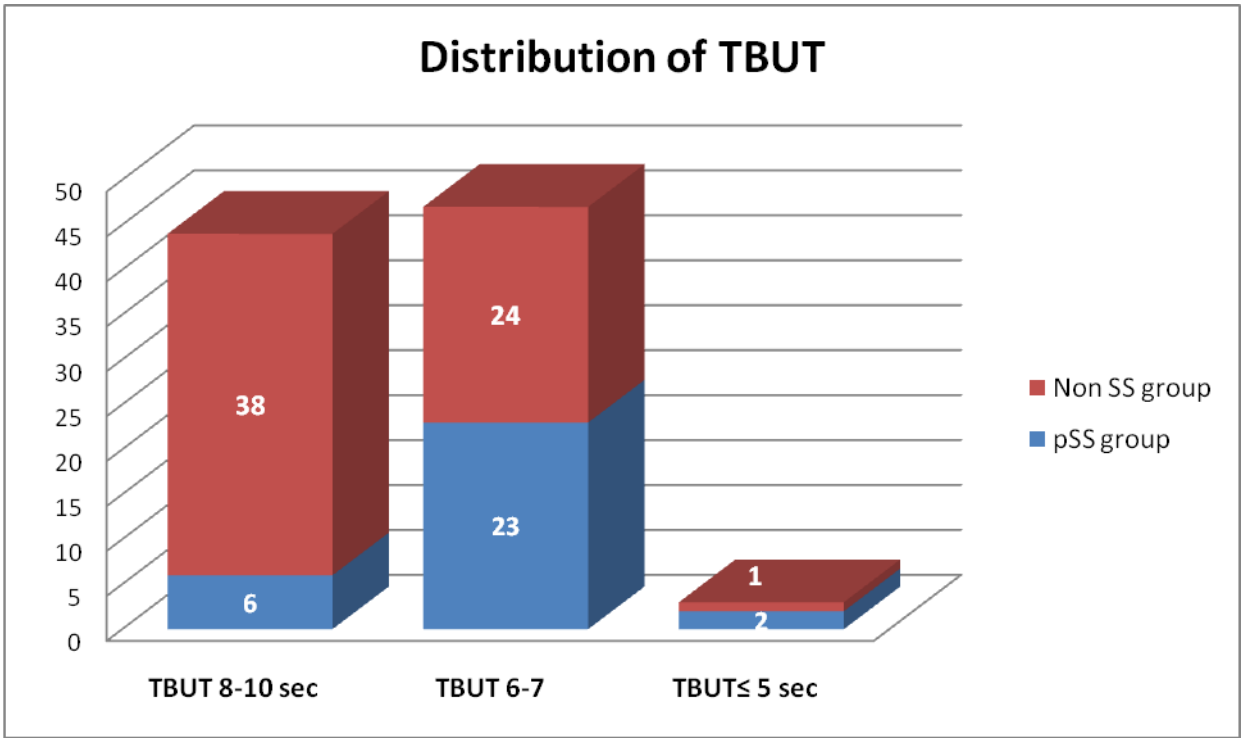

Fig.11, Distribution of TBUT

Ocular staining score (OSS)

OSS score of 6 or more was seen in 2 patients of pSS group and in only 1 patient of Non SS group. OSS score of 3-5 were seen in 17 patients of pSS group and 5 patients of Non SS group.OSS less than 3 was seen in 12 patients of pSS and most (58 patients) of the control group.

Table 4, Distribution of OSS

	OSS ≥6 (total=3)	OSS 3-5 (total=22)	OSS < 3 (total=70)
pSS	2/31=6.89%	17/31=54.8%	12/31=41.38%
Non SS	1/64=1.15%	5/64=7.08%	58/64=87.88%

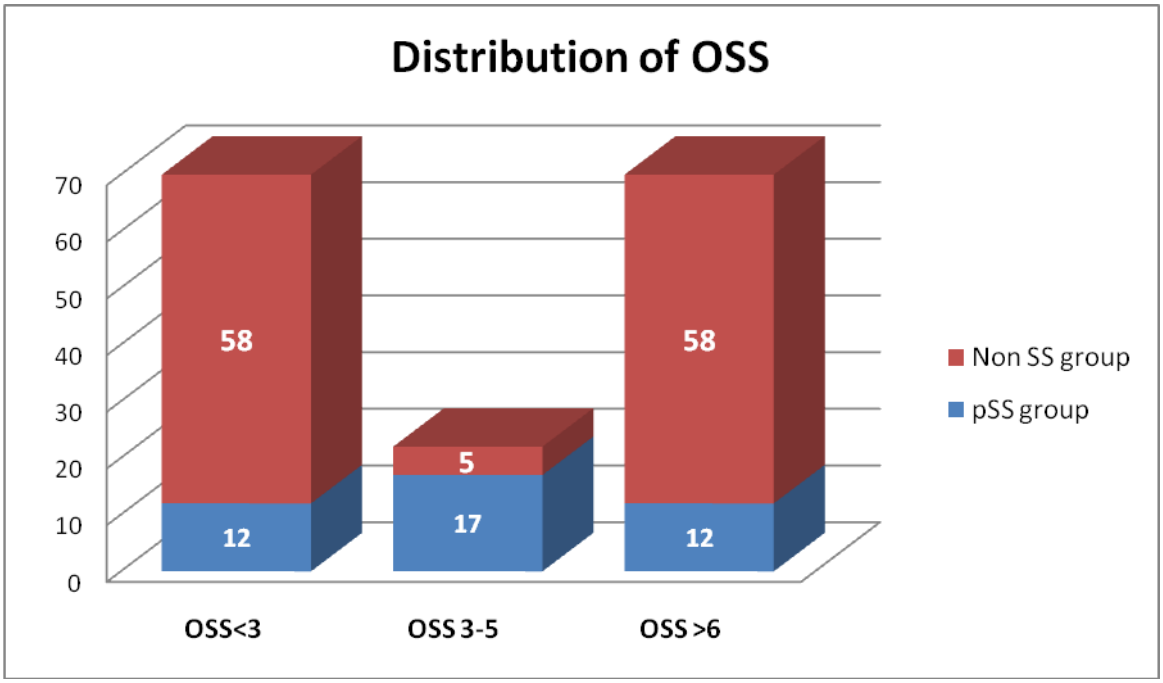

Fig.12, Distribution of OSS

OCULAR SUFACE DISEASE INDEX:

Ocular symptoms as expressed by Ocular surface disease index (OSDI) are presented by numeric value ranging from mild in Non SS groups to mild to moderate in pSS group. Medium values of OSDI seen in pSS patients were 24.60±9.36 and in Non SS patients were 17.8±5.3, with statistically significant difference ($p< 0.001$) between two groups.

Dry eye symptoms in varying severity were present in almost all patients who are suspected of having the disease ($p<0.015$).

The median value and the interquatile range for OSDI score in both the pSS group and the Non SS group is shown in the box plot in figure 13:

Table 5, Interquartile range and min-max values for OSDI score

Percentile	SS group	Non SS group
25	16.6700	13.63
50	22.2200	16.63
75	31.2500	21.63

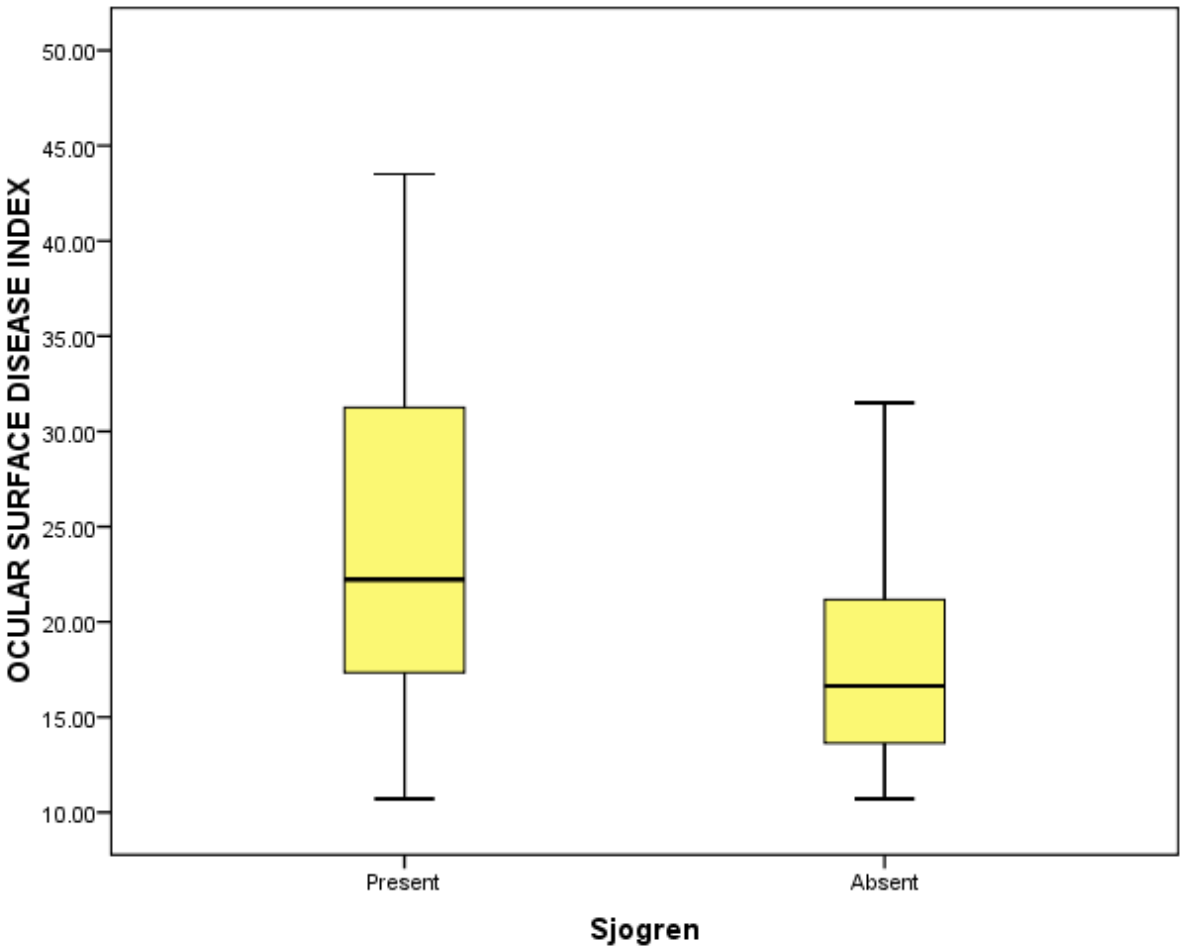

Fig.13, Box plot showing Median value, results from 25-75% and range min-max values for OSDI

To calculate the hinge point or the cutt off range for OSDI score ROC curve was use which shows the balance between its sensitivity and specificity as shown in figure 14 below.

In our study OSDI score for 18.7 showed a sensitivity of 71% and specificity of 65.00% and ROC plot anaysis demonstrate a curve approaching irregularly near the diagonal line, with area under the curve 0.718.

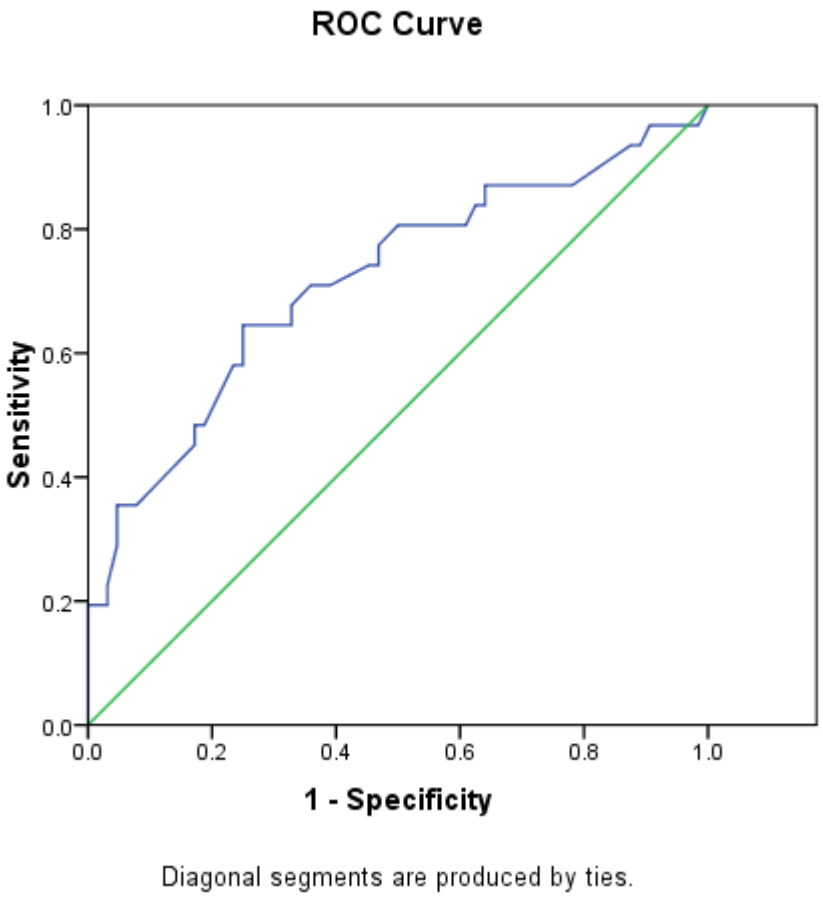

Fig. 14, ROC curve for OSDI

Table 6, Area under the curve for OSDI

			Asymptotic 95% Confidence Interval	
Area	Std. Error[a]	Asymptotic Sig.[b]	Lower Bound	Upper Bound
.718	.059	.001	.602	.835

SCHIRMER TEST:

Schirmer I (Sch-I) are expressed in mm/5minutes. According to box plot, median values of decrease in tear production seen in pSS patients were 12.77±5.37 mm/5mins and in Non SS patients were 19.21±4.97mm/5mins, with statistically significant difference ($p< 0.001$) between two groups.

Median value of pathological Schirmer I test of ≤ 5mm/min was seen in only 3 patient of pSS group and none of the patients of Non SS groups. The sensitivity and specificity for Sch-I ≤ 5 was found to be 19.4% and 96.9%. Hence concluding that the mean value of tear secretion is supposed to be higher than pathological threshold(≤ 5mm/5mins) between 2 groups.

For the cut off value of Schirmer I ≤ 15mm, the sensitivity and specificity was found to be 64.5% and 85.90% respectively. The positive predictive value was 69% and positive likelihood ratio was 4.57.

Table 7, Interquartile range and min-max values for Schirmer I

Percentile	SS group	Non SS group
25	10.00	15.00
50	12.00	20.00
75	17.00	22.00

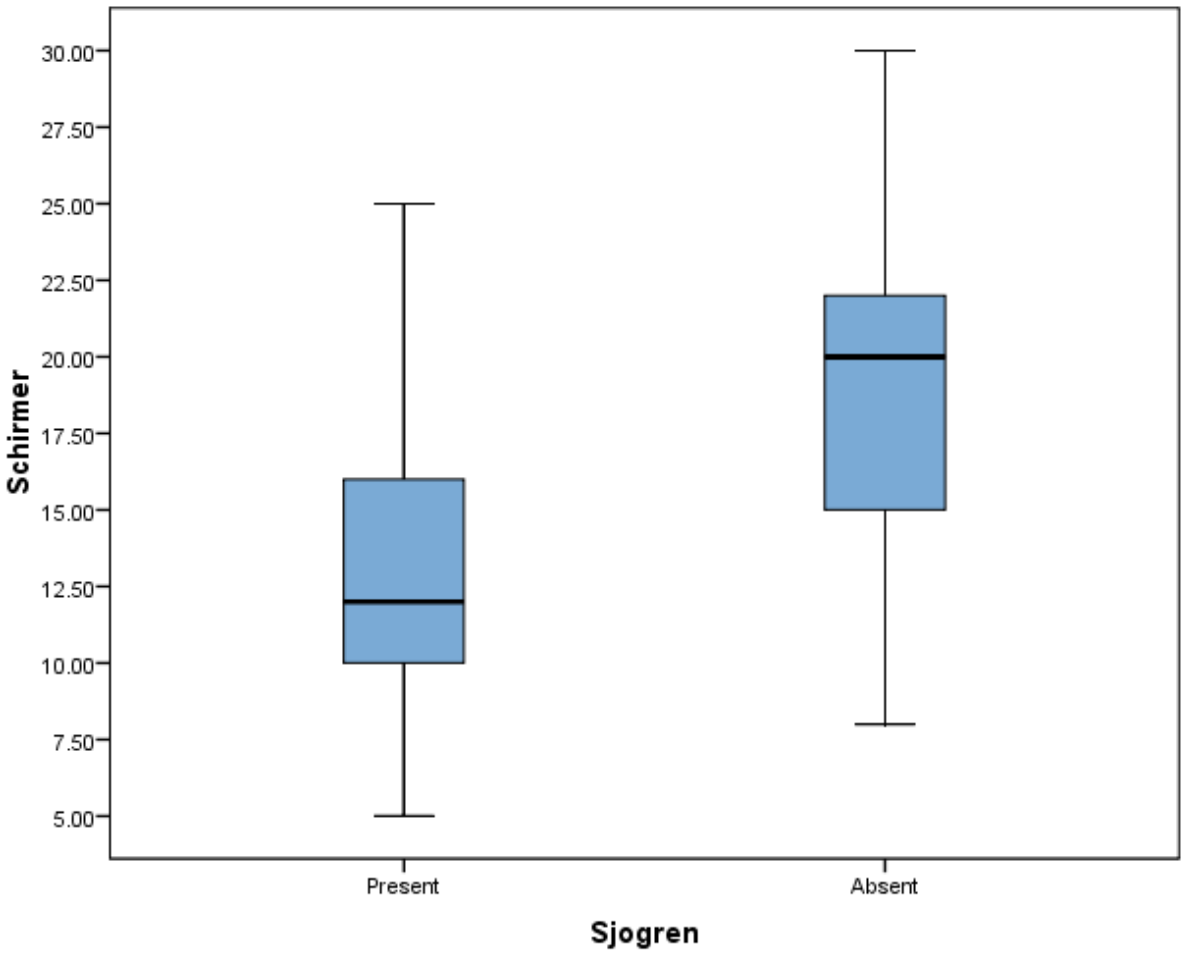

Fig.15 Box plot showing median value of Schirmer I in pSS group and Non SS group

In the above box plot (figure 15) the median value of the Schirmer I in diseased population of pSS group is around 12.7mm and in the control group of Non SS group population is 19.2mm.

ROC plot analysis demonstrate a curve approaching to upper left corner of the graph ,with area under the curve 0.779 suggesting the balance between sensitivity and specificity at Schirmer I value at 15mm.

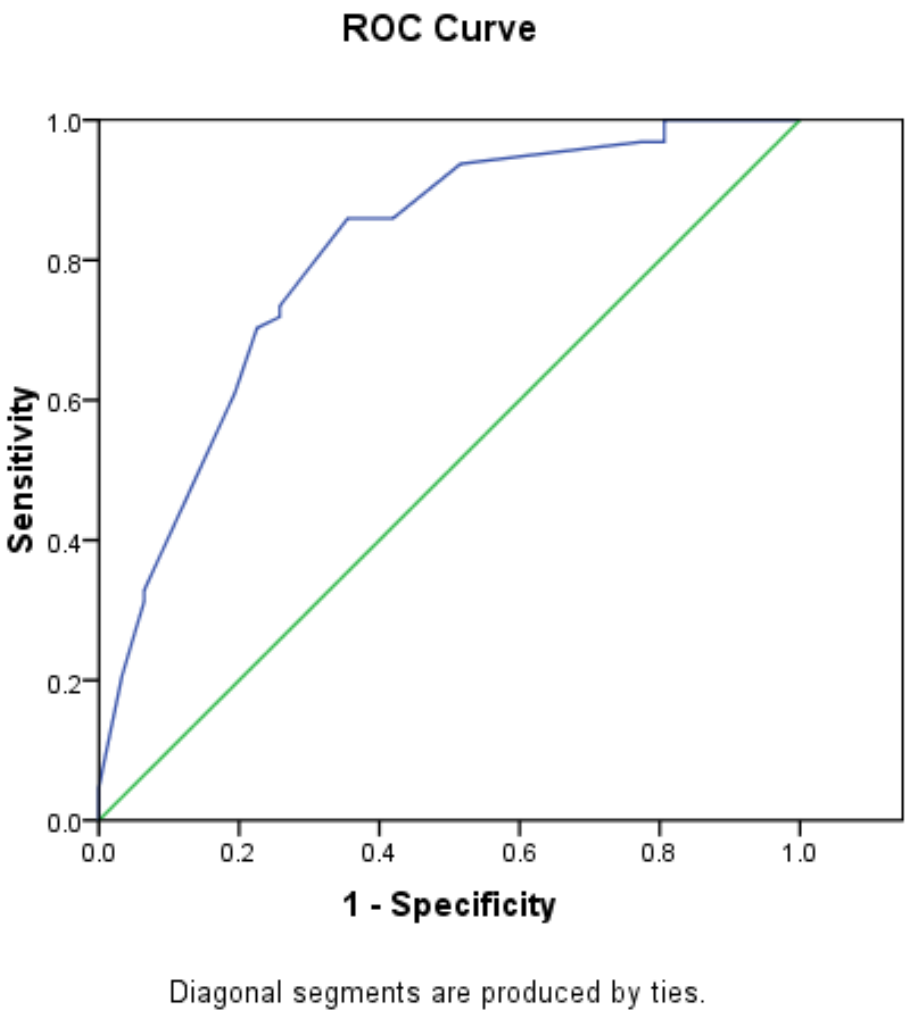

Fig.16, ROC curve for Schirmer I test

Table 8, Area under the curve for Schirmer I test

			Asymptotic 95% Confidence Interval	
Area	Std. Error[a]	Asymptotic Sig.[b]	Lower Bound	Upper Bound
.807	.049	.000	.711	.904

Tear breakup time (TBUT)

It is expressed in seconds. Medium values in pSS patients were 6.6±1.04 secs and in Non SS patients were 7.87±1.24 sec with statistically significant difference ($p< 0.001$) between two groups.

For a value of TBUT≤10 sec, the sensitivity and specificity was found to be 96.8% and 12.5%. The positive predictive value was 34.9%.

But the pathological cut off value,for a good sensitivity and specificity comes to around TBUT≤ 8 secs, the sensitivity and specificity was found to be 80.6 % and 60.90% respectively. The positive predictive value was 50% and the positive likelihood ratio was 2.06.

Table 9, Interquartile range and min-max values for TBUT

Percentile	SS group	Non SS group
25	6.00	7.00
50	6.00	8.00
75	7.00	8.00

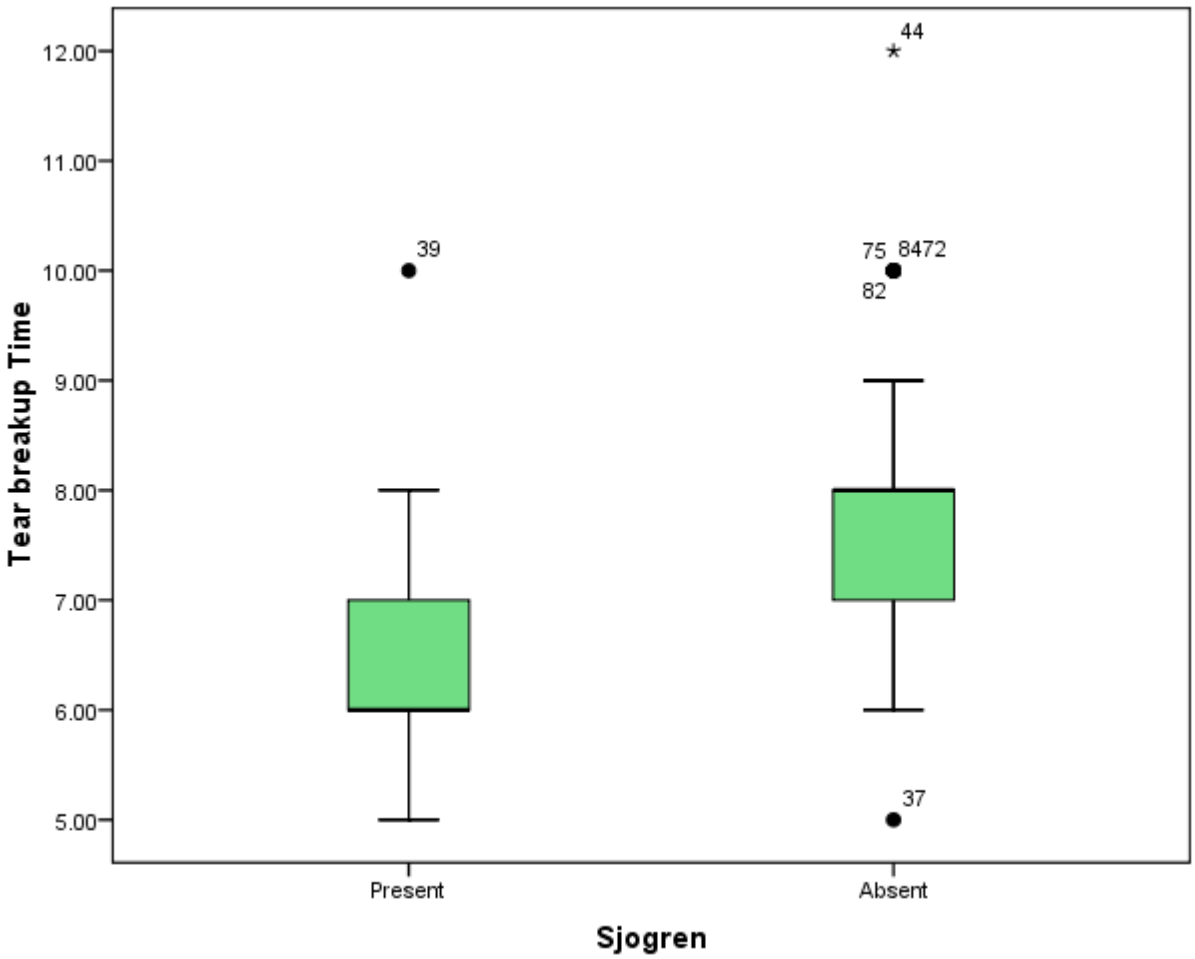

Fig.17, Box plot showing median value of TBUT test in pSS group and Non SS group

In the box plot shown above(fig 17), median value of TBUT in pSS group is 6.6secs except for one patient whose TBUT value is around 10 secs, whereas in Non SS group ther is variability in range of TBUT,with a median value of 7.8 secs, 4 patients having a value of 10 secs or more and only 1 patient have a TBUT of around 5secs.

ROC plot in figure 18, demonstrate a curve approaching to upper left corner with area under the curve 0.780 suggesting the balance between sensitivity and specificity at TBUT ≤8 secs.

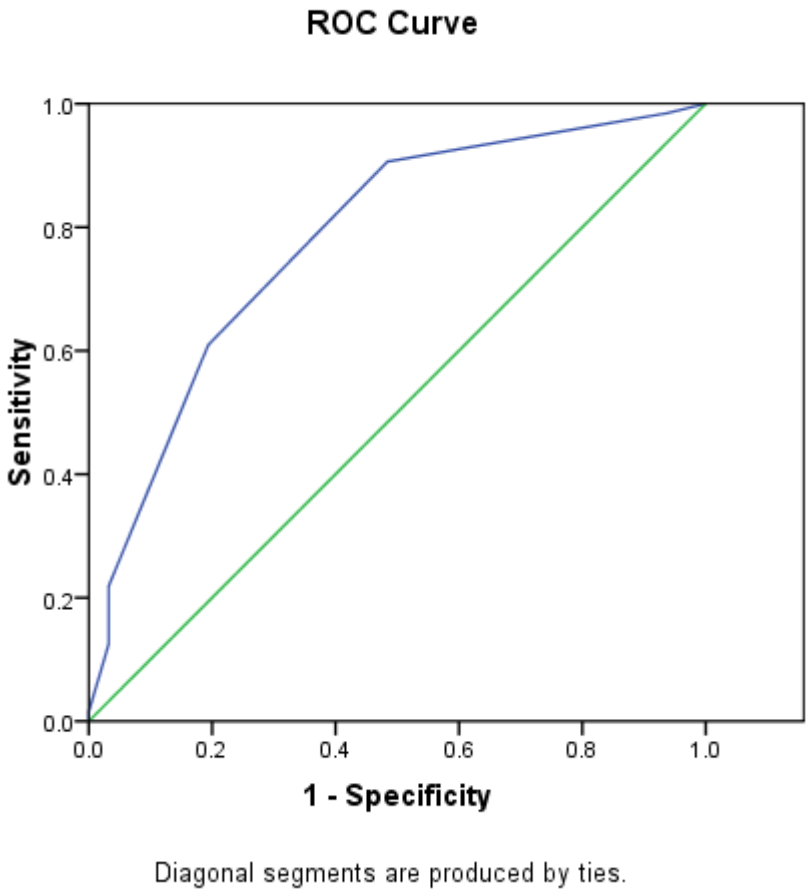

Fig.18, ROC curve for TBUT test

Table 10, Area under the curve TBUT

			Asymptotic 95% Confidence Interval	
Area	Std. Error[a]	Asymptotic Sig.[b]	Lower Bound	Upper Bound
.780	.052	.000	.679	.881

In figure 19, ROC curve shows a comparison between the Schirmer I and TBUT, demonstrating a close similarity between both the graph with Schirmer I curve having slightly more area under the curve than TBUT.

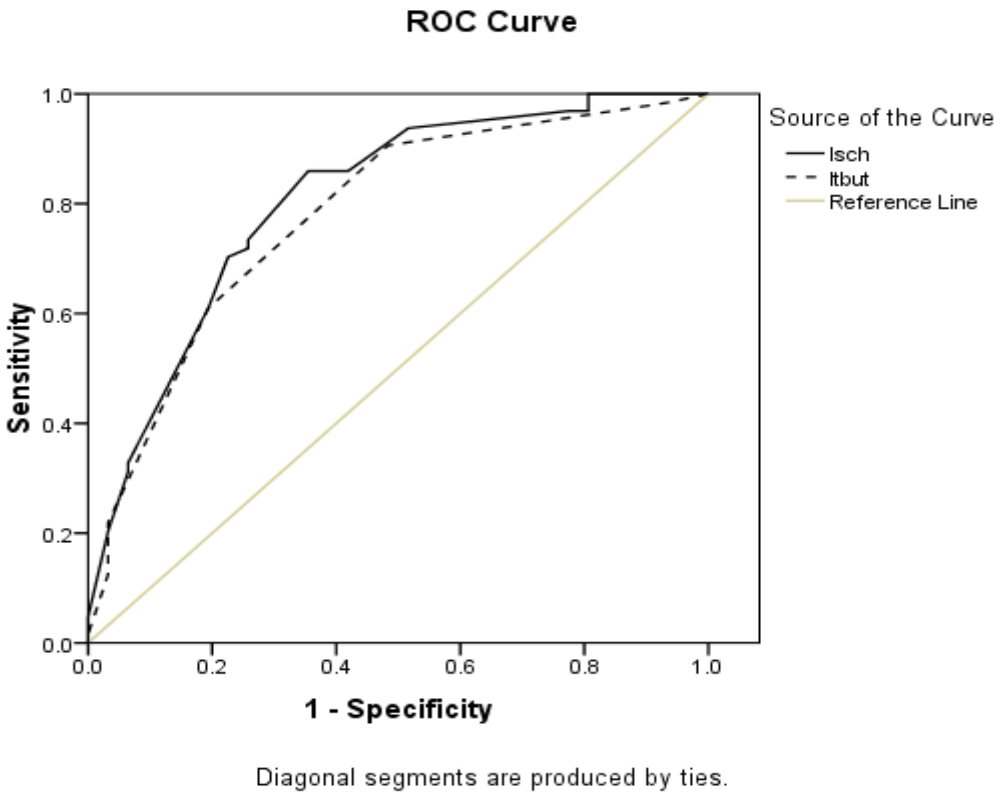

Fig.19, ROC curve showing the comparison of TBUT and Schirmer I

Table 11, Area under the curve of TBUT and Schirmer - I

Test Result Variable(s)				Asymptotic 95% Confidence Interval	
	Area	Std. Error[a]	Asymptotic Sig.[b]	Lower Bound	Upper Bound
Lsch	.807	.049	.000	.711	.904
Ltbut	.780	.052	.000	.679	.881

Ocular Surface staining (OSS) score:

It is presented in numeric value. Medium values in pSS patients were 2.48±1.84 and in Non SS patients were 0.84±1.19, with statistically significant difference ($p< 0.001$) between two groups.

For the cut off value of OSS ≥3, the sensitivity and specificity was found to be 61.3% and 90.60% respectively. The positive predictive value was 76% and positive likelihood ratio was 6.52.

Table 12, Median value,results from 25-75% and range min-max values for OSS

Percentile	SS Group	Non SS Group
25	1.00	0
50	3.00	0
75	4.00	1

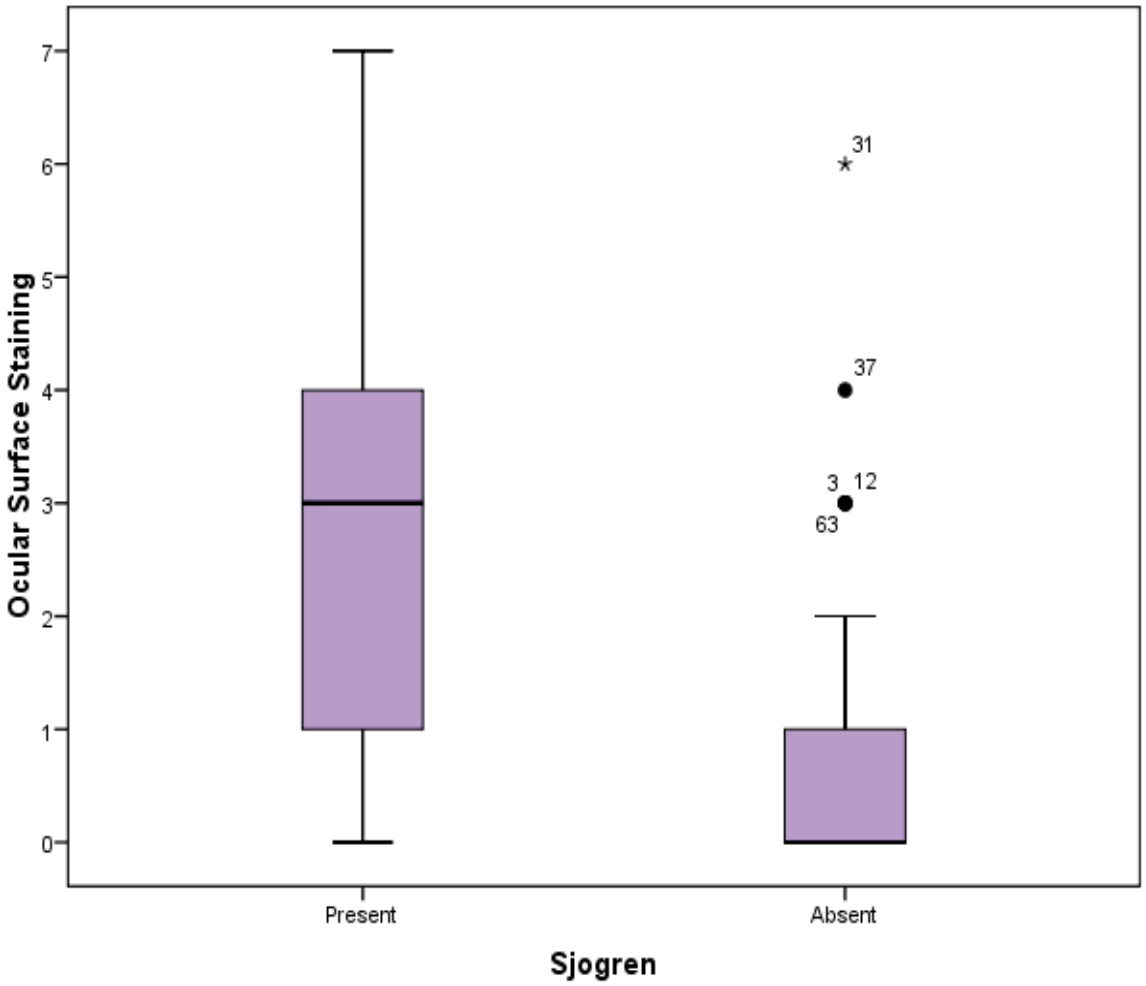

Fig.20, Box plot showing median value of OSS score in pSS group and Non SS group

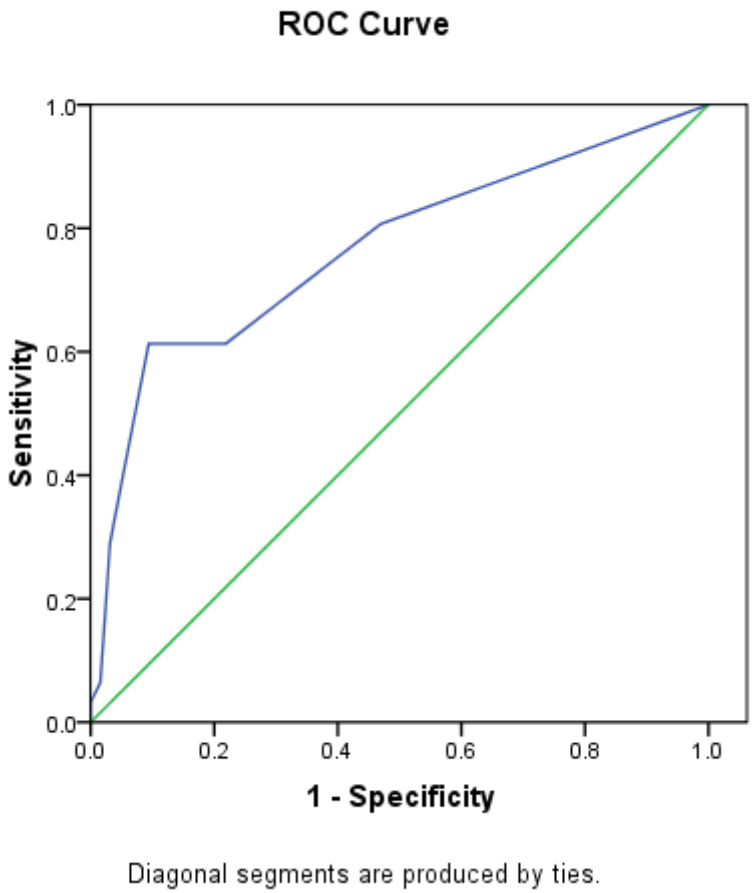

Fig.21, ROC curve for OSS score

Table 13, Area under the curve for OSS

			Asymptotic 95% Confidence Interval	
Area	Std. Error[a]	Asymptotic Sig.[b]	Lower Bound	Upper Bound
.766	.056	.000	.655	.876

Table 14, Association between subjective symptoms and objective tests

Correlations				
			OCULAR SURFACE DISEASE INDEX	Lsch
Spearman's rho	OCULAR SURFACE DISEASE INDEX	Correlation Coefficient	1.000	-.397**
		Sig. (2-tailed)	.	.000
		N	95	95
	Lsch	Correlation Coefficient	-.397**	1.000
		Sig. (2-tailed)	.000	.
		N	95	95
	ltbut	Correlation Coefficient	-.341**	.769**
		Sig. (2-tailed)	.001	.000
		N	95	95
	max_oss	Correlation Coefficient	.285**	-.652**
		Sig. (2-tailed)	.005	.000
		N	95	95
**. Correlation is significant at the 0.01 level (2-tailed).				

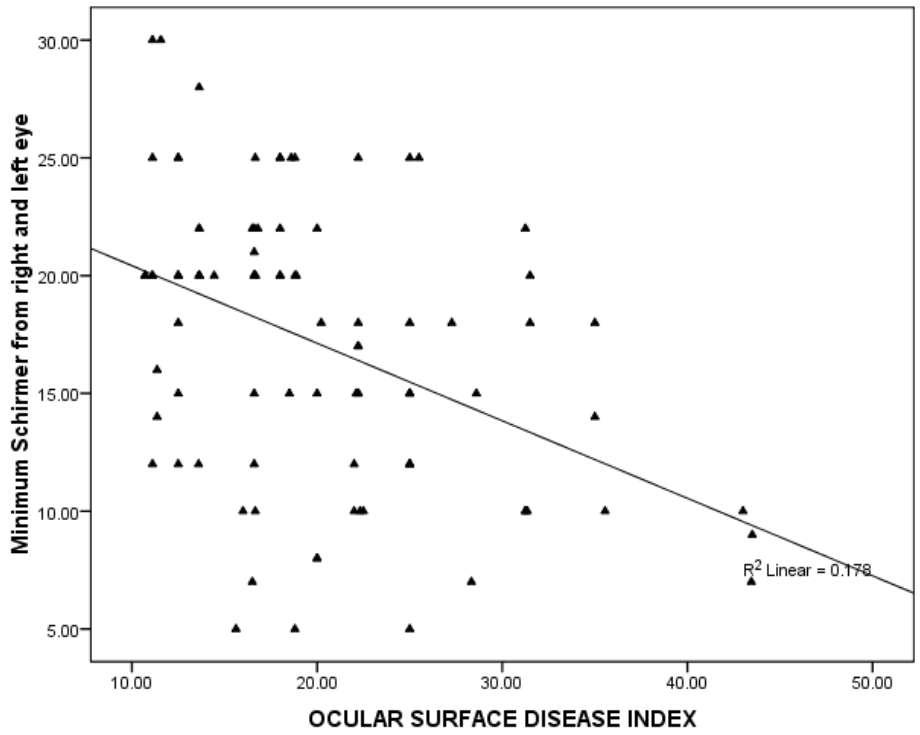

Fig.22, Scatter plot showing association between Schirmer I and OSDI

There is modest negative correlation as shown in figure 22 ,between subjective symptoms depicted by OSDI and Schirmer I test value, with correlation coefficient of -0.397 and p<0.001.

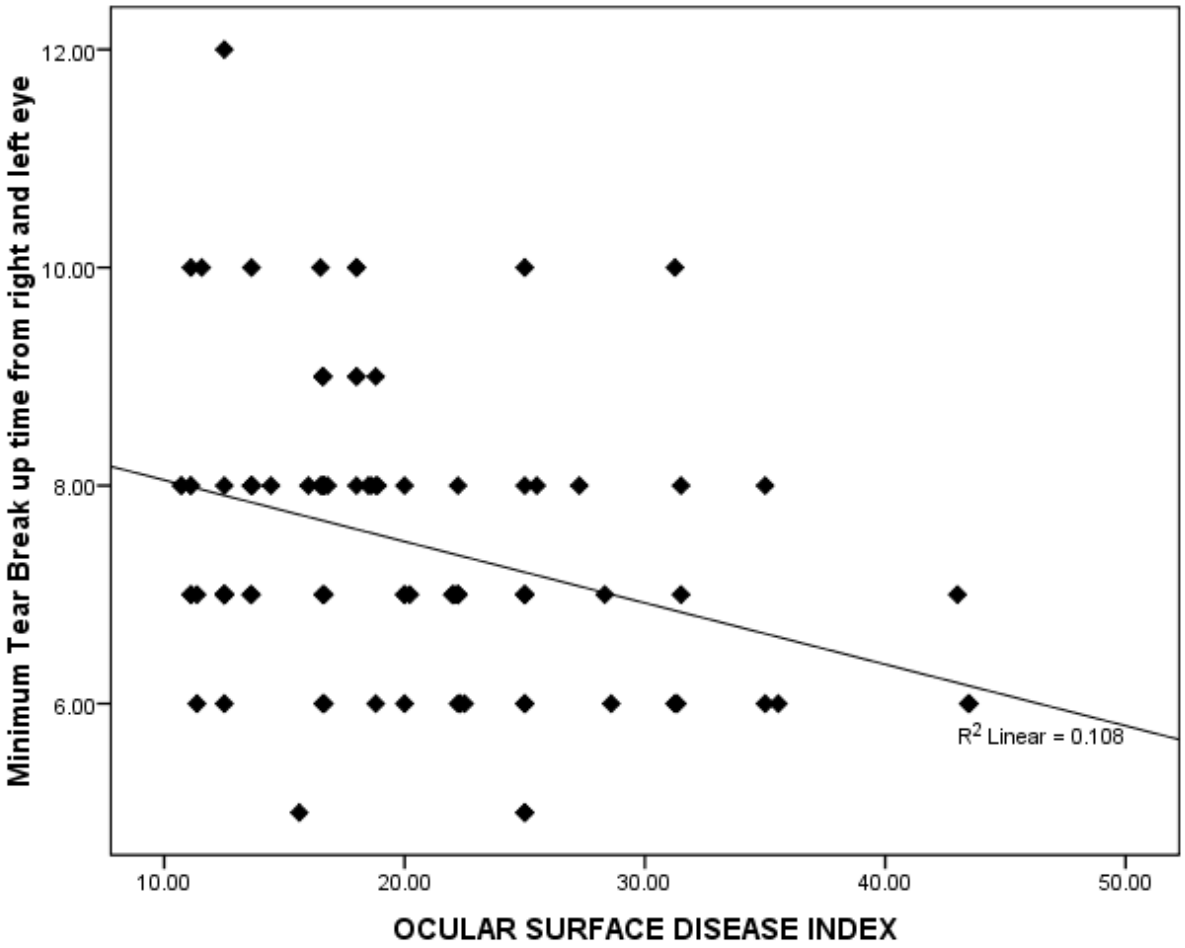

Fig.23, Association between TBUT and OSDI

There is modest negative correlation between subjective symptoms depicted by OSDI and TBUT test value, with correlation coefficient of -0.341 and p<0.001 as shown in figure23.

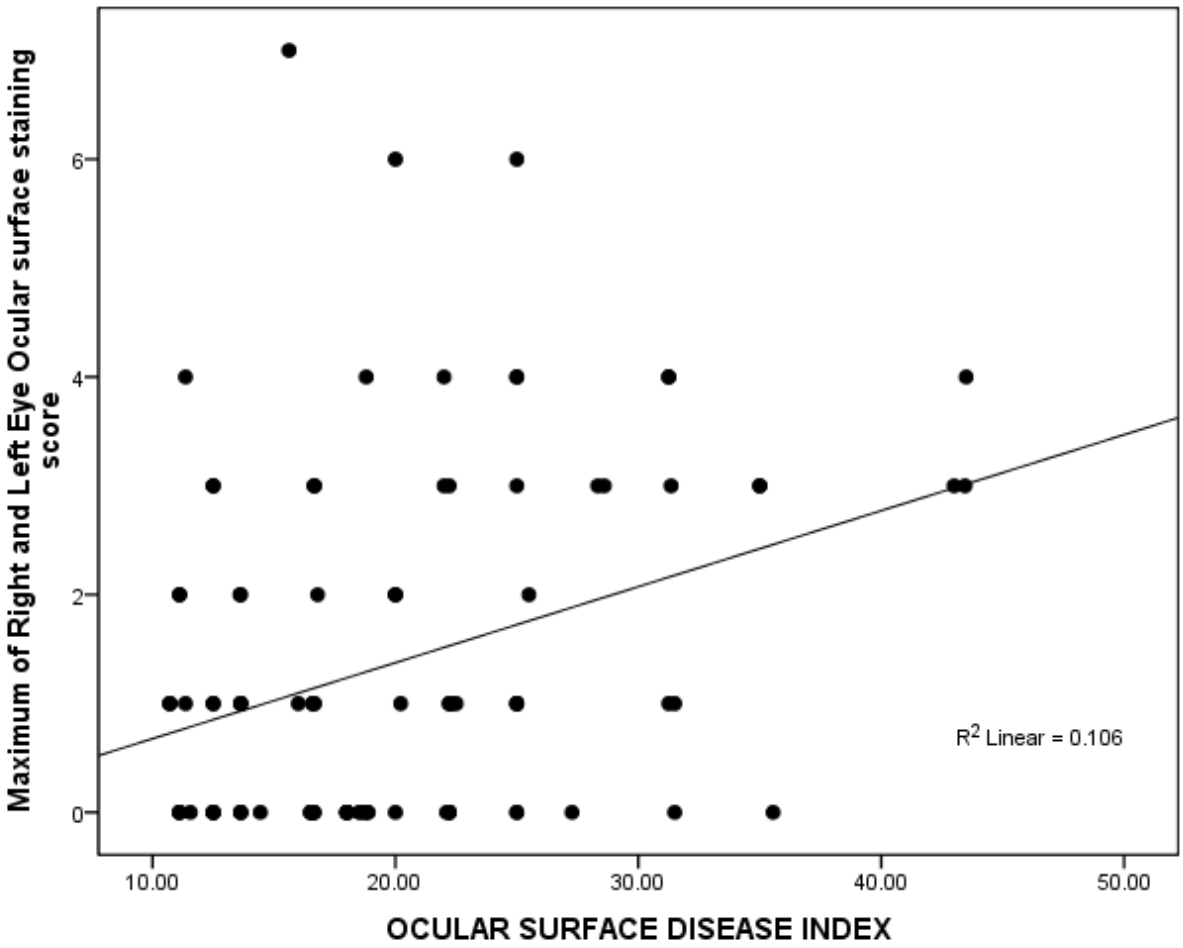

Fig.24, Association between OSS and OSDI

There is modest positive correlation between subjective symptoms depicted by OSDI and Schirmer I test value, with correlation coefficient of +0.285 and $p<0.001$ as shown in figure 24.

CORELATION BETWEEN IMMUNOLOGICAL VARIBLES (ANTI-SSA AND ANTI-SSB) WITH OBJECTIVE TESTS (SCHIRMER I, TBUT, OSS)

Corelation of anti SSA :

Corelation of anti SSA value with Schirmer I test,TBUT and OSS suggests a positive likehood ratio of 1.86,2.48 and 1.90 respectively

Table 15, Corelation of anti SSA value with Schirmer I test,TBUT and OSS

	Sensitivity(%)	Specificity(%)	PPV(%)	+LR
OSDI	60	60.32	41.86	1.51
Schirmer I	46.7	75.8	48.3	1.92
TBUT	63.3	51.6	38.8	1.31
OSS	40	79	48	1.90

Table 16, Corelation of anti SSA value with Schirmer I test,TBUT and OSS

Statistics						
ANTI SSA			OCULAR SURFACE DISEASE INDEX	max_oss	lsch	ltbut
Positive	N	Valid	30	30	30	30
		Missing	0	0	0	0
		Mean	23.2780	1.70	15.1667	7.1667
		Std. Deviation	8.83059	1.557	5.71196	1.23409
		Minimum	10.71	0	5.00	6.00
		Maximum	43.50	4	25.00	10.00
	Percentiles	25	16.6450	.00	10.0000	6.0000
		50	22.2200	1.00	15.0000	7.0000
		75	29.2625	3.00	20.0000	8.0000
Negative	N	Valid	62	62	62	62
		Missing	0	0	0	0
		Mean	18.6740	1.29	17.8387	7.6129
		Std. Deviation	6.60212	1.663	5.89858	1.33496
		Minimum	10.71	0	5.00	5.00
		Maximum	43.00	7	30.00	12.00
	Percentiles	25	13.6300	.00	14.7500	7.0000
		50	16.7300	1.00	20.0000	8.0000
		75	22.2200	2.00	22.0000	8.0000

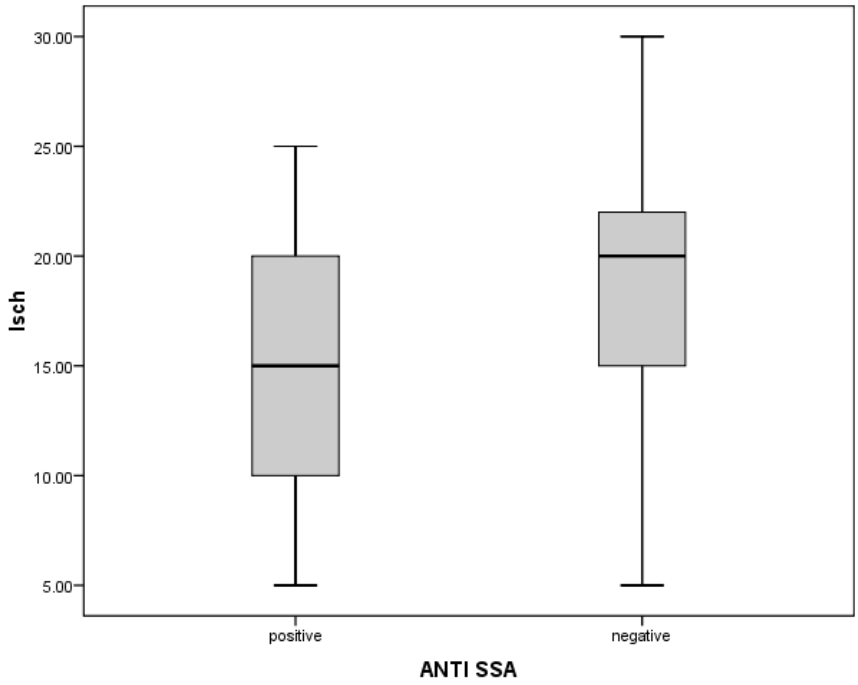

Fig.25, Box Plot Showing Median Value Of Schirmer I among two groups (anti SSA positive and anti SSA negative group)

In the box plot shown above in Figure 25 median value of Schirmer I test seen in anti SSA positive group is around 15mm± 5.7mm with a range of 5mm to 25mm.

The median value seen in anti SSA negative group which is around 17.8 mm± 5.8mm with a range of 5mm to 30mm.

The sensitivity and specificity of Schirmer I test is 46.7% and 75.8%, with a positive likehood ratio of 1.92.

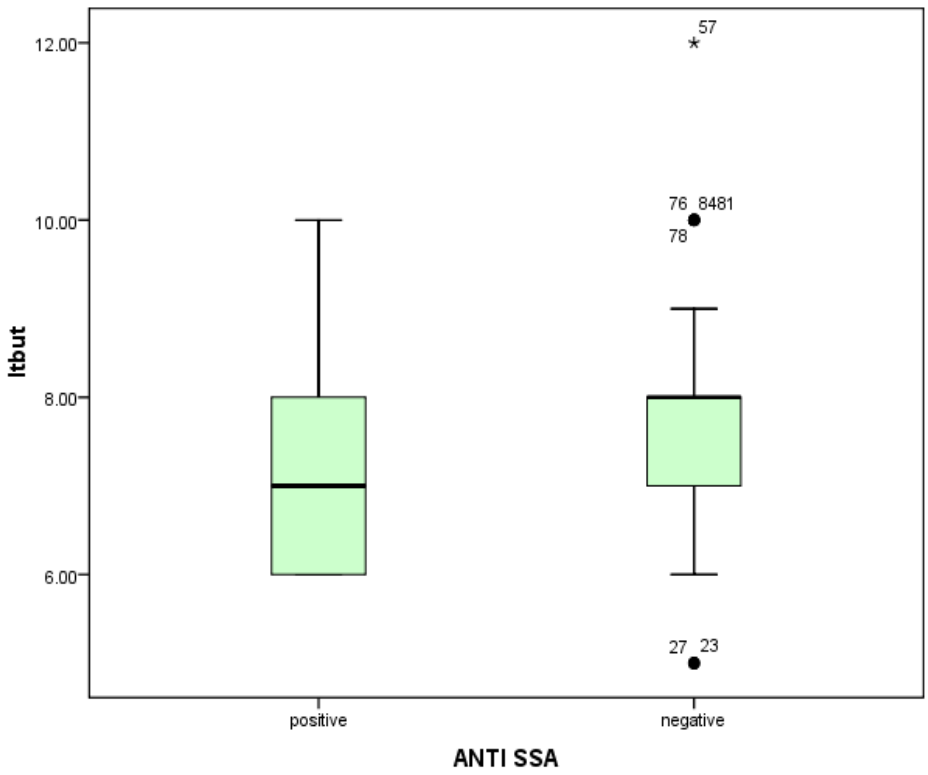

Fig.26, Box Plot Showing Median Value of TBUT among two groups (anti SSA positive and anti SSA negative group)

In the box plot shown above in Figure 26 median value of TBUT test seen in anti SSA positive group is around 7.1secs ± 1.2 secs with a range of 6secs to 10 secs.

The median value seen in anti SSA negative group which is around 7.6 secs±1.3sec with a range of 5 secs to 12 secs. However 2 patients have a very low TBUT score of around 4 secs in this group and 5 patients have a higher value for TBUT in this group.

The sensitivity and specificity of TBUT test is 63.3% and 51.6%, with a positive likehood ratio of 1.31.

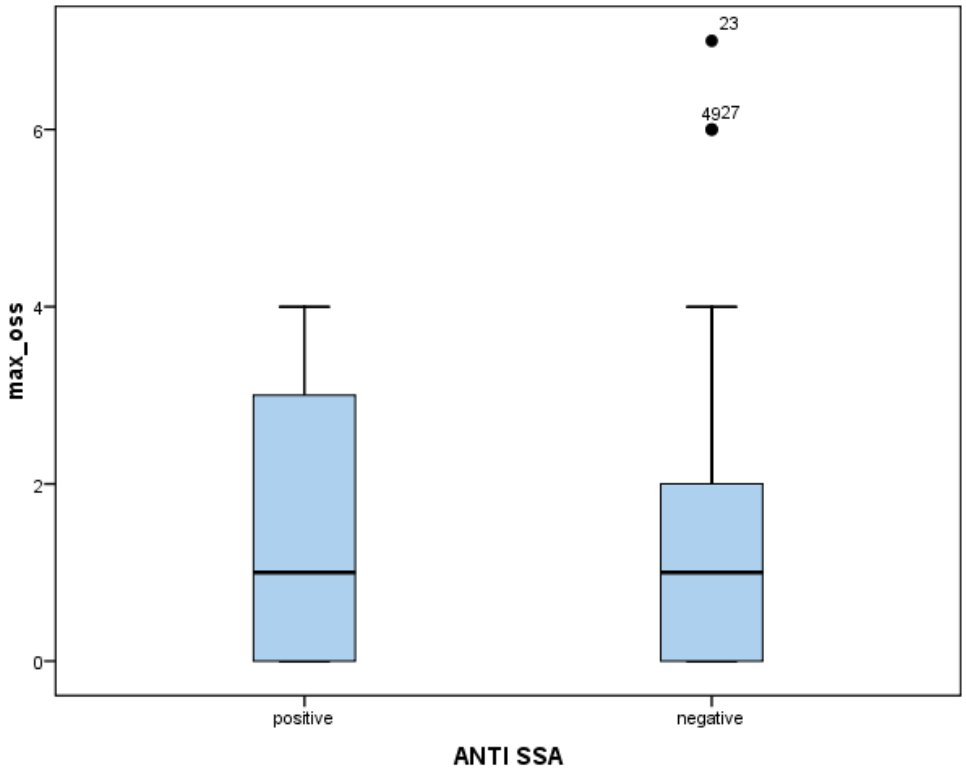

Fig.27, Box Plot Showing Median Value of OSS among two groups (anti SSA positive and anti SSA negative group)

In the box plot shown above in Figure 27 median value of OSS seen in anti SSA positive group is around 1.7 ± 1.7 with a range of 0 to 4.

The median value seen in anti SSA negative group which is around 1.2 ±1.6 with a range of 0 to 7. However 3 patients have a very high OSS score of around 6 in this group.

The sensitivity and specificity of OSS is 40% and 79%, with a positive likehood ratio of 1.90.

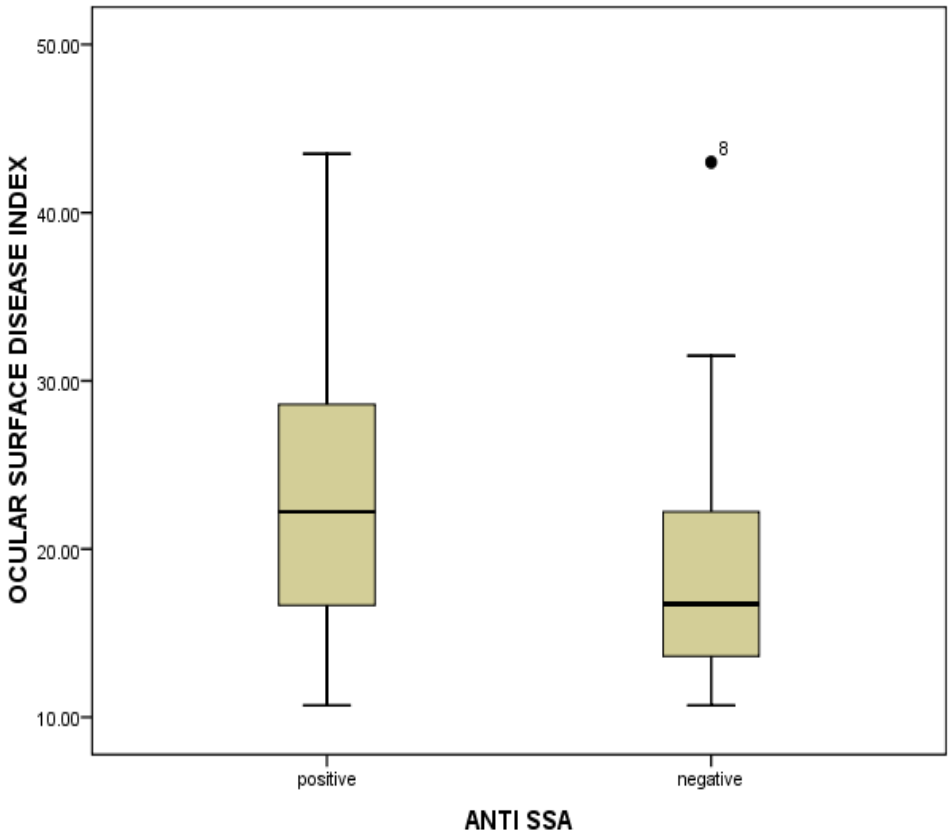

Fig.28, Box Plot Showing Median Value of OSDI among two groups (anti SSA positive and anti SSA negative group)

In the box plot shown above in Figure 28 median value of OSDI score seen in anti SSA positive group is around 23.2 ± 8.8 with a range of 10.7 to 43.5.

The median value seen in anti SSA negative group which is around 18.6 ±6.6 with a range of 10.7 to 43. However only 1 patient has an OSDI score of around 40 in this group.

The sensitivity and specificity of OSS is 60% and 60.3%, with a positive likehood ratio of 1.51.

Corelation of anti-SSB :

Corelation of anti SSB with Schirmer I test, TBUT and OSS suggests a positive likehood ratio of 1.72, 1.52 and 1.43 respectively as shown in table below

Table 17, Corelation of anti SSB with Schirmer I test, TBUT and OSS

	Sensitivity(%)	Specificity(%)	PPV(%)	+LR
OSDI	72.73	55.95	17.78	1.65
Schirmer I	54.5	68.4	33.3	1.72
TBUT	72.7	52.6	30.8	1.52
OSS	45.5	68.4	18.8	1.43

Table 18, Corelation of anti SSB with Schirmer I test, TBUT and OSS

Statistics						
ANTI SSB			OCULAR SURFACE DISEASE INDEX	max_oss	lsch	ltbut
positive	N	Valid	11	11	11	11
		Missing	0	0	0	0
		Mean	23.9527	1.82	13.0000	6.7273
		Std. Deviation	10.22217	1.779	5.56776	.90453
		Minimum	10.71	0	5.00	6.00
		Maximum	43.50	4	20.00	8.00
	Percentiles	25	16.5000	.00	9.0000	6.0000
		50	22.2200	1.00	10.0000	6.0000
		75	31.3500	4.00	20.0000	8.0000
negative	N	Valid	38	38	38	38
		Missing	0	0	0	0
		Mean	20.4721	1.58	17.5000	7.6579
		Std. Deviation	7.32232	1.855	5.82516	1.49370
		Minimum	11.11	0	5.00	5.00
		Maximum	43.00	7	28.00	12.00
	Percentiles	25	15.1225	.00	12.0000	7.0000
		50	18.4000	1.00	18.0000	8.0000
		75	25.0000	3.00	22.0000	8.2500

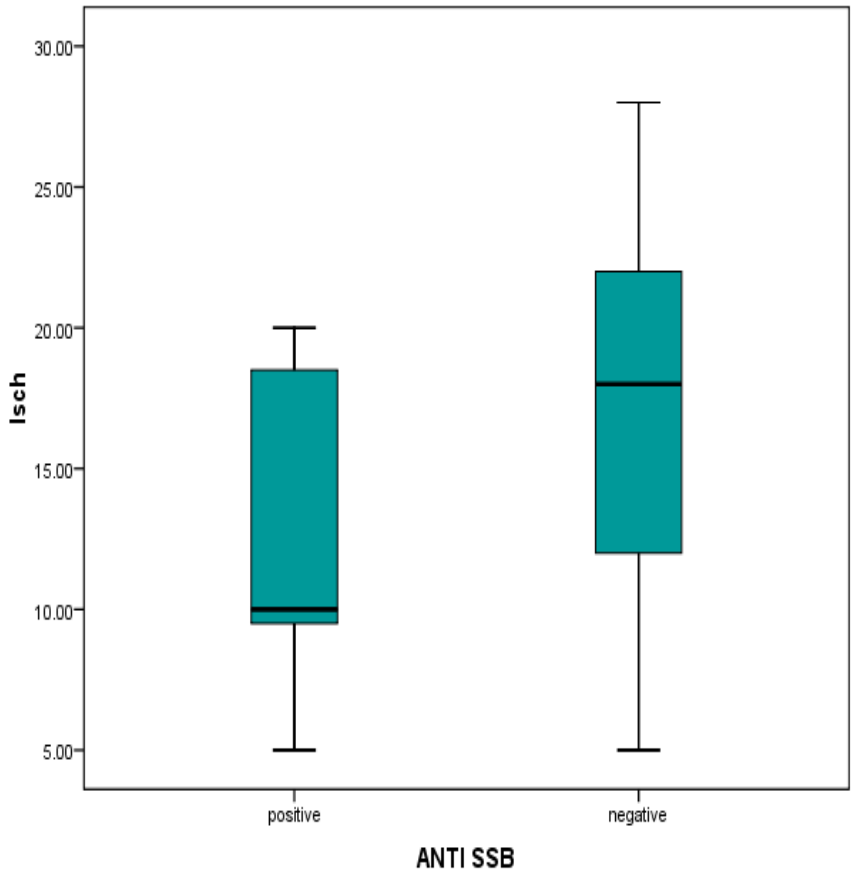

Fig.29, Box Plot Showing Median Value of Schirmer I among two groups (anti SSB positive and anti SSB negative group)

In the box plot shown above in Figure 29 median value of Schirmer I test seen in anti SSB positive group is around 13mm± 5.5mm with a range of 5mm to 20mm.

The median value seen in anti SSB negative group which is around 17.5 mm± 5.8mm with a range of 5mm to 28mm.

The sensitivity and specificity of Schirmer I test is 54.5% and 68.4%, with a positive likehood ratio of 1.72.

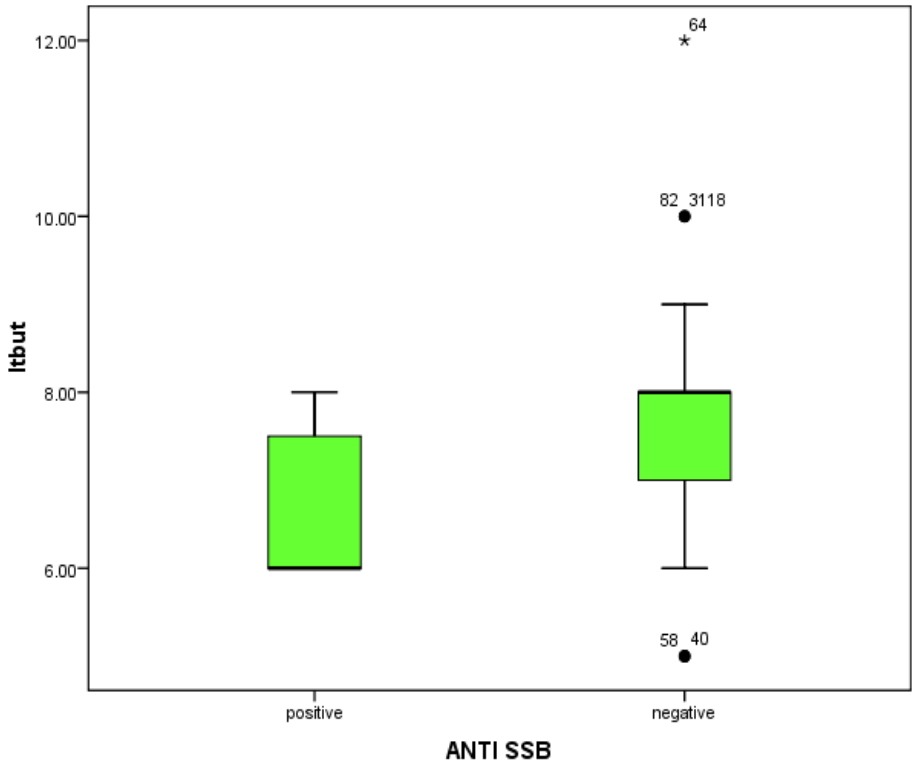

Fig.30, Box Plot Showing Median Value of TBUT among two groups

(anti SSB positive and anti SSB negative group)

In the box plot shown above in Figure 30 median value of TBUT test seen in anti SSB positive group is around 6.7secs ± 0.9 secs with a range of 6secs to 8 secs.

The median value seen in anti SSB negative group which is around 7.6 secs±1.4sec with a range of 5 secs to 12 secs. However 2 patients have a very low TBUT score of around 4 secs in this group and 4 patients have a higher value(>10secs) for TBUT in this group.

The sensitivity and specificity of TBUT test is 72.7% and 52.6%, with a positive likehood ratio of 1.52.

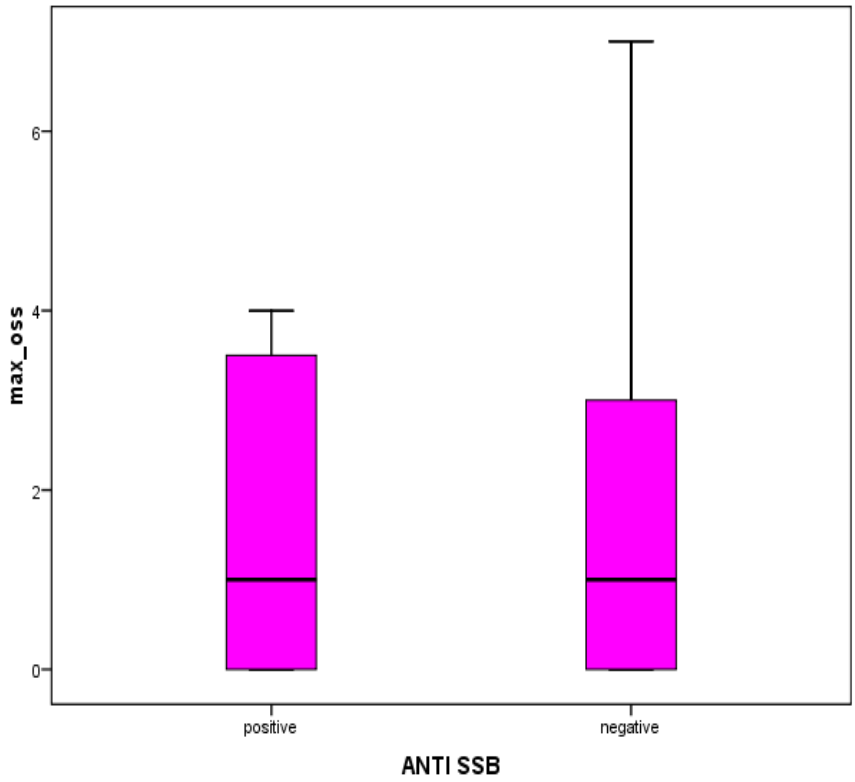

Fig.31, Box Plot Showing Median Value of OSS among two groups

(anti SSB positive and anti SSB negative group)

In the box plot shown above in Figure 31 ,median value of OSS seen in anti SSB positive group is around 1.82 ± 1.7 with a range of 0 to 4.

The median value seen in anti SSB negative group which is around 1.5 ±1.8 with a range of 0 to 7. However 3 patients have a very high OSS score of around 6 in this group.

The sensitivity and specificity of OSS is 45.5% and 68.4%, with a positive likehood ratio of 1.43.

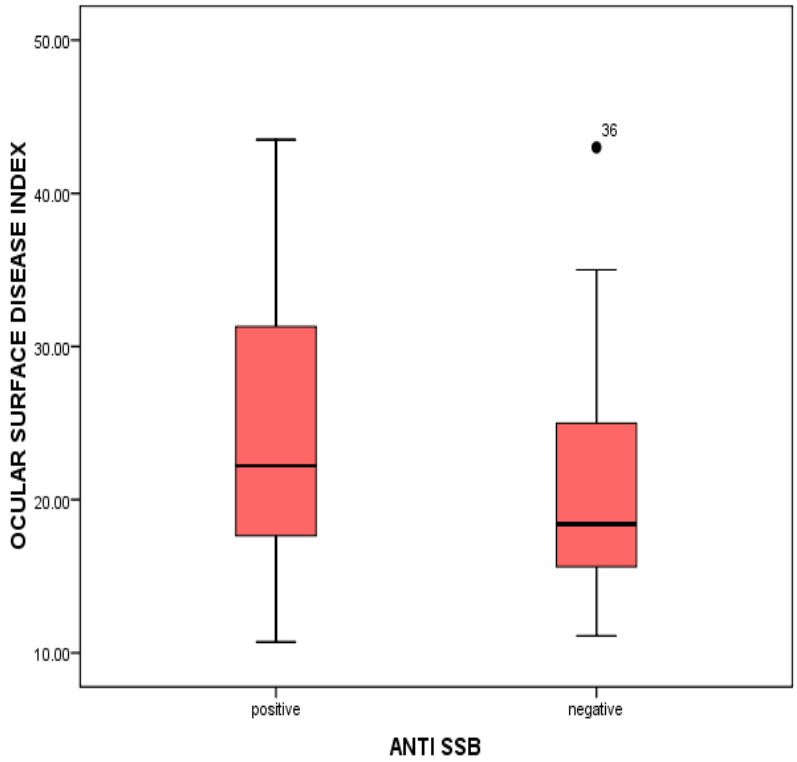

Fig.32, Box Plot Showing Median Value of OSDI among two groups

(anti SSB positive and anti SSB negative group)

In the box plot shown above in Figure 32 median value of OSDI score seen in anti SSB positive group is around 23.9 ± 10.2 with a range of 10.7 to 43.5.

The median value seen in anti SSB negative group which is around 20.46 ±7.3 with a range of 11.11 to 43. However only 1 patient has an OSDI score of around 40 in this group.

The sensitivity and specificity of OSS is 72.73% and 55.95%, with a positive likehood ratio of 1.65.

CORELATION BETWEEN LABIAL BIOPSY AND OSDI, SCHIRMER, TBUT, OSS

The corelation of labial biopsy with Schirmer I, TBUT and OSS suggest a likelihood ratio of 3.38,1.80 and 4.89 as shown in table below

Table 19, The corelation of labial biopsy with Schirmer I, TBUT and OSS

	Sensitivity(%)	Specificity(%)	PPV(%)	+LR
OSDI	70.27	67.24	57.78	2.15
Schirmer I	54.1	84.2	69	3.38
TBUT	73	59.6	54	1.80
OSS	51.4	89.5	76.0	4.89

Table 20, The corelation of labial biopsy with Schirmer I, TBUT and OSS

LABIAL BIOPSY			OCULAR SURFACE DISEASE INDEX	max_oss	lsch	ltbut
Positive	N	Valid	37	37	37	37
		Missing	0	0	0	0
		Mean	24.1586	2.22	13.9730	6.8919
		Minimum	10.71	0	5.00	5.00
		Maximum	43.50	7	25.00	10.00
	Percentiles	25	16.6650	1.00	10.0000	6.0000
		50	22.2200	3.00	14.0000	7.0000
		75	31.2500	3.50	20.0000	8.0000
		Std. Deviation	9.00369	1.797	5.57019	1.14949
Negative	N	Valid	57	57	57	57
		Missing	0	0	0	0
		Mean	17.4844	.82	19.1053	7.8596
		Minimum	11.10	0	8.00	5.00
		Maximum	35.55	6	30.00	12.00
	Percentiles	25	13.6150	.00	15.0000	7.0000
		50	16.6000	.00	20.0000	8.0000
		75	20.0000	1.00	22.0000	8.0000
		Std. Deviation	5.10798	1.255	5.30729	1.27389

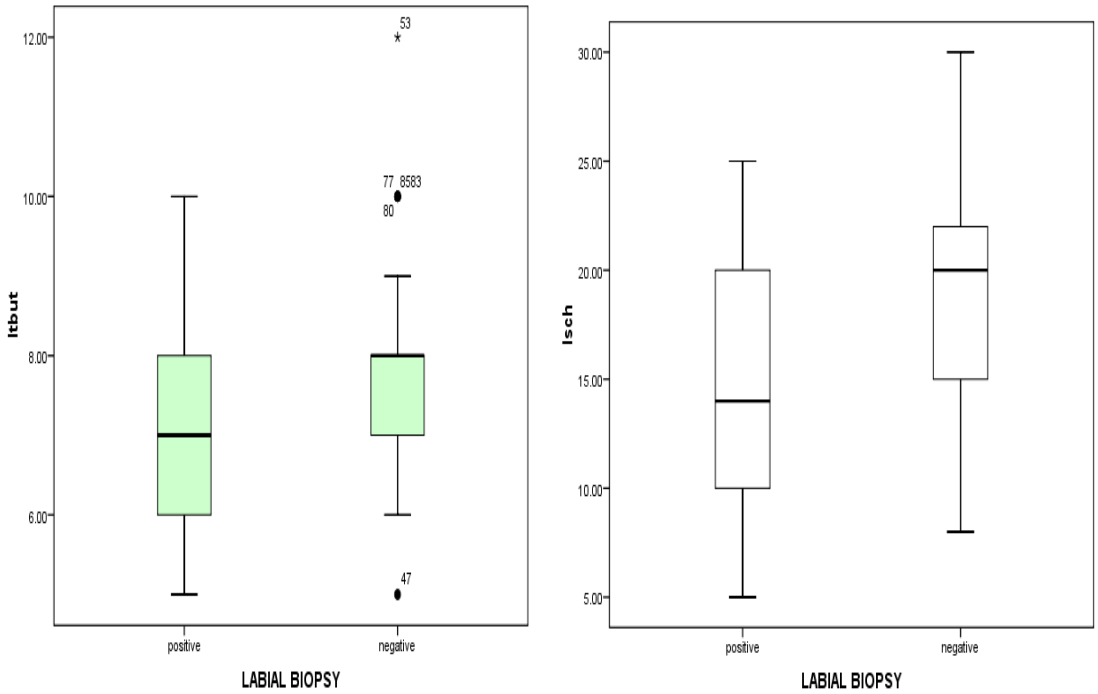

Fig.33 and 34, Box Plot Showing Median Value of TBUT and Schirmer I respectively among two groups

(labial biopsy positive and labial biopsy negative group)

In the box plot shown above in Figure 34, median value of Schirmer I test seen in biopsy positive group is around 13.9mm± 5mm with a range of 5mm to 25mm. The median value seen in labial biopsy negative group which is around 19.1 mm± 8mm with a range of 8 mm to 30mm. The sensitivity and specificity of Schirmer I test is 54.1% and 84.2%, with a positive likehood ratio of 3.38.

In the box plot shown above in Figure 33, median value of TBUT test seen in biopsy positive group is around 6.8secs ± 0.9 secs with a range of 5secs to 10 secs. The median value seen in biopsy negative group which is around 7.8 secs±1.4sec with a range of 5 secs to 12 secs. However 1 patients have a very low TBUT score of around 4 secs in this group and 5 patients have a higher value(>10secs) for TBUT in this group. The sensitivity and specificity of TBUT test is 73% and 59.6%, with a positive likehood ratio of 1.80.

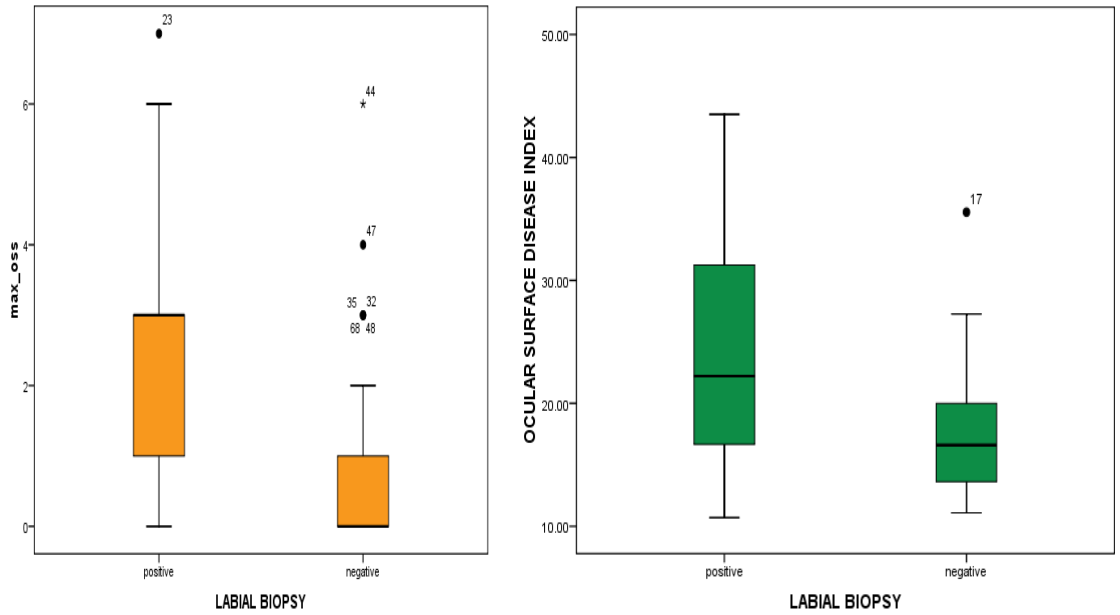

Fig.35 and 36, Box Plot Showing Median Value of OSS and OSDI respectively among two groups

(labial biopsy positive and labial biopsy negative group)

In the box plot shown above in Figure 35 ,median value of OSS seen in biopsy positive group is around 2.22 with a range of 0 to 7. The median value seen in biopsy negative group which is around 0.82 with a range of 0 to 6. However 6 patients have a very high OSS score of around 6 in this group. The sensitivity and specificity of OSS is 51.4% and 89.5%, with a positive likehood ratio of 4.89.

In the box plot shown above in Figure 36 median value of OSDI score seen in biopsy positive group is around 24.15 with a range of 10.7 to 43.5. The median value seen in biopsy negative group which is around 17.48 with a range of 11.11 to 35.5. However only 1 patient has an OSDI score of around 40 in this group. The sensitivity and specificity of OSS is 70.27% and 67.24%, with a positive likehood ratio of 2.15.

DISCUSSION

DISCUSSION

Many of the autoimmune diseases, especially Sjogren's syndrome presents with complaints of dry eye. The ocular surface, forms an integrated part of diagnostic algorithms, either as a part of questionnaires or as objective tests, such as Schirmer test I, Schirmer test II, TBUT, vital dye such as Rose bengal score (RBS), fluorescein and lissamine, ocular staining score (OSS).

Inspite of knowing the importance of proper usage of these diagnostic tests in our clinical decisions, many tests have still not been subjected for precise evaluation, in order to determine their clinical effectiveness in diagnosing the disease.

In our study, the incidence of primary Sjogren's syndrome was 32.63% (31 patients).

94.7% of the patients were female and most (56.8%) of the patients were in the age group of 41-60 years suggesting that the disease is more common among females and peak incidence is in 4^{th} to 5^{th} decade as seen in previous studies(3).

Ocular symptoms can be exaggerated by the decrease in humidity that exists in air-conditioning environment, dry weather and exposure to smoke of cigarette. The dry eye symptoms were not associated with the occupation of the patient, as most of the female patients (66 patients) were housewives and very few (3 patients) were working with air conditioner in their office out of which 2 of them were in SS group, but the difference is not statistically significant. Thereby in this study, the symptoms cannot be associated with the surrounding environmental condition.

Ocular complaints:

Ocular complaints were seen in most (90.5%) of the patients in our study and that may be the reason for the clinical suspicion of Sjogren's syndrome. The mean duration of symptoms was 2.15 years with a minimum of 1 month and maximum of 96 months. There was no difference in the duration of symptoms between male and female patients. The most common ocular complaints seen were itching and foreign body sensation (56.8% patients). Objective tests of dry eye (like Schirmer I, TBUT, OSS) in these symptomatic patients with complaints of itching and foreign body sensation, did not show statistically significant difference between SS and Non SS group ($p>0.05$).

The other ocular complaints like irritation, redness, stickiness, photophobia, gritty sensation, intolerance to CL, visual disturbance and swelling over cheek (parotid enlargement) had a varied distribution in between two groups.

Visual acuity of most of the patients (85.26%) was 6/6 and only 2 patients of age group 50-60 years have decreased vision that may be due to age related cataract.

Anti- SSA /anti- SSB:

Many studies(36) found the association of anti SSA and anti SSB with the diagnosis of pSS. Study conducted by **Hammi et al**(32) found that anti SSA/Ro and anti SSB/La antibodies in serum were more useful than in saliva for diagnosing the disease($p=0.001$). **Hansen** et al(72) conducted a study in103 patients of pSS diagnosed by Copenhagen criteria and proposed that 67% were positive for anti SSB and 71% patients were positive for anti SSA. They also concluded that in his study all anti SSB positive patients had anti SSA also. **Toker et** al(34) found the association of these

antibodies with the severity of the disease and also noted that the percentage of patients who were positive for anti SSA were more than for anti SSB as seen in our study. **Jacobson et al**(56) found increased level of anti SSA and anti SSB in patients with symptoms of dry eye but difference was not significant.

In our study anti SSA was positive in 23 patients and anti SSB was positive in 11 patients who were diagnosed to have pSS. So in our study there is good association between anti SSA and diagnosis of pSS (sensitivity of 76.7% and specificity of 88.7% positive predictive value of 76.7%, +LR of 6.78).

The sensitivity of anti SSB was found to be poor (52.4%) but good specificity (73.7%). The positive likelihood ratio was found to be 1.99. Most (72.7%) of the patients who were positive for anti SSB were also positive for anti SSA which is in line with other studies.(34) It can account that anti SSA test is feasible and can be done alone as a diagnostic test to make it affordable.

Labial biopsy:

Minor salivary is considered to be the 'gold standard' in diagnosing primary Sjogren's syndrome. **Nakamura et al** (36)(73) conducted a retrospective study and found an association between minor salivary gland biopsy and the diagnosis of pSS (odds ratio 105;95% CI 13, 849). **Yazisiz et al** (74)concluded that MSGB has the best predictive value for diagnosis of pSS with highest sensitivity and specificity($p<0.001$). **Guellec et al** (37) failed to found the association between MSGB and the disease.

Our study found a good association of MSGB with the diagnosis of the disease (sensitivity of 96.8% and specificity of 88.9% and Positive predictive value of 81.1%, + LR of 8.72).

Depending on the attitudes of individual researchers, labial biopsy is indicated if there is suspicion in final diagnosis based on clinical symptoms. However, it is important to note that the biopsy has a wider clinical utility, because it can be detected and other diseases, such as the sarcoidosis.

Diagnostic criteria:

We found 31 patients diagnosed of pSS in our study on the basis of ACR criteria (6),in which the patients who were positive for OSS score were also considered. Most of them fall into the diagnostic criteria as they have anti SSA positive and labial biopsy positive. We had an added advantage of not including the patients on the basis of AECG criteria(47) which takes into account the subjective symptoms and misclassify most of the symptomatic patients as seen in other studies(2) but the inclusion of OSS score in ACR criteria becomes the limitation of our study.

In the American-European Community (AECG) criteria, positive objective ocular signs includes positive test result of Schirmer I or positive Rose Bengal staining (RBS)(75). Most of the studies recruit the patients as Sjogren's syndrome, based on the results of these tests making a major limitation of incorporation bias. In our study patients were recruited on the basis of ACR criteria(6) which does not include Sch-I.

OSDI score

OSDI score of severe (36) was seen in 3 patients and all 3 were having pSS but this could not account for good predictive value as the high score was seen in very small portion of the study group. Most of the patients (64.5%) were in range of mild to moderate OSDI score (18-36). This distribution suggest that most patients of pSS were having mild to moderate symptoms thereby making OSDI as one of the useful diagnostic

tool. Few patients (25%) were having OSDI in normal range which can be explained either due to reduced severity of the disease or due to use of lubricants.

OSDI has a moderate performance in diagnosing the disease (sensitivity of 71%, specificity of 65%, $p<0.001$) with the median value seen in the disease group (pSS) as 24.60± 9.36 with area under curve of 0.718 and a positive likelihood ratio of 2.02.

OSDI score used in many research(9)(61)(76), showed high specificity and a relative diagnostic features used by clinician for diagnosis of pSS.

Schiffman et al (9) concluded that OSDI has good sensitivity and specificity which is effective in discriminating normal and various grades of dry eyes as defined by physician's evaluation of severity and a composite disease severity score.

Vitale et al (53) found a modest association between objective measures of dry eye and questionnaire of VT-HRQ, whereas NEI-VFQ and OSDI was found to have similar impact of SS-related dry eye on VT-HRQ.

As the process of collecting information related to patient's ocular complaint is tedious due to heterogenicity of symptoms. In this study we included OSDI questionnaire as it is fast in evaluating symptoms and later it can also be used for comparison of same symptoms over time or after therapy. Although it has been described in studies that ocular surface damage may not always be associated with symptoms.

But in our study 74% patients were found to have a score of 18 or more suggesting its association with the disease damage, but 45% of the Non SS group was also found to have a score of 18 or more which can be due to age related dry eye or some other pathology. The average score found in our study in pSS group was 24.6. One

possibility of difference in our result in comparison to Vitale(53) may be the stoppage of lubricant in our study one day prior to test.

Schirmer I test:

The utility and diagnostic efficacy of Schirmer I is still a topic of debate. **Vitali et al**(75), demonstrated that Schirmer test is one of the reliable test for diagnosis of SS which shows a balance between sensitivity and specificity, which is also supported by the study of **Hay et al**(1) who found a good sensitivity and specificity of Schirmer test in hospital setting against the clinician 'gold standard' diagnosis of Sjogren's syndrome. **Whitcher et al**(7) showed a significant difference in test results of Schirmer test in SS-KCS and KCS only group. But some of the studies(77)(64) revealed that Schirmer test has poor diagnostic accuracy and there is a weak correlation between the tests results and patients symptoms (63).

The most widely contained opinion is that Schirmer test is not very reliable test and have a poor reproducibility(55) (78)(79)(80)which vary at every visit. And it is also shown to have less diagnostic value(1) in mild to moderate dry eyes, but a very low Schirmer I value can be considered as a good indicator of aqueous deficient tear film.

Schirmer I value of ≤ 5mm/5min was the cut off mentioned in AECG criteria for pSS in many studies(62)(61). In our study only 9.67% of the pSS group has a Schirmer value ≤ 5 with a very low sensitivity (19.4%) and high specificity (96.9%). If we use this as a limit value then this would significantly diminishes its clinical importance and will give a high false negative result. In this study, as projected in other similar studies, more than 50% of the patients showed negative results for Sch-I (77)(78) and if the cut off value of the test is not raised, differential diagnostic performance of the same will

remains relatively weak. Therefore, the mean value of tear secretion is higher than the pathological threshold (≤ 5mm /5mins) between 2 groups.

In our study cut off value for Schirmer I is more than reference range with ≤ 15mm (sensitivity of 64.5% and specificity 85.90%).The likelihood ratio is high (4.57) with ROC curve showing the large area under the curve (0.779) which is almost equal to the AUC of TBUT (0.780), thereby making both Sch I and TBUT equally effective in diagnosing the disease. No significant differences between ROC curves of TBUT test and Sch-I tests ($p<0.001$). Schirmer I (done without use of local anesthesia) alone, act as a relative single diagnostic test for viewing the effect of staging of the disease and effect of therapy on the test score.

So in our study Schirmer I has better diagnostic performance than OSS in an Indian population, since there is statistically significant difference between two group of patients ($p<0.001$, Mann whitney, 94). Findings in this study are in mild discrepancy with other similar research.

Mean values of Schirmer I test in patients with pSS group amounted to 12.77 mm± 5.37, and in patients with Non SS group is 19.21 mm ± 4.97.

TBUT test values

In our study, for TBUT ≤ 10secs, sensitivity was high (96.8%) but specificity was low (12.5 %) which means that if the test is negative the possibility of having disease cannot be excluded as seen in other studies(66). Most commonly described marginal TBUT test value is 10 sec in many studies.

TBUT depicting a limit value of 8 secs was found to have a balance of sensitivity (80.6%) and specificity (60.90%) in our study, which is in line with other studies(80).

There was a statistically significant difference ($p<0.001$) seen in TBUT value between two groups. Mean TBUT in patients with pSS group is 6.6±1.04 sec and in Non SS group is 7.87±1.24 sec. The role of TBUT in diagnosis of pSS is shown by ROC curve which is shifted towards upper left corner and area under the curve is 0.780 which is almost same as that of Schirmer I (0.779), thereby having equally good efficacy in diagnosing the disease. The standard error seen was 0.052 with 95% confidence interval of 0.679 -0.881.

We found good diagnostic performance of TBUT (+LR of 2.06) in our population with statistically significant difference between the two groups ($p<0.001$).

OSS score

In our study, for OSS of 3 or more, sensitivity is high (90.60%) with average specificity (61.3%) It is the most common limit range value seen in other studies and also in ACR criteria ((6)(68). There was a statistically significant difference ($p<0.001$) seen in OSS value between the two groups. Mean OSS in patients with pSS group is 2.48±1.84 sec and in Non SS group is 0.84±1.19 sec. The role of OSS in diagnosis of pSS is shown by ROC curve which is shifted towards upper left corner with area under the curve is 0.766 and positive likelihood ratio of 2.34 which is less than that of Schirmer I and TBUT. We found an average diagnostic performance of OSS in our population with statistically significant difference between the two groups ($p<0.001$).

Whitcher et al(68) found that among participant with KCS only, median OSS (Ocular staining score) was 5 compared to 9 among those with SS-KCS with statistically significant difference between 2 subgroups ($p<0.0001$). This study also showed

significant difference in Schirmer I and TBUT among 2 subgroups with no difference in symptoms of dry eye or dry mouth.

Corelation between subjective symptoms by (OSS score) and SchirmerI,TBUT and OSS

In our study, OSDI shows a moderate correlation with other tests such as Schirmer I, TBUT and OSS which is in line with other studies(49).This moderate correlation can be because of heterogenous group of patients with dry eyes, these measures do not have sufficient sensitivity to assess the complete range of dry eye abnormalities. And in some patients, these measures may correlate closely to patient perception of disease severity. Therefore OSDI is unique in quantitative assessment of both frequency of dry eye symptoms and impact of these on the vision related functioning. It also has required psychometric ability to be used as an end point for clinical trials of dry eye disease.

Hay et al (1) found no association was seen between antibody to SSA or SSB and either symptoms or signs of dry eyes or dry mouth. Strongest association was seen in subjects with both ocular and oral symptoms and objective tests. He concluded a weak association between the presence of oral or ocular symptoms and test results of USF (unstimulated salivary flow) or Schirmer I. They analysed the association separately for subjects less than and over 55 years of age and found a higher frequencies of abnormal findings in the elderly. It was due to age related changes causing dysfunction of lacrimal and salivary glands. Ocular symptom in elderly was assumed to be probably due to other causes like blepharitis thereby not giving an abnormal Schirmer test.

Barboza et al (63) showed a weak correlation between the symptoms of patients with Sjögren's syndrome and ocular signs that indicate disease severity concluding that

all symptomatic patients did not showed positivity for corresponding tests. This weak correlation was attributed to variation in corneal sensitivity.

Nichols et al (65) found a poor correlation between symptoms of dry eyes and their tests after adjustment for age and use of lubricants which was also in support of whitcher study (68).

In our studies there is a positive correlation seen between subjective symptoms as depicted by OSDI score and subjective test of Schirmer I, TBUT and OSS score respectively (p value of 0.001, 0.001 and 0.005 respectively).There is a positive correlation seen in between OSDI and OSS (R=+0.285) and a negative correlation of OSDI with Schirmer I and TBUT (R= -.397, R= -.341).

CONCLUSION

CONCLUSION

- Primary Sjogren's syndrome is more common in females, with peak incidence seen in 4^{th} to 5^{th} decade.
- The commonest ocular complaints seen in this study, in patients with pSS were itching and foreign body sensation. Visual disturbance was rare in our study population.
- The mean duration of symptoms was 2.15 years.
- There is a good likelihood of diagnosing pSS with anti SSA than with anti SSB, but biopsy holds the strongest association with the disease (+LR; 8.72). Since it is an invasive method, the results of our study indicate the possibility of performing noninvasive tests in differential diagnosis of pSS, such as Schirmer I, TBUT and OSS, which have good statistical parameters and thereby in future may lead to simplification of the diagnostic protocol for pSS.
- ACR criteria selected in our study for recruitment of patients avoid the misclassification of symptomatic patients as seen in AECG criteria which include subjective symptoms.
- In our study Schirmer I, TBUT, OSS and OSDI scores were statistically worse in patients with pSS compared with patients with Non-SS group.
- Our study shows that if we assume the cut off range of Schirmer I $\leq$ 5mm/5mins and TBUT $\leq$ 10 secs, the clinical importance of the tests is decreased and rate of false negatives increases.
- Our study indicates that the cut off value of Schirmer I $\leq$ 15mm/5mins, TBUT $\leq$ 8 secs and OSS score $\geq$ 3 may offer better diagnostic yield for diagnosing pSS in Indian population.

- Schirmer I was found to have better diagnostic performance with highest likelihood ratio (4.52) than TBUT and OSS (+ LR for TBUT and OSS was 2.06 and 2.34 respectively). So in Indian population, Schirmer I still holds its significance as the test of choice for diagnosis of pSS.
- There is good correlation of symptoms as depicted by OSDI score, with tests like Schirmer I, TBUT and OSS score with $p<0.001$.
- Ophthalmic examination aids to answer to the question, whether patient has Sjogren's syndrome or not, if the above tests are performed properly and understood as to what each of these represent.
- The results of our present study support an increased index of suspicion for dry eye and the possibility of pSS should be considered in all patients with clinically significant dry eyes.
- Sjogren’s syndrome leads to slow and progressive impairment of exocrine gland specially salivary and lacrimal gland function. Therefore it is imperative to perform dry eye tests for early recognition, timely management and monitor response to treatment.

LIMITATION

LIMITATION

- It is assumed that a significant part of pSS patients included in our study have met the ocular sign criteria of ACR, therefore introducing incorporation bias.
- The results of the objective tests (Schirmer I, TBUT and OSS) used in our study may be influenced by the stage of the disease and/or by the therapy.
- Although in our study with the sample size of 95 patients, we were able to correlate the ocular symptoms with dry eye tests, we need to demonstrate this in a larger population.

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APPENDIX : A IRB APPROVAL FORM

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

April 19, 2014

Dr. Roma Johri
PG Registrar
Department of Ophthalmology
Christian Medical College, Vellore 632 004

Sub: **Fluid Research grant project:**
Diagnostic performance of Dry Eye tests in Primary Sjogren's syndrome patients in Indian setting.
Dr. Roma Johri, PG Registrar, Dr. Sarada David, Dr. Jayanthi Peter, Ophthalmology, Dr. Debashish Danda, Dr Sandhya, Rheumatology, CMC, Vellore.

Ref: IRB Min No: 8671 [DIAGNOSE] dated 19.02.2014

Dear Dr. Roma Johri,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Sarada David, Ophthalmology CMC, Vellore

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
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OFFICE OF RESEARCH
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Ref: IRB Min No: 8671 [DIAGNOSE] dated 19.02.2014

Dear Dr. Roma Johri,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Diagnostic performance of Dry Eye tests in Primary Sjogren's syndrome patients in Indian setting." on February 19, 2014.

The Committees reviewed the following documents:

1. IRB Approval Letter
2. Curriculum Vitae' of Drs. Roma Johri, Sarada David, Jayanthi Peter, Debashish Danda.
3. Informed Consent form (English, Tamil, Hindi, Bengali & Telugu)
4. Information sheet (English, Tamil, Hindi, Bengali & Telugu)
5. No of documents 1-4

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on February 19, 2014 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Name	Qualification	Designation	Other Affiliations
Dr. T. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMCH.	Internal, Clinician
Dr. J. Visalakshi	MPH, PhD	Lecturer, Dept. of Biostatistics, CMC.	Internal, Statistician
Dr. Ranjith K Moorthy	MBBS M Ch	Professor, Neurological Sciences, CMCH.	Internal, Clinician
Dr. Chandra Singh	MS, MCH, DMB	Professor, Urology, CMCH.	Internal, Clinician
Dr. Paul Ravindran	PhD, Dip RP, FCCPM	Professor, Radiotherapy, CMCH.	Internal, Clinician
Dr. Bobby John	MBBS, MD, DM, Ph D, MAMS	Professor, Cardiology, CMCH.	Internal, Clinician
Dr. Anup Ramachandran	Ph. D	The Wellcome Trust Research Laboratory Gastrointestinal Sciences, CMCH.	Internal, Basic Medical Scientist
Dr. Inian Samarasam	MS, FRCS, FRACS	Professor, Surgery, CMC	Internal, Clinician
Dr. Niranjan Thomas	DCH, MD, DNB (Paediatrics)	Professor, Neonatology, CMC	Internal, Clinician
Dr. Jacob John	MBBS, MD	Associate Professor, Community Health, CMC	Internal, Clinician
Dr. Rajesh Kannangai	MD, Ph D.	Professor & In-charge Retrovirus Laboratory (NRL under NACO), Department of Clinical Virology, CMCH	Internal, Clinician
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL.	Sr. Legal Officer, CMCH	Internal, Legal Expert

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Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Dr. Shirley David	M.Sc, PhD	Professor, Head of Fundamentals Nursing Department, CMCH	Internal, Nurse
Mrs. Pattabiraman	B. Sc, DSSA	Social Worker, Vellore	External, Lay person
Mr. C. Sampath	B. Sc, BL	Legal Expert, Vellore	External, Legal Expert
Dr. Denise H. Fleming	B. Sc (Hons), PhD	Honorary Professor, Clinical Pharmacology, CMCH.	Internal, Scientist & Pharmacologist
Dr. Vathsala Sadan	M.Sc, PhD	Professor, Community Health Nursing, CMCH.	Internal, Nurse
Dr. Anuradha Rose	MBBS, MD	Assistant Professor, Community Health, CMCH.	Internal, Clinician
Dr. Nihal Thomas	MD, MNAMS, DNB(Endo), FRACP(Endo) FRCP(Edin) FRCP (Glasg)	Professor & Head, Endocrinology. Additional Vice Principal (Research), CMCH. Deputy Chairperson, IRB, Member Secretary (Ethics Committee), IRB	Internal, Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be

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downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:

A sum of 18,950/- INR (Rupees Eighteen Thousand Nine Hundred and Fifty only) will be granted for 1 year.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

NOT TO BE MINISTERED UNTO BUT TO MINISTER
CHRISTIAN MEDICAL COLLEGE
VELLORE
INDIA

Cc: Dr. Sarada David, Ophthalmology CMC, Vellore

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APPENDIX B

INFORMATION SHEET

Title: Diagnostic performance of dry eye tests in Primary Sjogren's Syndrome in an Indian setting.

You are invited to take part in this study. The information in this document is meant to help you decide whether or not to take part in the study. Please feel free to ask if you have any queries or concerns.

What is the study about? Sjögren syndrome is an immunological disease in which your body's immune cells attack and destroy the glands that produces tears and saliva leading to dry eye and dry mouth. It can also affect other organs including lungs, kidneys, skin and the nervous system. Eye symptoms are related to decreased tear secretion. Patients sometimes may not be troubled until symptoms start affecting their daily activities leading to a poor quality of life.

It can occur in two forms: Primary Sjogren syndrome, in which there are symptoms of dry eye and mouth and Secondary Sjogren Syndrome, where it is associated with other disorder like Rheumatoid Arthritis, Systemic Lupus Erythematosis etc .Early recognition of Sjogren syndrome may prevent complication such as corneal ulceration, dental caries, chronic mouth infection and development of serious illnesses like vasculitis, peripheral neuropathy, renal and pulmonary involvement.

However, there is no straightforward and simple diagnostic test for Sjogrens syndrome .The diagnosis depends on clinical signs and symptoms, pathological findings of lower lip biopsy, or the presence of anti SSA and/or anti SSB antibodies in the blood. The tear secretion in the eye can be measured by various tests. They are Schirmer I, Tear Break-up time, Ocular surface staining score. This helps in early recognition of Sjogrens syndrome in a way which is simple, inexpensive, non invasive and easily available so that early treatment plan can be made.

If you take part, what will you have to do?
If you take part in the study, an appointment will be arranged for you to have an eye check up in the Outpatient clinic of the Eye Department. You will have to spend about two to three hours in the department. A routine eye examination will be performed. You will not be required to come for any follow up visits for the purpose of this study.

Are there any risks for you if you take part in the study?
Participation in the study only involves undergoing a routine eye check up. We do not expect any injury to happen to you, but if you do develop any side effects or problems due to the study, these will be treated at no cost to you. However, we are unable to provide any monetary compensation.

Do you have to pay?
As participation in the study involves a routine eye check up in the Outpatient clinic of the Eye department, you will have to pay for a General OPD appointment.

What are the benefits to you if you take part in the study?
As a patient with Primary Sjogren's Syndrome, you are at increased risk of developing dry eye and its complication. If you participate in the study,
1. You will be screened for dry eye, which if detected and treated promptly, can prevent serious ocular complications like corneal scarring, infection, ulceration and loss of vision.
2. You will be counseled regarding the symptoms of dry eye and preventive measures.
3. You will also be able to have a general eye check up and treatment for other unrelated eye problems that you may have.

What are the possible benefits to other people?
The results of the research may provide benefits to the society in terms of advancement of medical knowledge and to help in diagnosing the disease with simple tests.

Can you decide not to participate?
Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way. Your doctor will still take care of you and you will not lose any benefits to which you are entitled.

Will your personal details be kept confidential?
The results of this study may be published in a medical journal, but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask Dr. Roma Johri or Dr. Jayanthi Peter (Tel: 0416 2281201) or email: roma_johri@yahoo.co.in

CONSENT FORM

Study Title- DIAGNOSTIC PERFORMANCE OF DRY EYE TESTS IN PRIMARY SJOGREN SYNDROME PATIENT IN AN INDIAN SETTING

Study Number:
Subject's Initials:
Subject's Name:

Please put your signature here
(Subject)

i I confirm that I have read and understood the information sheet dated for the above study and have had the opportunity to ask questions.

ii. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

iii. I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.

iv. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)

v. I agree to take part in the above study.

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:
Date:
Signatory's Name: _____
Signature of the Investigator: _____
Date: Study Investigator's Name: _____
Signature of the Witness: _____
Date:
Name of the Witness: _____

தகவல் பிரதி
ஒப்புதல் படிவம்

இந்திய அமைப்பில் முதன்மை நிலை ஜோக்ரன் நோய்க்கு உலர் கண் நோயின் சோதனைகளின் மூலம் அதன் செயல்திறனை கண்டறிதல்.

உங்களுக்கு கொடுக்கப்பட்ட தகவல் தாளை படித்து அதில் உங்களுக்கு ஏதாவது கேள்விகள் / சந்தேகங்ளக் இருக்குமானால் தயவு செய்து கேட்டு, பின்னர் இந்த ஆய்வில் பங்கேற்கலாமா, வேண்டாமா என தீர்மானித்த பின்னர் பங்கேற்க விருப்பம் தெரிவிக்கலாம்.

ஜோக்ரன் நோய் (Sojgren Syndrome) என்பது நோய் எதிர்ப்பு சக்தியின்மை நோயாகும். இது உங்கள் உடலில் உள்ள நோய் எதிர்ப்பு செல்களை தாக்கி கண்ணீர் மற்றும் எச்சில் உற்பத்தி செய்யும் சுரப்பிகளை நிறுத்தி கண் மற்றும் வாய் போன்ற உறுப்புகளை உலர்ந்து, காய வழி வகுக்கும். இது மேலும் நுரையீரல்,. சிறுநீரகம், தோல் மற்றும் நரம்பு மண்டலம் உள்ளிட்ட மற்ற உறுப்புகளையும் பாதிக்கும். கண்ணீல் நீர் சுரப்பது குறையும் பட்சத்தில் இந்த நோய் கண்ணை தாக்கியுள்ளது என அறியலாம். முதலில் இந்த நோயின் பாதிப்பை அறிந்து கொள்ள முடியாது. இந்த நோயினால் பாதிக்கப்பட்டவர்களின் அன்றாட நடவடிக்கைகளில் மாற்றம் ஏற்பட்டு வாழ்க்கைத் தரம் மிகவும் மோசமானதாக தோன்றும். இந்த நோய் இரண்டு நிலைகளில் காணப்படும்.

1) முதல்நிலை ஜோக்ரன் நோய் (Sjogren Syndrome) :

இந்த நோயினால் பாதிக்கப்பட்டவர்களின் கண் மற்றும் வாய் உலர்ந்த நிலையில் காணப்படும்.

2) இரண்டாம் நிலை ஜோக்ரன் நோய் (Sjogren Syndrome) :

இந்த நோயினால் பாதிக்கப்பட்டவர்களின் நிலை, முடக்குவாதம் மற்றும் செந்தடிப்பு தோல் படை மற்றும் பல நோய்களுக்கு காரணமாக இருக்கும். இந்த நோயை ஆரம்ப நிலையிலேயே கண்டறியப்படுமானால் கருவிழியில் ஏற்படும் புண், பல் சொத்தை, நாள்பட்ட வாய் தொற்று, ரத்த நாளத்தின் தாக்கம், புற நரம்பு கோளாறு மற்றும் நுரையீரல் சம்மந்தப்பட்ட நோய்களை தவிர்க்கலாம்.

தொடர்ச்சி 2...

இந்த நோயை குணப்படுத்த நேரிடையாகவோ, அல்லது எளிய முறையில் கண்டறிய எந்த பரிசோதனையும் இல்லை. ஆனால் மருத்துவ துறையின் அறிகுறிகளின் மூலமாக, அதாவது கீழ் உதட்டின் திசு ஆய்வியல் மூலமாகவும் மற்றும் இரத்தத்தில் உள்ள நோய் எதிர்ப்பு பொருள்களான SSA மற்றும் SSB ன் அளவைக் கொண்டு நோயின் தாக்கத்தை அறியலாம். கண்ணில் உள்ள கண்ணீர் சுரப்பை பல்வேறு சோதனைகள் மூலம் அறியலாம். அவைகள் ஷீமர்I, கண்ணீர் இடைவெளி நேரம் மற்றும் கண்ணின் விழி மேற்பரப்பில் ஏற்படும் கறை (அ) அழுக்கு போன்றவைகளின் அளவைக் கொண்டு அளவிட முடியும்.

மேற்கூறிய முறைகளில் ஜோக்ரன் நோயை (Sjogren Syndrome) கண்டறியலாம். இந்த சோதனைகள் மிகவும் எளியவை. மலிவானவை மற்றும் ஊசியை பயன்படுத்தாமல் எளிதாக சிகிச்சையை மேற்கொள்ளலாம்.

நீங்கள் இந்த ஆய்வில் பங்கேற்க விரும்பினால் கண் மருத்துவ துறையின் புறநோயாளி மருத்துவ பிரிவில் கண் மருத்துவரை சந்திக்க ஏற்பாடு செய்து தரப்படுவீர்கள். இங்கு நீங்கள் இரண்டு அல்லது மூன்று மணி நேரம் தங்க நேரிடலாம். எல்லோருக்கும் அளிக்கப்படும் வழக்கமான சிகிச்சை தான் உங்களுக்கு அளிக்கப்படும். மீண்டும் இந்த ஆய்வுக்காக வர நேரிடாது. இந்த ஆய்வில் நீங்கள் பங்கேற்பதினால் எந்த காயமும் ஏற்படாது. பக்க விளைவுகள் ஏற்பட்டால் அதற்கான சிகிச்சையை இலவசமாக அளிக்கப்படும். இதற்காக நஷ்ட ஈடு ஏதும் அளிக்கப்பட மாட்டாது.

நீங்கள் கண் சிகிச்சைக்கு வழக்கமாக செலுத்தப்படும் தொகையை செலுத்தி சிகிச்சை பெறும் நாட்களிலேயே இந்த ஆய்வு மேற்கொள்ளப்படும்.

முதல்நிலை ஜோக்ரன் (Syogren Syndrome) நோயாளியாக, அதிகபட்சமான கண்ணில் நீர் உலர்ந்து காணப்பட்டு இந்த ஆய்வில் பங்கேற்பதினால்

- உங்களுக்கு உலர் கண் பாதிப்பு இருப்பதை அறிந்து உடனடியாக சிகிச்சையை மேற்கொண்டு தீவிர கண் வியாதிகளான கருவிழி வடு, தொற்று, கண்ணில் ஏற்படும் புண் மற்றும் பார்வை குறைபாடு போன்றவைகளை தடுக்கலாம்.
- கண் உலர் நோயை மேலும் பரவாமல் தடுக்க நோயின் அறிகுறிகள் நோய் தடுப்பு நடவடிக்கைகள் இவற்றைக் குறித்த ஆலோசனைகள் வழங்கப்படும்.
- உங்களுக்கு பொதுவான கண் சிகிச்சை மற்றும் கண் தொடர்பில்லாத மற்ற பிரச்சனைகளுக்கு சிகிச்சை மேற்கொள்ள வழிவகைகள் செய்யப்படும்.

தொடர்ச்சி 3...

இந்த ஆய்வின் முடிவுகள் மூலம் இந்த சமூகத்து மக்களுக்கு மருத்துவ துறையில் ஏற்பட்ட அறிவு சார்ந்த முன்னேற்றத்தின் துணைக் கொண்டு நோய்களுக்கு எளிய முறையில் தீர்வு கண்டறிவது பற்றி விளக்க முடியும்.

நீங்கள் இந்த ஆய்வில் பங்கேற்பது உங்களுடைய விருப்பத்தின் / தன்னார்வத்தின் பேரில் தான் என்றும் எந்த நேரத்திலும் நிபந்தனையின்றி விலகிக் கொள்ளலாம் என்றும் அப்படி விலகும் பட்சத்தில் உங்களது வழக்கமாக அளிக்கப்படும் சிகிச்சையில் எந்த பாதிப்பும் இருக்காது என்றும் உங்களுடைய உரிமைகள் பாதிக்காத வகையில் இருக்கும் என உறுதியளிக்கப்படுகிறது.

இந்த ஆய்வின் முடிவுகள் மருத்துவ இதழில் வெளியிடப்படும். ஆனால் உங்களின் அடையாளங்களை மருத்துவ இதழில் வெளியிடப்படாது. உங்கள் மூலமாக பெறப்பட்ட மருத்துவ விவரங்களை உங்களுடைய அனுமதியின்றி மீண்டும் பயன்படுத்த நேரிடலாம் என்று அறிவுறுத்தப் படுகிறீர்கள். எனவே நீங்கள் இந்த ஆய்வில் பங்கு பெற உங்களிடம் அனுமதி கேட்கிறோம்.

மேலும் விவரங்களுக்கு Dr. ரோமா ஜோரி (அ) Dr. ஜெயந்தி பீட்டர் என்பவர்களை அணுக 0416–2281201 என்ற எண்ணிலும் roma_johri.co.in என்ற மின் அஞ்சலிலும் தொடர்பு கொள்ளலாம்.

தகவல் பிரதி
ஒப்புதல் படிவம்

இந்திய அமைப்பில் முதன்மை நிலை ஜோக்ரன் நோய்க்கு உலர் கண் நோயின் சோதனைகளின் மூலம் அதன் செயல்திறனை கண்டறிதல்.

ஆய்வு எண் :
பங்கேற்பாளரின் முதல் எழுத்து விரிவாக்கம் :
பங்கேற்பாளரின் பெயர் :

தயவு செய்து உங்கள் கையொப்பம் இடவும்

நீங்க தேதியிட்டு கொடுத்த தகவல் தாளை படித்து மேற்குறிப்பிட்ட ஆய்வைக் குறித்த சந்தேகங்களை கேட்க வாய்ப்பு கொடுக்கப்பட்டதால் முழு விவரங்களையும் அறிந்து கொண்டேன்.

இந்த ஆய்வில் நான் பங்கேற்பது என்னுடைய விருப்பத்தின் பேரில் என்றும், எந்த நேரத்திலும் நிபந்தனையின்றி விலகிக் கொள்ளலாம் என்றும் இதனால் என்னுடைய சட்ட உரிமைகள் மற்றும் எனக்கு அளிக்கப்படும் வழக்கமானசிகிச்சைகளில் எந்த பாதிப்பும் இருக்காது என்றும் அறிவேன்.

இந்த ஆய்வை மேற்கொள்ளும் ஆய்வாளர் அல்லது ஆய்வாளர் சார்பாக அவருடன் இணைந்து வேலை செய்பவர்கள், மனித நன்னெறி ஆலோசனைக் குழு உறுப்பினர்கள் மற்றம் கட்டுப்பாட்டு அதிகாரிகள், இவர்கள் ஆய்வின் மூலம் பெறப்பட்ட என்னுடைய மருத்துவ விவரங்கள் என்னுடைய அனுமதியின்றி தற்போதைய ஆய்வு மற்றும் வேறு சில ஆராய்சிக்கும் பயன்படுத்தலாம் என்றும் இந்த ஆய்வில் நான் விலகினாலும் பயன்படுத்த தடையில்லை என்றும் அறிவேன். என்னுடைய அடையாளங்களை யாருக்கும் வெளிப்படுத்தப்பட மாட்டாது என்று புரிந்து கொண்டேன்.

இந்த ஆய்வு மூலம் பெறப்பட்ட மருத்துவ விவரங்கள் மற்றும் முடிவுகளை அறிவியல் பயன்பாடுகளுக்கு / நோக்கங்களுக்கு பயன்படுத்த தடையில்லை என ஒப்புக் கொள்கிறேன்.

இந்த ஆய்வில் பங்கு பெற சம்மதிக்கிறேன்.

பங்கேற்பாளரின் கைரேகை பதிவு / கையொப்பம் :

சட்டப்பூர்வமா பெற்றுக் கொள்ளப்பட்ட பிரதிநிதி :

தேதி :

பங்கேற்பாளரின் பெயர் :

ஆய்வாளரின் கையொப்பம் :

தேதி :

ஆள்வாளரின் பெயர் :

சாட்சியின் கையொப்பம் :

தேதி :

சாட்சியின் பெயர் :

రోగి_సమాచార_పత్రము

శీర్షిక: భారత నేపధ్యంలో ప్రాథమిక జగ్రెన్స్ సిండ్రోమ్ లో పొడి కన్ను పరీక్షల రోగనిర్ధారణ ఖచ్చితత్వం .

మీరు ఈ అధ్యయనంలో పాల్గొనడానికి ఆహ్వానితులు. ఈ పత్రంలోని సమాచారం మీరు ఈ అధ్యయనంలో పాల్గొనడానికి నిర్ణయం తీసుకోవడానికి సహాయం చేస్తుంది.మీకు ఏ రకమైన ప్రశ్నలు లేదా సమస్యలు ఉంటే సంకోచించకండ అడగండి.

దేని గురించి అధ్యయనం ?
జగ్రెన్స్ సిండ్రోమ్ అనేది ఒక రకమైన రోగనిరోధక వ్యాధి, ఇందులో మీ శరీరం యొక్క వ్యాధి నిరోధక కణాలు కన్నీళ్లు మరియు లాలాజలము ఉత్పత్తి చేసే గ్రంధులపై దాడి చేసి కళ్లు మరియు నోరు పొడిబారేల చేస్తుంది. ఇది ఊపిరితిత్తులు, కిడ్నీలు , చర్మం,నాడీ వ్యవస్థ మరియు ఇతర అవయవాలను ప్రభావితం చేయవచ్చు. కళ్లకు సంబంధించి కన్నీటి ఊటను తగ్గిస్తుంది. కొన్నిసార్లు ఈ వ్యాధి బారిన పడిన రోగులు, వ్యాధి లక్షణాలు వారి దినందిక జీవితం మీద ప్రబావం చుపానంతవరకు ఇబ్బంది పడరు.

ఇది రెండు రూపాల్లో సంభవించవచ్చు : ప్రాథమిక జగ్రెన్స్ సిండ్రోమ్: దీని లక్షణాలు కన్ను మరియు నోరు పొడిబారటం.రెండో జగ్రెన్స్ సిండ్రోమ్: రుమటాయిడ్ ఆర్థరైటిస్ , సిస్టమిక్ లుపుస్ ఎరతిమాటోసిస్ వంటి ఇతర రుగ్మతలతో కలసి ఉంటుంది. జగ్రెన్స్ సిండ్రోమ్ ను ముందుగ గుర్తించడం వలన శుక్ల వ్రణోత్పత్తి , దంత క్షయం , దీర్ఘకాలిక నోటి వ్యాధి మరియు వాస్కులైటిస్లో , నరాల వ్యాధి, మూత్రపిండాల వ్యాధుల వంటి తీవ్రమైన సమస్యలను నిరోధించవచ్చు.

అయితే , జగ్రెన్స్ సిండ్రోమ్ ను గుర్తించడానికి సరి అయిన రోగనిర్ధారణ పరీక్షలు లేవు. కంటి లో కన్నీటి స్రావం వివిధ పరీక్షల ద్వారా కనుక్కోవచ్చు. అవి టియర్ విడిపోవడానికి సమయం , ప్రత్యక్షమైన ఉపరితల రంజనం స్కోరు. ఇవి జగ్రెన్స్ సిండ్రోమ్ ను గుర్తించడానికి చవకైన మరియు సులభమైన పద్దతులు, వీటితో ముందస్తు చికిత్స ప్రణాళికను తయారు చేయవచ్చు.

మీరు పాల్గొంటే, మీరు ఏమి చేయాల్సి ఉంటుంది ?

మీరు అధ్యయనంలో పాల్గొంటే, ఆసుపత్రిలో కంటి విభాగంలో కళ్ల పరీక్షల కోసం అపాయింట్మెంట్ ఏర్పాటు చేయబడుతుంది. మీరు ఈ విభాగంలో రెండు లేదా మూడు గంటల సమయం ఉండాల్సి ఉంటుంది. మీకు ఒక సాధారణ కంటి పరీక్ష చేయబడుతుంది. మీరు ఈ అధ్యయనం కోసం మరల రావాల్సిన అవసరం ఉండదు.

మీరు అధ్యయనంలో పాల్గొంటే ఎమైన సమస్యలు ఉంటాయా ?

ఈ అధ్యయనంలో మీకు ఒక సాధారణ కంటి పరీక్ష మాత్రమే చేయబడుతుంది. మీకు ఎటువంటి హాని కలగదు, ఒకవేళ మీకు అధ్యయనం కారణంగా ఏ దుష్ప్రభావాలు లేదా సమస్యలు వస్తే, మీకు ఎటువంటి వ్యయం లేకుండ చికిత్స చేయబడుతుంది. అయితే, పరిహారం కింద ధన రూపేన ఏది చెల్లించబడదు.

మీరు డబ్బు చెల్లించాల్సిన అవసరం ఉందా ?

ఈ అధ్యయనంలో ఆసుపత్రిలో కంటి విభాగంలో కళ్ల పరీక్ష చేయబడుతుంది, మీరు సాధారణ అవుట్ పేషెంట్ అపాయింట్మెంట్ రుసుము చెల్లించాల్సి ఉంటుంది.

మీరు ఈ అధ్యయనంలో పాల్గొంటే ప్రయోజనాలు ఏమిటి ?

ప్రాథమిక జగ్రెన్స్ సిండ్రోమ్ ఉన్న రోగి, పొడి కన్ను మరియు దాని వల్ల వచ్చే ఇతర సమస్యల బారిన పడే ప్రమాదం ఉంది. మీరు అధ్యయనంలో పాల్గొంటే,

1. మీకు పొడి కన్ను పరీక్ష చేయబడుతుంది, నిర్ధారణ అయితే వెంటనే చికిత్స ఉంటుంది, దాని వల్ల కంటి మచ్చలు , సంక్రమణ , వ్రణోత్పత్తి మరియు దృష్టి కోల్పోవడం వంటి తీవ్రమైన కంటి సమస్యలు నిరోధించవచ్చు.
2. మీకు పొడి కన్ను లక్షణాలు మరియు నివారణ చర్యలకు సంబంధించి సలహా ఇవ్వబడుతుంది.
3. మీకు సాధారణ కంటి పరీక్ష చేయబడుతుంది, మీకు ఉన్న ఇతర కంటి సమస్యలకు చికిత్స చేయబడుతుంది.

ఇతరులకు కలిగే ప్రయోజనాలు ఏమిటి?

ఈ పరిశోధన ఫలితాలు సమాజానికి వైద్య విజ్ఞాన అభివృద్ధి పరంగా మరియు సాధారణ పరీక్షలు ద్వార వ్యాధి నిర్ధారణ చేయటానికి సహాయ పడతాయి.

ఈ అధ్యయనంలో పాల్గొనను అని మీరు నిర్ణయం తీసుకొనగలరా ?

ఈ అధ్యయనంలో మీ భాగస్వామ్యం పూర్తిగా స్వచ్ఛందమైనది మరియు ఈ అధ్యయనంలో మీ భాగస్వామ్యన్ని ఉపసంహరించుకోవాడనికి మీకు అన్ని విధాల అధికారం ఉంది. ఒకవేళ మీరు ఉపసంహరించుకుంటే, అది ఆసుపత్రిలో మీ సాధారణ చికిత్సను ప్రభావితం చేయదు మరియు అన్ని ప్రయోజనాలకు మీరు అర్హులు.

మీ వ్యక్తిగత వివరాలు గోప్యంగా ఉంచబడతాయ ?

ఈ అధ్యయనం యొక్క ఫలితాలు వైద్య పత్రికలో ప్రచురించబడవచ్చు, కాని మీ పేరు ఏ ప్రచురణ లేదా ప్రదర్శనలో చేర్చబడదు. అయితే , మీ వైద్య ఫలితాలు మీ అదనపు అనుమతి లేకుండా అధ్యయనంతో సంబంధం ఉన్న వ్యక్తులు సమీక్షిస్తారు.

మీరు ఏ ఇతర ప్రశ్నలు ఉన్న Dr. Roma Johri లేదా Dr. Jayanthi Peter (ఫో: 0416 2281201) లేదా ఇమెయిల్: roma_johri@yahoo.co.in అడగండి.

ఆమోద పత్రము

శీర్షిక: భారత నేపధ్యంలో ప్రాథమిక జగ్రెన్స్ సిండ్రోమ్ లో పొడి కన్ను పరీక్షల రోగనిర్ధారణ ఖచ్చితత్వం.

అధ్యయన సంఖ్య:

వ్యక్తి పూర్తి పేరు:

ఇక్కడ మీ సంతకం  చేయండి:

(విషయం)

i. నేను పై అధ్యయన సమాచార పత్రమును చదివి అర్థం చేసుకున్నాను మరియు ప్రశ్నలు అడిగే అవకాశం కలిగి ఉన్నాను.
ii. ఈ అధ్యయనంలో నా భాగస్వామ్యం పూర్తిగా స్వచ్ఛందమైనది మరియు ఏ సమయంలో ఆయన నేను నా భాగస్వామ్యన్ని నా వైద్య సంరక్షణ లేదా చట్టపరమైన హక్కులను కోల్పోకుండ ఏ కారణం లేకుండా ఉపసంహరించుకోగలను.
iii. ఈ అధ్యయనంతో సంబంధం ఉన్న వ్యక్తులు నా వైద్య ఫలితాలను, నేను నా భాగస్వామ్యన్ని ఉపసంహరించున్న, నా అదనపు అనుమతి లేకుండా సమీక్షి జరపడానికి ఒప్పుకుంటూన్నాను. కానీ, నా పేరు ఏ ప్రచురణ లేదా ప్రదర్శనలో బహిర్గతం కాకూడదు.
iv. ఈ అధ్యయనం నుండి ఉత్పన్నమయ్యే ఫలితాలు శాస్త్రీయ ప్రయోజనల కోసం ఉపయోగించడానికి అంగీకరిస్తున్నాను.
v. నేను పై అధ్యయనం పాల్గొనడానికి అంగీకరిస్తున్నాను.

వ్యక్తి /ఆమోదనీయమైన ప్రతినిధి యొక్క సంతకం (లేదా బొటనవేలి ముద్ర) :

తేదీ :

సంతకదారుని పేరు : _____

పరిశోధకుడిని సంతకం : _____

విషయ పరిశోధకుడి పేరు : _____

తేదీ :

సాక్షి యొక్క సంతకం : _____

సాక్షి యొక్క పేరు : _____

রোগীর সূচনা পত্র।

বিষয়– ভারতে শুষ্ক চোখের পরীক্ষা অর্থাৎ SJOGREN SYNDROME সম্বন্ধে জন জাগরনের উদ্দেশ্যে সচেতনতা।

এই বিষয়ে অংশগ্রহন করার জন্য আপনাকে স্বাগতম। এই তালিকা আপনাকে সাহায্য করবে যে আপনি এই বিষয়ে অংশগ্রহন করবেন কিনা? কোন সন্দেহ হলে আপনি অনায়াসে জিজ্ঞাসা করতে পারেন।

SJOGREN SYNDROME এক ইমিউনোলজিকেল অসুখ যা লালা ও চোখের জল তৈরি করা গ্লান্ড গুলিকে শুকিয়ে দেয় যার ফলে চোখ ও মুখের শুষ্কতা ভাব এসে পড়ে, এই রোগ ফুসফুস, বৃক্ক, ত্বক এবং স্নায়ুতন্ত্রেরও ক্ষতি সাধন করে। চোখ শুষ্কতার ফলে চোখের জলের পরিমান কমে যায়। রোগি প্রথমে বুঝতে পারেনা কিন্তু পরে চোখ এতই খারাপ হয়ে যাবে যে রোগি প্রচুর অসুবিধার মধ্যে পড়ে।

এটা দুই ভাবে হতে পারে প্রাইমারি ও সেকেন্ডারি, প্রাইমারিতে কেবল চোখ ও মুখের শুষ্কতা হয় কিন্তু সেকেন্ডারিতে অন্য অসুখও সাথে হতে পারে যেমন রিউমাটাইডেট আর্থ্রাইটিস, লিউপাস এরিথ্যামেটোসিস অটিক অবস্থা এই রোগ নির্নয় করা না হলে চোখে ঘা, মুখের ও দাতের ঘা এবং বড় রোগ হতে পারে, যেমন ভাসকুলাইটিস পেরিফিরিয়েল নিউরোপ্যাথি, কিডনি, ফুসফুস ইত্যাদি অকেজো হয়ে যেতে পারে।

এমনও পর্যন্ত SJOGREN SYNDROME কোন ডাইরেক্ট পরীক্ষা নেই, এমন পর্যন্ত রোগির লক্ষন, লেবরেটরি পরীক্ষা এবং রক্ত থাওয়া এন্টিবডির ওপর করা হয়, চোখের জল মাপার পরীক্ষা গুলো যে জাতিয় হলো টিয়ার ব্রেকআপ টাইম ওকুলার সারফেস স্টেইনিং কোর ইত্যাদি, এই পরীক্ষাগুলোর সাহায্য আমরা অতি সহজেই SJOGREN SYNDROME হয়েছে কিনা জানা যায়, শরীরে কোন ভুই না ঢুকিয়ে যাতে এই রোগের অতি তাড়াতাড়ি চিকিৎসা করা যায়,

যদি আপনি এই বিষয়ে অংশগ্রহন করতে ইচ্ছুক তবে আপনাকে আই ডিপার্টমেন্ট এ ডাকা হবে, সেখানে আপনার খুলো চোক্ষের পরীক্ষা করা হবে ও সেচকে ৩ মিনিট লাগবে, এই বিষয়ে জানার জন্য আপনার দুবার আসতে হবে না,

এই বিষয়ে আপনার নিম্নমিত সাধারন চোখের পরীক্ষা হবে যাতে আপনার চোখের কোন ক্ষতি হবেনা, যদি আপনার চোখ কিছু অসুবিধা দেখা দেয় তবে আমরা বেগন ওষুধ না দিয়ে ভালো করব, কিন্তু আপনাকে কোন টাকা পয়সা দিয়ে সাহায্য করা হবেনা,

এই বিষয় ভাস নেওয়ার জন্য আপনাকে general (সাধারণ) OPD তে জেতে হবে যাতে কোন পয়সা দিতে হবে

এই বিষয়ে ভাস নেওয়ার জন্য আমন্ত্রন,
যদি আপনি ভাগ নিতে চান তবে:

1. আপনার শুষ্ক চোখের পরীক্ষা হবে, যদি রোজ শুষ্কাবস্থায় ধরা পড়ে তবে ভবিষ্যতে অনেক বড় রোগের হাত থেকে আপনি রক্ষা পাবেন, অর্থাৎ চক্ষু রশ্মি লোস হওয়ার হাত থেকে রক্ষা পাবেন,

২. চোখের শুষ্কতার লক্ষনকে জানার ও তার থেকে বাঁচার জন্য পরামর্শ দেওয়া হবে,

3. আপনার চোখে অন্য কোন রোগ থাকলে তার ট্রিটমেন্ট করা হবে,

ইহা সমাজে এই রোগের বিষয়ে জাগুরুকতা করবে এই সাধারন পরীক্ষা দ্বারা,
আপনি স্বইচ্ছায় এই বিষয় অংশগ্রহন করতে পারেন, আপনাকে কোন জোর করা হবেনা, যদি আপনি অংশগ্রহন নাও করেন তবুনি আপনার চোখ পরীক্ষা করা হবে, আপনার জন্য আপনার খুলো মেয়াল রাখবেন এবং আপনাকে কোন পরীক্ষা থেকে বাদ দেওয়া হবে না,

এই বিষয়ের ফলাফল মেডিকেল জার্নালে প্রকাশিত হবে কিন্তু আপনার নাম ও পরিচয়ে গোপন রাখা হবে, কোথাও ছাপা বা প্রচার হবেনা, আপনার পরীক্ষার ফলগুলো অন্যলোক আপনার মতামত ছাড়াও দেখতে পারবে,

যদি আপনার মনে আরও কিছু প্রশ্ন বা সন্দেহ থাকে তবে আপনি Dr. রোমা বা Dr. জয়ন্তি কে নিচের নম্বরে যোগাযোগ করতে পারেন,

Ph- ০৪৯৬২২৮৯২০৯।

रोगी सूचना पत्र

शीर्षक: भारतीय जनसंख्या में प्राथमिक Sjogren सिंड्रोम की पहचान में शुष्क आँखों के परीक्षण का योगदान

आप इस अध्ययन में भाग लेने के लिए आमंत्रित हैं। इस दस्तावेज में अंतर्निहित जानकारी आपको इस अध्ययन में भाग लेने या ना लेने के निर्णय में मदद करेगी। आप किसी भी प्रश्न या शंका को पूछने के लिए स्वतंत्र हैं।

Sjogren सिंड्रोम एक प्रतिरक्षाविज्ञानी रोग है जो शरीर में आँसू और लार का उत्पादन करने वाली ग्रंथियों को नष्ट कर देता है जिसके कारण आँख और मुँह शुष्क हो जाते हैं। ये फेफड़े, गुर्दे, त्वचा और तंत्रिका तंत्र सहित अन्य अंगों को प्रभावित कर सकता है। रोगी को कभी कभी लक्षण का पता तब तक नहीं चलता जब तक यह बीमारी उसकी दैनिक गतिविधियों को प्रभावित नहीं करती।

यह बीमारी दो प्रकार से हो सकती है: प्राथमिक Sjogren सिंड्रोम में केवल मुँह और आँखे शुष्क होती हैं। सेकंडरी Sjogren सिंड्रोम रुमेटिक गठिया और लूपस इरीथेमेटोसस जैसे अन्य विकार के साथ जुड़ा हुआ हो सकता है।

शोगरन सिंड्रोम की जल्द पहचान से गंभीर बीमारियों जैसे कि कैंसरयुक्त लिंफ, यंत्र क्षय, वाहिकाशोथ, तंत्रिकाविकृति, गुर्दे और फेफड़े [illegible] से बचा सकती है।

हालांकि, Sjogren सिंड्रोम की पहचान के लिए कोई सीधा और सरल नैदानिक परीक्षण नहीं है, इसकी पहचान रोगी के लक्षण, परीक्षण, निचले होंठ की बायोप्सी और रक्त मे Anti-SSA और Anti SSB की मदद से होती है।

आंखो मे आंसू स्राव विभिन्न परीक्षणो से मापा जा सकता है जैसे कि Schirmer I, Tear Break Up Time Ocular Surface Staining Score आदि इन परिक्षण की मदद से बीमारी को सरल, सस्ते और गैर इनवेसिव तरीके से पहचाना जा सकता है और उसके प्रारंभिक उपचार की योजना लगाई जा सकती है।

इस अध्ययन मे भाग लेने के लिए आपको नेत्र विभाग OPD मे जांच के लिए नियुक्ती की व्यवस्था की जायेगी, यहाँ आपको दो से तीन घंटे व्यतित करने होंगे। नियमित नेत्र परिक्षण किया जायेगा और आपको इस अध्ययन के लिए दोबारा नहीं आना पड़ेगा।

अध्ययन मे भागीदारी से केवल एक नियमित नेत्र जांच होगी। इससे आपकी आंखो को कोई हानि नहीं पहुंचेगी, लेकिन अगर कोई हानि होती है तो उसका निशुल्क इलाज किया जायेगा। हम कोई भी मुआवजा राशि प्रदान करने मे असमर्थ है, और आपको नेत्र विभाग मे जांच के लिए सामान्य राशि भरनी होगी।

प्राथमिक Sjogren सिंड्रोम के रोगी के मामले मे, आप शुष्क आंखो के और इसकी जटिलता के विषय के खतरे मे है इसलिए

1. आपकी आँखो मे सुरक्षण की जाँच के साथ साथ इसकी जटिलता जैसे कि कार्नियल Scarring, संक्रमण, दाब और दृष्टि के नुकसान से बचने मे मदद करेगी।
2. आपको सुरक्षा आँखो से निवारण की विधियां बताई जाएगी।
3) अन्य असंबंधित आँख की संगरचाओं की पहचान और ईलाज होगा।

अध्ययन के परिणामो से चिकित्सा ज्ञान मे उन्नति होगी और सरल, साधारण परीक्षण से रोग के निदान मे मदद होगी।

इस अध्ययन मे आपकी भागीदारी स्वैच्छिक है। और आप किसी भी क्षण इससे वापिस हट सकते है जिससे आपके ईलाज मे कोई फर्क नहीं पड़ेगा

इस अध्ययन के परिणामों को एक मेडिकल जर्नल मे प्रकाशित किया जा सकता है। लेकिन किसी भी प्रकाशन या प्रस्तुति मे आपकी पहचान गुप्त रखी जाएगी। आपके परिणाम को अध्ययन से जुड़े लोग आपकी अनुमति के बगैर पढ़ सकते है।

यदि कोई प्रश्न या शंका है तो डा रोमा जोशी या डा जगती पीटर से पूछें (0416 228120)
Email Id: romajohi@yahoo.co.in.

सहमति पत्र

शीर्षक : भारतीय जनसंख्या में प्राथमिक Sjogren सिंड्रोम की पहचान में शुष्क आँखों के परीक्षण का दौरदौरा

अध्ययन संख्या :
रोगी के प्रथमाक्षर :
विषय का नाम
कृपया यहाँ हस्ताक्षर करे [ ]

1) मैं पुष्टि करता हूँ कि मैंने उपरोक्त जानकारी पत्र पढ़ा और समझा है।
2) मैं समझता हूँ कि अध्ययन में मेरी भागीदारी स्वैच्छिक है और किसी भी क्षण मैं बिना कारण बताए इससे पीछे हट सकता हूँ। मेरी चिकित्सा देखभाल या कानूनी अधिकार इससे प्रभावित नहीं होंगे।
3) मैं समझता हूँ कि नैदानिक परीक्षण में प्रायोजक, दूसरे को प्रायोजक की ओर से, काम करने की नैतिकता समिति और अनिष्ट अध्ययन में मेरे स्वास्थ्य अभिलेख देख सकते हैं, जिसके लिए मेरी आनुमति नहीं चाहिए।
4) मैं समझता हूँ कि मेरी पहचान गुप्त रखी जाएगी। मेरे परिक्षण का उपयोग किसी भी वैज्ञानिक उद्देश्य के लिए किया जा सकता है
5) मैं उपरोक्त अध्ययन में भाग लेने के लिए सहमत हूँ . . .

(4)

रोगी के हस्ताक्षर (अंगूठे की छाप)

हस्ताक्षरकर्ता का नाम

अन्वेषक के हस्ताक्षर

अन्वेषक का नाम

साक्षी के हस्ताक्षर

दिनांक

साक्षी का नाम

APPENDIX C

PROFORMA

DIAGNOSTIC PERFORMANCE OF DRY EYE TESTS IN PRIMARY SJOGREN'S SYNDROME PATIENT IN INDIAN SETTING

SERIAL NUMBER:

NAME: AGE: SEX: M /F

OCCUPATION: CONTACT NO.:

CMC HOSPITAL NO.: SCHELL HOSPITAL NO:

OCULAR SYMPTOMS:--

a. CHIEF COMPLAINTS :-
b. DURATION OF SYMPTOMS:
c. TREATMENT:
d. DRUG HISTORY:
e. OSDI:

	RIGHT EYE	**LEFT EYE**
VISUAL ACUITY		
SCHIRMER'S I (in mm)		
TBUT (in sec)		
CORNEAL FLUORESCEIN STAINING GRADE-OSS 1		
OCULAR SURFACE EXMINATION		

CONJUNCTIVAL LISSAMINE STAINING GRADE—OSS II		
TOTAL OCULAR STAINING SCORE		

INVESTIGATIONS:

1. ANTI SSA

2. ANTI SSB

3. MINOR SALIVARY GLAND BIOPSY (DATE:)

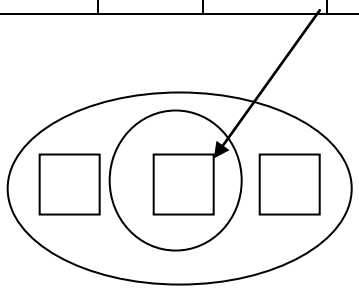
4. OTHERS

APPENDIX D:

SICCA Ocular staining score (OSS)

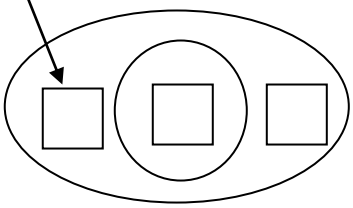
Right Eye

Lissamine green (conjunctiva only)		Fluorescein (cornea only)	
Grades	Dots	Grades	Dots
0	0-9	0	0
1	10-32	1	1-5
2	33-100	2	6-30
3	>100	3	>30



Left Eye

Lissamine green (conjunctiva only)		Fluorescein (cornea only)	
Grades	Dots	Grades	Dots
0	0-9	0	0
1	10-32	1	1-5
2	33-100	2	6-30
3	>100	3	>30



Extra points (fluorescein only): +1 for patch of confluent staining

+1 for staining in papillary area

+1 for Filaments

Total score ranges from 3 to 12 per eye for assessment of severity of keratoconjunctivitis sicca

APPENDIX E: OCULAR SURFACE DISEASE INDEX

Circle the number in the box that best represents each answer

HAVE YOU EXPERIENCED ANY OF THE FOLLOWING DURING THE LAST WEEK:

		ALL OF THE TIME	MOST OF THE TIME	HALF OF THE TIME	SOME OF THE TIME	NONE OF THE TIME
1.	Eyes that are sensitive to light?	4	3	2	1	0
2.	Eyes that feel girtty?	4	3	2	1	0
3.	Painful or Sore eyes?	4	3	2	1	0
4.	Blurred vision?	4	3	2	1	0
5.	Poor vision?	4	3	2	1	0
				Sub Total score fo ranswr 1 to 5		

HAVE PROBLEMS WITH YOUR EYES LIMITED YOU IN PERFORMING ANY OF THE FOLLOWING DURING THE LAST WEEK:

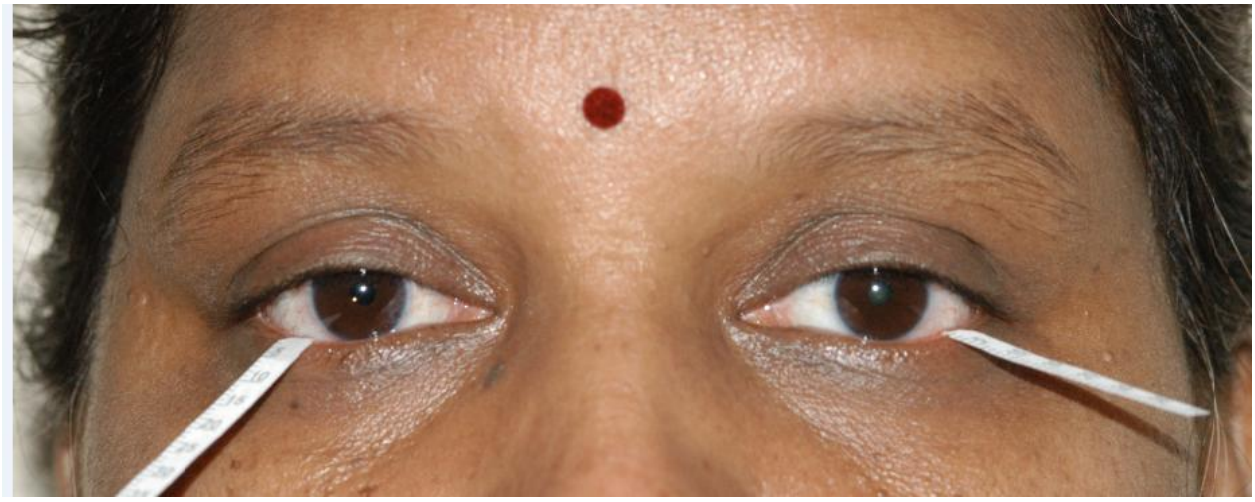
		ALL OF THE TIME	MOST OF THE TIME	HALF OF THE TIME	SOME OF THE TIME	NONE OF THE TIME	
6.	Reading?	4	3	2	1	0	N/A
7.	Driving at night?	4	3	2	1	0	N/A
8.	Working with computer or bank machine (ATM)?	4	3	2	1	0	N/A
9.	Watching TV?	4	3	2	1	0	N/A
				Sub Total score fo ranswr 1 to 5			

HAVE YOUR EYES FELT UNCOMFORTABLE IN ANY OF THE FOLLOWING SITUATION DURING THE LAST WEEK:

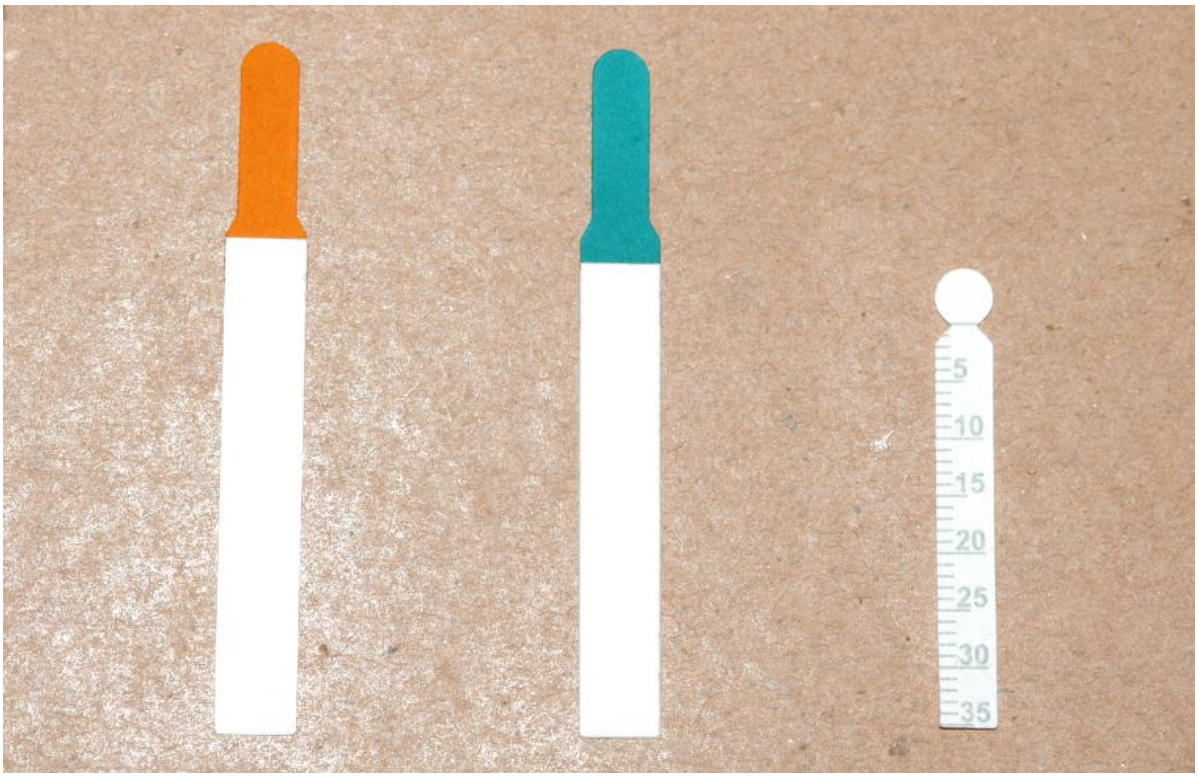
		ALL OF THE TIME	MOST OF THE TIME	HALF OF THE TIME	SOME OF THE TIME	NONE OF THE TIME	
10	Windy conditions?	4	3	2	1	0	N/A
11.	Places or areas with low humidity?	4	3	2	1	0	N/A
12.	Areas that are air conditioned?	4	3	2	1	0	N/A
				Sub Total score for answr 1 to 5			

SUM OF SCORE FOR ALL QUESTIONS ANSWERED

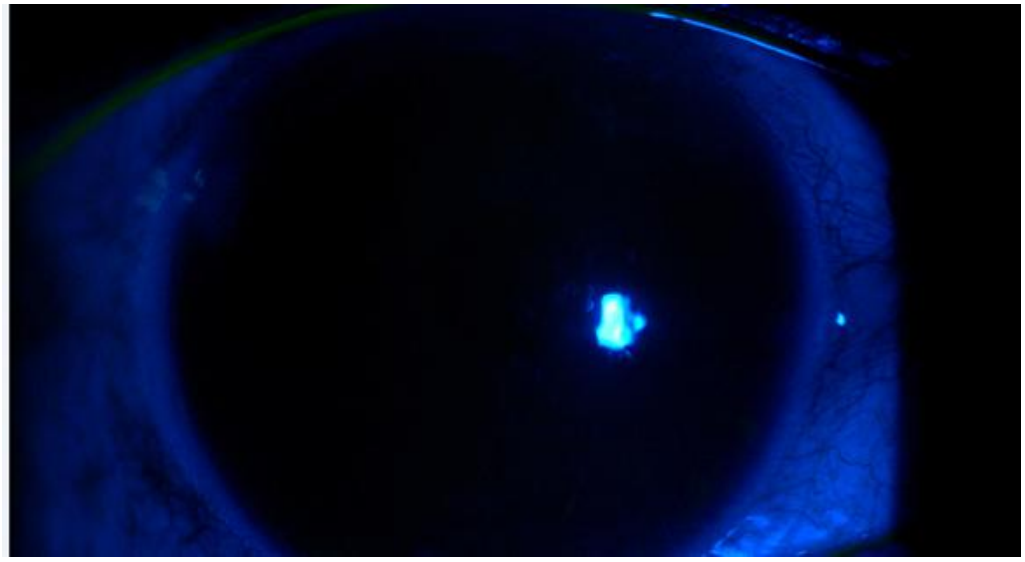
APPENDIX F: COLOUR PLATES



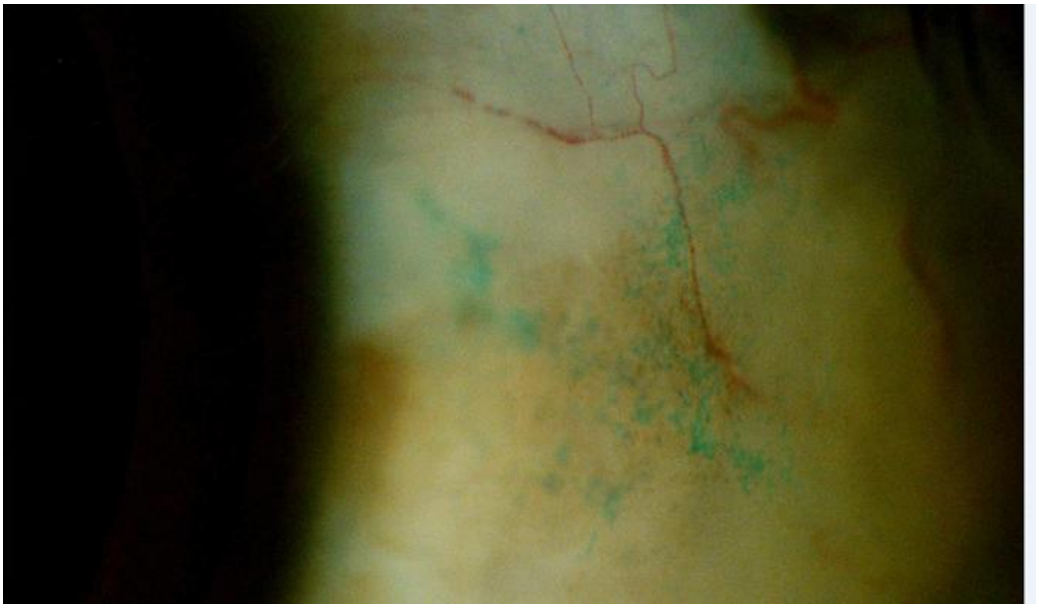
Piture 1: showing the Schirmer I test being done in patient



Picture 2: showing Fluorescein strip, Lissamine green strip and Schirmer strip



Picture 3 :showing the fluorescein stain used in TBUT and OSS (cornea staining pattern)



Picture 4 :showing Lissamine green staning pattern of conjunctiva

APPENDIX G: EXCEL DATA SHEET

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH
1	ser	name	age	sex	occu	cmc	schell	dr	br	fr	intol	stick	rd	visual	itc	photo	intcl	gland	timem	timey	drops	drugs	osdi	visn	visd	schr	schl	tbutr	tbutl	oscr	oscl	sca	scb	biopsy
2	1	maharvicl	44	2	2	980145c	625074:	2	1	2	2	2	2	2	1	2	2	2		4	1	2	22.5	6	6	12	10	8	6	1	1	1		1
3	2	dipali	30	2	3	199281d	433108:	1	2	1	2	1	2	2	1	2	2	2		7	1	2	31.25	6	6	10	10	7	6	4	4	2	1	1
4	3	nabanita	34	2	3	618156d	443683	2	2	2	2	2	2	2	1	2	2	2		1	2	2	12.5	6	6	25	25	12	12	0	0	2	2	2
5	4	govinda	48	2	3	790781f	440334	2	1	1	2	2	2	2	1	1	2	2		1	1	2	28.33	6	6	7	15	7	8	3	3	2		1
6	5	sathiya b	40	2	3	989008	450733:	1	2	2	2	2	2	2	1	2	2	2		2	1		18.88	6	6	20	22	8	8	0	0		1	1
7	6	amuthavi	50	2	3	912701f	452975:	1	1	1	2	2	2	1	1	2	2	2		1	1		16.5	6	9	7	10	8	8	0	0	1	1	1
8	7	lisina ma	39		3	017516g	454528:	1	2	2	2	2	2	2	2	2	2	2		1	2	2	16.6	6	6	20	20	7	7	0	0	2		2
9	8	jyoti	45	2	3	797227c	456731:	1	1	2	2	2	2	2	2	2	2	2		3	1		12.5	6	6	12	15	7	7	0	1	1		1
10	9	sujatha	28	2	2	835030l	994753:	1	1	1	2	2	2	2	1	2	2	2		4	1		16.67	6	6	20	20	8	9	1	1	1		1
11	10	pampa	37	2	3	032551g	457541:	2	2	1	2	1	2	2	1	2	2	2		2	1		10.71	6	6	20	25	8	8	0	1	2		1
12	11	janaki	71	2	3	685276d	411322:	1	1	1	2	1	2	1	2	2	2	2		2	1	2	15.62	6	18	5	7	5	5	7	7	2	2	1
13	12	poonam	44	2	3	850384c	457465:	2	1	1	2	2	2	2	2	2	2	2		1	1	2	16.6	6	6	21	24	8	8	0	0	2	2	1
14	13	gowri	31	2	4	211828f	449210:	1	2	1	2	2	2	2	1	2	2	2		3	1	2	22.22	6	6	15	15	6	6	1	1	1	1	1
15	14	jyothi	65	2	3	508036(	456638:	1	1	2	2	2	2	2	1	2	2	2		2	1		10.71	6	6	20	20	8	8	1	1	1	1	1
16	15	sujata	46	2	3	000637(	454118:	1	2	2	2	2	2	2	1	2	2	2		2	1	2	25	6	6	12	13	7	6	1	1	2		1
17	16	ruma	46	2	3	847500f	456616:	2	2	1	2	2	2	2	2	2	2	2		1	2	2	13.63	6	6	20	20	7	7	0	0	2		2
18	17	sumana	39	2	4	873409l	452934:	2	1	2	2	2	2	2	2	2	2	2	5		2	2	11.36	6	6	18	16	7	8	1	0	2		2
19	18	ishita	27	2	4	557083(	2992401	2	2	1	2	2	2	2	2	2	2	2	2		2	2	12.5	6	6	22	25	8	8	0	0	2		2
20	19	brajeshw	65	2	3	966733(	164213:	1	1	1	2	1	1	1	1	1	2	2		3	1	2	22.22	6	9	17	17	7	8	0	0	1	1	1
21	20	rina	43	2	3	858597f	453146f	2	2	2	2	2	2	2	1	2	2	2	4		2	2	13.63	6	6	20	20	8	8	0	0	2		2
22	21	gangann	54	1	1	837372f	443959:	2	1	1	2	1	2	2	1	2	2	2	10		1		11.36	6	9	14	15	6	6	3	4	2	2	1
23	22	sudipta	51	2	3	560926(	445882:	1	1	1	2	1	2	2	1	1	2	2		1	1		12.5	6	6	20	22	7	7	3	3	1	1	1
24	23	inba	32	2	4	858643l	445300:	2	2	2	2	2	2	2	1	2	2	2	2		2	2	11.56	6	6	30	32	10	10	0	0	2		2
25	24	moni	32	2	4	205412(	232029	2	2	2	1	2	2	2	2	2	2	2	1		2	2	13.63	6	6	22	25	8	8	0	0	2		2
26	25	momena	57	2	4	725434(	448239	2	1	1	2	2	2	2	2	1	2	2		3	2	2	12.5	6	9	25	20	8	7	0	0	2	2	2
27	26	pompas	47	1	1	670300	982251e	2	1	1	2	2	2	2	1	2	2	2		1	2	2	16.66	6	6	22	20	7	7	3	2	2	2	2
28	27	sumita	49	2	3	443404(	877234f	1	2	2	2	2	2	2	1	2	2	2		1	1		25	6	6	15	12	5	6	4	2	2	2	2
29	28	gitaka	47	2	3	385735f	452390:	2	2	1	2	2	2	2	1	2	2	2	6		2		22.22	6	6	20	17	7	7	1	0	2		2
30	29	sonamat	56	2	3	883262	450687:	2	2	2	2	2	2	2	1	2	2	2		1	2		11.1	6	6	20	20	8	8	0	0	2		2
31	30	suraiya	37	2	3	908730l	450886:	1	2	1	1	1	1	2	1	2	2	2		8	1	1	18.8	6	6	5	6	6	6	4	2	1	1	1
32	31	kiran	37	2	3	288634(	450943:	2	1	1	2	2	2	2	1	1	2	2		4	1		16	6	6	10	12	8	8	0	1	2		2
33	32	iti	45	2	3	896105f	451971:	2	1	2	1	2	2	2	2	2	2	2	3		2		12.5	6	6	15	15	6	7	2	3	2		2
34	33	naogami	45	2	3	301650c	215803:	2	2	2	2	2	2	2	2	2	2	2		1	2		11.11	6	6	30	30	10	10	0	0	2		2
35	34	uma	41	2	3	862808	446298	2	1	1	2	2	2	2	1	2	2	2	9		2	2	22.22	6	6	20	15	7	7	3	1	2		2
36	35	poonam	44	2	3	865775f	447533:	2	2	1	2	2	2	2	2	2	2	2		2	2		11.11	6	6	12	12	7	7	2	1	2	2	2
37	36	shikha	26	2	4	711671f	431056:	2	2	2	2	2	2	2	2	2	2	2		1	2	2	13.63	6	6	20	20	8	8	2	2	2		
38	37	shanti	48	2	3	502758(	234121:	2	1	2	2	2	2	2	1	2	2	2		5	1	2	12.5	6	6	20	20	8	8	0	0	2		2
39	38	pragati	52	2	3	079308(	445508:	2	2	1	2	2	2	2	2	2	2	2		8	1	2	22.22	6	6	30	25	8	7	0	0	1		1
40	39	oimi	43	2	2	854256(	446363	2	1	1	1	1	2	2	1	2	2	2		6	1	2	31.25	6	6	10	10	6	6	4	3	1		1
41	40	madhu	38	2	3	863066	446396	2	2	2	2	2	2	2	1	2	2	2		3	2	2	12.5	6	6	20	18	7	7	1	1	2	2	2
42	41	kalaiyara	47	2	3	507306(	446389	2	2	2	2	2	2	2	2	2	2	2		2	2	2	16.6	6	6	20	15	9	9	1	1	2	2	2
43	42	sandhya	51	2	3	813872(	446325:	2	2	2	2	2	2	2	1	2	2	2		2	2		18.8	6	6	20	25	8	8	0	0	2		2
44	43	lobin	56	2	3	854267f	44403e	2	2	1	2	2	2	1	1	1	2	2		2	1		25.5	6	12	30	25	8	8	2	2	1	2	2
45	44	vijaykum	51	2	3	837172f	444568:	2	1	1	1	2	2	2	2	2	2	2		1	1	2	16.8	6	6	25	22	8	8	2	2	2		2
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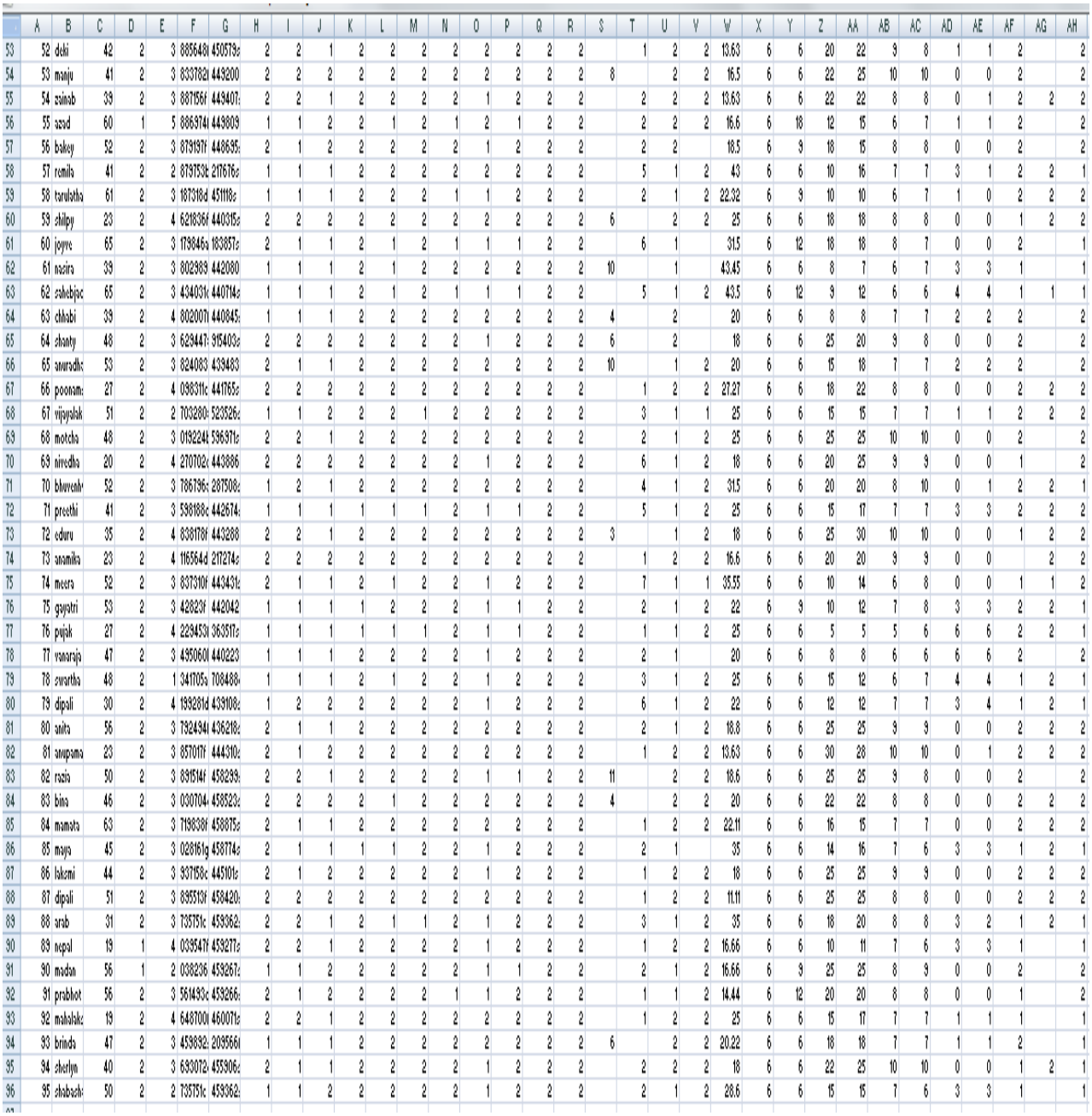

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