PREVALENCE OF SJOGREN'S SYNDROME IN PATIENTS WITH DRY EYE DISEASE IN A TERTIARY HOSPITAL IN NEPAL

Report of the study

B.P. Koirala Lions Center for Ophthalmic Studies,
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NHRC Provincial Grant Research 2021

2022

Government of Nepal

Nepal Health Research Council (NHRC)

Estd. 1991

Ref. No.: 1538

27 December 2021

Dr. Meenu Chaudhary

Principal Investigator

B.P.Koirala Lions Center for Ophthalmic Studies, Institute of Medicine

Kathmandu

Ref: Approval of research proposal

Dear Dr. Chaudhary,

This is to certify that the following protocol and related documents have been reviewed and granted approval through the expedite review process by the Expedited Review Sub-Committee meeting for it's implementation.

Protocol Registration No/ Submitted Date	623/2021 P 23 October 2021	**Sponsor Protocol No**	NA
Principal Investigator/s	Dr. Meenu Chaudhary	**Sponsor Institution**	NHRC Grant
Title	Prevalence of Sjogren's syndrome in patients with Dry Eye disease in a tertiary hospital in Kathmandu		
Protocol Version No	NA	**Version Date**	NA
Other Documents	1. Data collection tools 2. Informed Consent Form 3. Support letter	**Risk Category**	Minimal risk
Co-Investigator/s	1. Dr. Sanjeeta Sitaula 2. Dr. Saket Jha 3. Assoc. Prof. Anil Dev Pant		
Study Site	B. P. Koirala Lions Centre for Ophthalmic Studies (BPKLCOS)		
Type of Review	√ **Expedited** ☐ Full Board **Meeting Date:** 27 December 2021	**Duration of Approval** 27 December 2021 to 27 December 2022	**Frequency of continuing review** NA

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Government of Nepal

Nepal Health Research Council (NHRC)

Estd. 1991

Ref. No.: 1538

Total budget of research	**NRs 1,30,000.00**
Ethical review processing fee	**Waiver as the researcher had received NHRC Grant**

Investigator Responsibilities

- Any amendments shall be approved from the ERB before implementing them
- Submit progress report every 3 months
- Submit final report after completion of protocol procedures at the study site
- Report protocol deviation / violation within 7 days
- Comply with all relevant international and NHRC guidelines
- Abide by the principles of Good Clinical Practice and ethical conduct of the research

If you have any questions, please contact the Ethical Review M & E Section at NHRC.

Thanking you,

Dr. Pradip Gyanwali
Member- Secretary

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Nepal Health Research Council (NHRC)

Estd. 1991

Ref. No.:

Contractual Service Agreement (CSA)

An agreement made between the Nepal Health Research Council and the Contractor on 20 November 2021.

Dr. Meenu Chaudhary (hereafter called Contractor) has been awarded by Nepal Health Research Council (NHRC) for the **Provincial Health Research Grant** of the Year 2021 entitled **"Prevalence of Sjogren's syndrome in patients with Dry Eye disease in a tertiary hospital in Nepal"** on the terms and conditions mentioned below:

1. **Nature of the service:** The contractor should initiate the research work after the agreement with NHRC and submit final research report latest by May 15, 2022.

2. **Duration of the project**: The duration of the study is six months.

3. **Payment schedule:**
   a. After signing the agreement – 50%
   b. After the submission of Final Report – 50%
   c. The total amount – NRs. 1,30,000/-

4. **Deliverables:**
   - Submit two copies of the final report in hard copy.
   - Provide the electronic version of the final report.

5. **Income tax:**
   NHRC will deduct tax as per rule of Government of Nepal.

6. In cases where the contractor does not submit the completed project reports within the timeline agreed between the parties, the contractor is obliged to return the whole amount provided by the NHRC. If solution is not found, NHRC reserves the right to take legal action according to applicable laws of the Government of Nepal.

Dr. Pradip Gyanwali
Member-Secretary (Executive Chief)
NHRC

Contractor
Dr. Meenu Chaudhary
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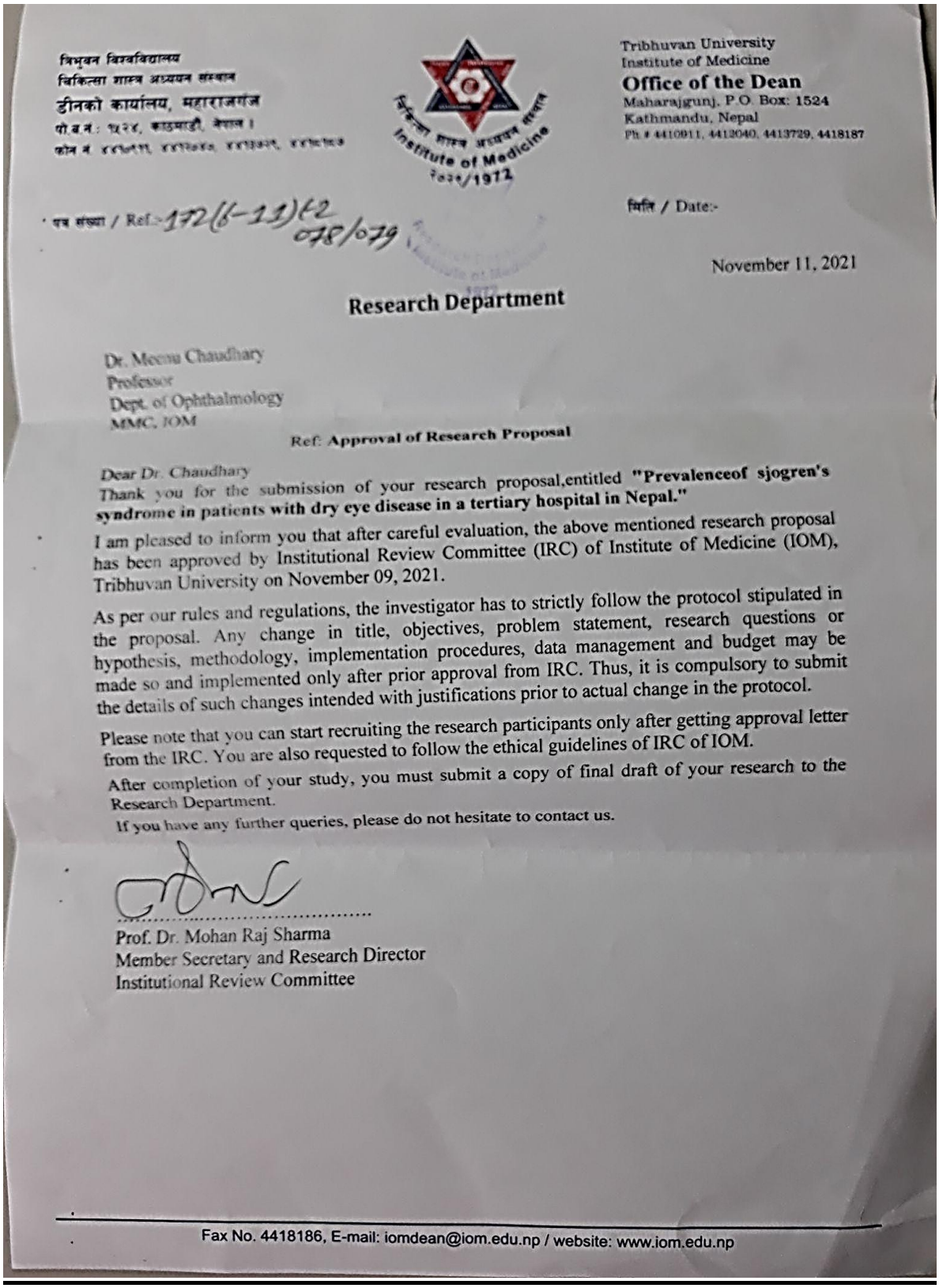
IRC APPROVAL LETTER



त्रिभुवन विश्वविद्यालय
चिकित्सा शास्त्र अध्ययन संस्थान
डीनको कार्यालय, महाराजगंज
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पत्र संख्या / Ref.:- 172(6-11)E2 078/079

मिति / Date:-

November 11, 2021

Research Department

Dr. Meenu Chaudhary
Professor
Dept. of Ophthalmology
MMC, IOM

Ref: **Approval of Research Proposal**

Dear Dr. Chaudhary
Thank you for the submission of your research proposal,entitled **"Prevalenceof sjogren's syndrome in patients with dry eye disease in a tertiary hospital in Nepal."**

I am pleased to inform you that after careful evaluation, the above mentioned research proposal has been approved by Institutional Review Committee (IRC) of Institute of Medicine (IOM), Tribhuvan University on November 09, 2021.

As per our rules and regulations, the investigator has to strictly follow the protocol stipulated in the proposal. Any change in title, objectives, problem statement, research questions or hypothesis, methodology, implementation procedures, data management and budget may be made so and implemented only after prior approval from IRC. Thus, it is compulsory to submit the details of such changes intended with justifications prior to actual change in the protocol.

Please note that you can start recruiting the research participants only after getting approval letter from the IRC. You are also requested to follow the ethical guidelines of IRC of IOM.

After completion of your study, you must submit a copy of final draft of your research to the Research Department.

If you have any further queries, please do not hesitate to contact us.

.....
Prof. Dr. Mohan Raj Sharma
Member Secretary and Research Director
Institutional Review Committee

Fax No. 4418186, E-mail: iomdean@iom.edu.np / website: www.iom.edu.np

THE RESEARCH TEAM

1) **Principal Investigator: Prof. Dr. Meenu Chaudhary**

2) **CO-Principal Investigator:**

   a) **Dr. Sanjeeta Sitaula**

   b) **Dr. Saket Jha**

   c) **Dr. Anil Dev Pant**

3) **Research Consultant: Prof. Dr. Anand Kumar Sharma**

4) **Research Assistant: Dr. Ashutosh Kumar Singh**

1.	**Cornea specialist, B.P. Koirala Lions center for Ophthalmic studies, Institute of Medicine, TU, Kathmandu, Nepal**
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PREFACE

This report is a culmination and final analysis of data which has been collected for a period of 6 months to find out the prevalence of Sjogren's syndrome in dry eye patients in a tertiary hospital in Nepal. This study has been funded by NHRC under "Provincial Health Research Grant 2021". Dry eye syndrome is often an unrecognized, unattended condition affecting a significant proportion of the population. Dry eye syndrome is a multifactorial disease. A variety of risk factors for dry eye have been identified including advanced age, female sex, menopausal hormone therapy, low androgen levels, and medication use. There is a well-known association of several systemic diseases with dry eye syndrome such as Sjögren's syndrome (SS), rheumatoid arthritis, scleroderma, polymyositis, lymphoma, amyloidosis, hemochromatosis, sarcoidosis, and systemic lupus erythematosus. Primary SS consists of the occurrence of aqueous deficient dry eye syndrome in combination with symptoms of dry mouth, in the presence of autoantibodies, evidence of reduced salivary secretion and with a positive focus score on minor salivary gland biopsy. Secondary SS consists of the features of primary SS together with the features of an overt autoimmune connective tissue disease, most common of which is rheumatoid arthritis. Primary Sjögren syndrome is an autoimmune disease that mainly affects exocrine glands such as the salivary and lacrimal glands. In addition, systemic involvement is common. Primary Sjögren syndrome is of particular interest to ophthalmologists as it constitutes an important differential diagnosis in conditions with dry eye disease. In addition, ocular tests for more precisely diagnosing and monitoring primary Sjögren syndrome have become increasingly important, and new therapeutics for local and systemic treatment evolve as a result of increased understanding of immunological mechanisms and molecular pathways in the pathogenesis of primary Sjögren syndrome. Although the rate of dry eye in various diseases has been reported, the frequency of SS among patients with dry eye is unknown in Nepal. To our knowledge there is no data available on the prevalence of Sjogren's syndrome in dry eye patients in Nepal.

Hence, this study was undertaken to find out the prevalence of Sjogren's syndrome in dry eye patients in a tertiary hospital in Nepal.

ACKNOWLEDGEMENTS

We would like to thank MD ophthalmology residents who helped us in research sample collection, referral and counseling. We would like to thank Mr. Brijkishore Swarnakar, Mrs. Ranjeeta Sapkota, Mrs. Tara Suwal, Miss. Malati Kuwar, Miss Sabina and Mr. Raju Budhathoki who actively participated in this research and helped us with notification of cases.

Special mention to Dr. Ashutosh Singh a dental surgeon for helping us in labial gland biopsy for confirmation of diagnosis of Sjogren's syndrome. In the end we would also like to thank Prof. Anand Kumar Sharma for giving us consultation on this research project whenever needed.

ABSTRACT

Purpose: To study the prevalence of Sjogren's syndrome in Dry eye patients in a tertiary hospital in Nepal.

Methods: 42 patients presenting to the eye out patient department of BPKLCOS & Rheumatology department of TUTH with dry eye symptoms were evaluated for dry eyes for a period of 6 months (Dec 2021- April 2022) . Investigations done included unanaesthetized Schirmer's test, NIBUT, Ocular staining for cornea and conjunctiva with Fluorescein stain & Lissamine green dye. Blood investigations included ENA profile and minor salivary gland labial biopsy was also done for further confirmation of diagnosis of pSS if ENA profile was negative. Proforma was filled & consent was taken before investigations. Data was entered in SPSS 20 and statistical analysis was done.

Results: 42 patients presenting with dry eyes were evaluated which included 31 (73.80%) females and 11 (26.19%) males. The number of patients who had Primary Sjogren's syndrome in patients with DED was 8 (19.04%) which included 6 (14.28%) females and 2 (4.76%) males. Primary SS was more common in the 60-70 years age group in females. Thus, the patients with purely DED were 62%, Prevalence of Primary SS was 19% and secondary SS was 19%. Out of 42 DED patients ENA profile was positive in 8 cases and only one case had positive histopathological finding on Labial salivary gland biopsy to be confirmed as Primary SS. Our study revealed a statistically significant correlation between duration of DED and duration of systemic disease. But, none of the predictors, including the duration of DED and severity of clinical markers of DED were able to predict the diagnosis in our study.

Conclusion: Primary & Secondary SS were found to be prevalent in dry eye patients in our hospital and thus, should be the focus of diagnostic evaluations. A minor salivary gland biopsy might be required for a definitive diagnosis in a significant proportion of the patients with SS. Population based studies need to be undertaken.

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LIST OF ACRONYMS

AECG	**:**	American-European Census Group
ANA	**:**	Antinuclear antibodies
BPKLCOS	**:**	B.P. Koirala Lions Center for Ophthalmic Studies
CL	**:**	Contact lens
DED	**:**	Dry Eye Disease
DES	**:**	Dry Eye Syndrome
HLA	**:**	Histocompatibility antigens
MMC	**:**	Maharajgunj Medical Campus
NIBUT	**:**	Noninvasive Tear Break up Time
pSS	**:**	Primary Sjogren's Syndrome
RA	**:**	Rheumatoid arthritis
Sch-I test	**:**	Schirmer's test I (without anesthesia)
SJS	**:**	Steven Johnson Syndrome
SLE	**:**	Systemic lupus erythematosus
SS	**:**	Sjogren's syndrome
QoL	**:**	Quality of life
TBUT	**:**	Tear Break up Time
TUTH	**:**	Tribhuvan University Teaching Hospital

CHAPTER 1

INTRODUCTION

Dry eye syndrome (DES) is one of the most common disorders in ophthalmology services. Surveys show different figures regarding prevalence, from around 5% to 35% [1,2] differences that might be due to sampling methods and population demographics. It was believed that prevalence of dry eye syndrome is higher in Asian populations than those in Western countries, based on ethnic differences [3]. Dry eye disease (DED) is also a growing public health concern causing ocular discomfort, fatigue and visual disturbance that interferes with quality of life (QoL), including aspects of physical, social, psychological functioning, daily activities and workplace productivity.

Dry eye is a multifactorial disease in which tears and ocular surface are accompanied with the characteristic symptoms of discomfort, visual disturbance, and tear film instability as well as increased permeability of tear film and ocular surface inflammation [4-6]. Dry eye syndrome is significant, not only because DES typically makes patients suffer from dry sensation, redness, burning, photophobia, and even fluctuating blurry vision, which decrease patients' life quality, but also because it could be a presentation of autoimmune diseases, such as Sjögren's syndrome (SS) or other autoimmune disorders.

An estimated 2 to 4 million persons in the United States have SS. Approximately 1million have an established diagnosis; however, because of the heterogeneity and often nonspecific nature of its clinical manifestations, it is likely that the disease remains undiagnosed in most cases. Sjogren's syndrome primarily affects women, with a female-male ratio of 9:1, and may occur in patients of all ages but typically has its onset in the fourth to sixth decades of life. Approximately 60% of SS patients have the disease secondary to an accompanying autoimmune disorder such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or systemic sclerosis. Although estimates vary, information from rheumatology clinics suggests that approximately 25% of patients with RA or SLE have histologic evidence of SS. [7]

In the Rheumatology clinics, primary SS may appear as commonly as systemic lupus erythematosus. Furthermore, approximately 25% of rheumatoid arthritis and systemic lupus erythematosus patients present at least histological evidence of SS. [8] Given that rheumatoid arthritis affects 0.2–5.3% of the general population,[9] SS can be considered a frequent medical problem. Among people without autoimmune connective tissue disease, necropsy studies have shown approximately 2–3% of people with focal infiltrates of the labial minor salivary gland compatible with SS. [7]

Dr. Henrik Sjögren [8, 9] first published in 1933 a case series observation of 19 females with dry eye symptoms; most of them had rheumatoid arthritis. After that, other clinical features were unveiled accordingly, including dry mouth and dry mucosal membranes. Many studies have echoed the female preponderance of Sjogren's syndrome and associations with autoimmune disorders. Sjogren's syndrome could be primary or secondary to other autoimmune disorders such as systemic lupus erythematosus, dermatomyositis, systemic sclerosis, and so on. The diagnostic criteria were based on the American-European Census Group (AECG) in 2002, mainly through clinical presentations and laboratory results. Besides, there is evidence that Sjogren's syndrome would increase the risk of developing malignancy, especially non-Hodgkin's lymphoma B cell type [10].

Sjogren's syndrome (SS) is a multisystem autoimmune disease characterized by lymphocytic infiltration of exocrine glands and other organs.[11] Involvement of lacrimal and salivary glands results in dry eye and dry mouth, hallmark features of the disease.[12] Indeed, phenotypic characteristics of the eye have been a key component in diagnosing this disorder. Although common, SS is under recognized in clinical practice,[13,14] largely as a result of its diverse presentation leading to a significant delay in diagnosis.[15,16] This delay is of great clinical significance because patients with SS are likely to have reduced quality of life as a result of pain, fatigue, depressed mood, and cognitive symptoms.[17] More importantly, systemic involvement is common in SS.[11,18] Approximately one third of patients with primary SS have non visceral (vasculitic skin lesions, arthritis, and peripheral neuropathies) and visceral (interstitial lung or kidney disease, autoimmune hepatitis, or pancreatitis) manifestations.[13,14,18] Lymphoma is one of the most serious complications of SS and the primary source of increased mortality resulting from this disease. Multiple

studies consistently have identified SS as an independent risk factor for non-Hodgkin's lymphoma.[19] Extra glandular ocular manifestations, such as sterile corneal necrosis, [20-23] uveitis, and scleritis,[24] have been reported to occur in SS particularly as a presenting symptom in previously undiagnosed SS patients. As many as 1 in 10 patients with clinically significant dry eye have underlying primary SS, [22,23] and only approximately a third of these have a known diagnosis at the time of presentation to eye care providers.[23] However, screening for SS by ophthalmologists caring for patients with dry eye is not a common practice, partly because serious ocular complications secondary to SS are not widely recognized.

Several studies have shown various differences between people with SS alone and those with SS and another connective tissue disease. Because of these differences, Sjogren's syndrome is termed primary Sjogren's syndrome when it occurs by itself and secondary Sjogren's syndrome when associated with another connective tissue disease.

The diagnostic criteria for Sjogren's syndrome include [13]**:**

- dry mouth
- poor salivary (saliva-producing) gland production
- dry eyes
- often the presence of antinuclear antibodies
- The presence of a positive rheumatoid factor.

Because the disease is mild in many people, the first signs of mucosal dryness may be present for years before the disease becomes clearly evident.

Laboratory abnormalities in Sjogren's syndrome are

Autoantibodies are common in SS.

- 80 percent of those with SS test positive for antinuclear antibodies (ANA).
- Rheumatoid factor is present in 75- 95 percent of those with SS.
- Elevated protein levels will be seen in 80 percent of those with SS.

- Other nonspecific laboratory abnormalities that are commonly noted in SS are elevated erythrocyte sedimentation rates (a sign of inflammation), mild anemia, and low albumin levels.

Certain genes may also be found more frequently in people with primary SS. These "histocompatibility antigens" may include HLA-B8 and HLA-DR3.

Diagnostic tests and procedures in Sjogren's syndrome [13]

Several tests are commonly used to confirm a suspected diagnosis of SS:

- In the Schirmer's test, a piece of filter paper is placed in the corner of the eye to measure the degree of wetting after five minutes.
- The Rose-Bengal staining test determines whether there is inflammation of the cornea.
- Salivary gland flow rates help to determine whether there is decreased saliva production.
- Salivary gland biopsy of the lip or parotid gland may help to establish the diagnosis.

The research results from different studies show us clinically that it is necessary to look out and pay attention to the potential ocular surface problems in patients with autoimmune diseases like Sjogren's syndrome in the aspect of diagnosis. The clinical symptoms and signs and inflammation reactions of the dry eye caused by the SS became more general and more serious. The progression of SS is closely related to the progression of ocular surface diseases. Therefore, in the treatment, it is necessary to actively promote the functional recovery of lacrimal glands and the tear secretion as well as the repair of ocular surface epithelial cells, actively and to effectively control the ocular surface inflammatory reactions, and to actively and systematically treat the systemic autoimmune disease of SS.

Basnet et al from Nepal have reported dry eye disease in Nepal. The study revealed that the patients who presented with dry eyes were mostly females of premenopausal age group, and exposed to modifiable risk factors which included residing at urban areas, indoor work, and exposure to environmental pollutants. [25]

Although many studies have been published on the association of dry eye syndrome and Sjogren's syndrome, no such study till date to our knowledge has been published from Nepal about prevalence of Sjogren's syndrome in Dry eye patients. Therefore, we proposed to study the prevalence of Sjögren's syndrome and its association with DES in a tertiary hospital in Nepal which will help us to understand the ocular manifestations of Sjogren's syndrome and its impact on vision, psychology, social and economic effect on the patient and its family.

a. Rationale: Potential Impact of the Project

Although SS is a benign and non–life-threatening disorder, patients should be prescribed appropriate treatments to improve quality of life and avoid complications. SS can lead to vision-threatening ocular complications. Additionally, these patients can have serious systemic complications resulting from SS, such as interstitial nephritis, autoimmune lung disease, vasculitis, primary biliary cirrhosis, autoimmune hepatitis, and lymphoma.

Unfortunately, no treatment is currently available to decrease the glandular lymphocytic infiltration that contributes to the exocrine gland dysfunction of SS. Moisture replacement and preservation methods, such as tear and saliva substitutes and moisturizing lotions, can help to relieve oral and ocular dryness by stimulating exocrine secretions. Corticosteroids and therapies specific to affected organs or systems (eg, ursodeoxycholic acid and intravenous immunoglobulin for liver and neurologic involvement, respectively) can be used to treat systemic manifestations of disease. The use of all available diagnostic and treatment modalities will help to reduce the time to diagnosis and preserve the health and quality of life of patients with SS. Thus, SS is associated with vision and life-threatening complications in a significant proportion of the patients.

Hence, this study will help us to assess the prevalence of SS in patients with clinically significant dry eye because dry eye precedes the occurrence of these manifestation**s.** The burden of DED on the patient and society also includes a substantial economic burden, which can be divided into two categories: direct costs such as medical fees; and indirect costs such as low employment, absence from work, and impaired productivity.

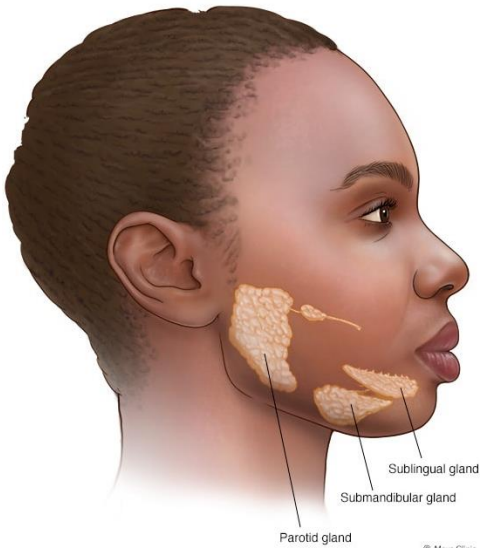
As this type of study has not been done till now in Nepal, this study will be able to give the prevalence, baseline data of ocular & systemic morbidity of Sjogren's syndrome, financial & economic burden and the psychological effect on the patient & family due to this disease.

b. Literature Review

Overview

Sjogren's syndrome is a disorder of your immune system identified by its two most common symptoms — dry eyes and a dry mouth. The condition often accompanies other immune system disorders, such as rheumatoid arthritis and lupus. In Sjogren's syndrome, the mucous membranes and moisture-secreting glands of your eyes and mouth are usually affected first — resulting in decreased tears and saliva. Although you can develop Sjogren's syndrome at any age, most people are older than 40 at the time of diagnosis. The condition is much more common in women. Treatment focuses on relieving symptoms.

Symptoms



The two main symptoms of Sjogren's syndrome are:

- Dry eyes. Your eyes might burn, itch or feel gritty — as if there's sand in them.

- Dry mouth. Your mouth might feel like it's full of cotton, making it difficult to swallow or speak.

Some people with Sjogren's syndrome also have one or more of the following:

- Joint pain, swelling and stiffness
- Swollen salivary glands — particularly the set located behind your jaw and in front of your ears
- Skin rashes or dry skin
- Vaginal dryness
- Persistent dry cough
- Prolonged fatigue

Uses: Sjogren's syndrome is an autoimmune disorder. Your immune system mistakenly attacks your body's own cells and tissues. Scientists aren't certain why some people develop Sjogren's syndrome. Certain genes put people at higher risk of the disorder, but it appears that a triggering mechanism — such as infection with a particular virus or strain of bacteria — is also necessary. In Sjogren's syndrome, your immune system first targets the glands that make tears and saliva.

But it can also damage other parts of your body, such as:

- Joints
- Thyroid
- Kidneys
- Liver
- Lungs
- Skin
- Nerves

Risk factors: Sjogren's syndrome typically occurs in people with one or more known risk factors, including:

- Age. Sjogren's syndrome is usually diagnosed in people older than 40.

- Sex. Women are much more likely to have Sjogren's syndrome.
- Rheumatic disease. It's common for people who have Sjogren's syndrome to also have a rheumatic disease — such as rheumatoid arthritis or lupus.

Complications: The most common complications of Sjogren's syndrome involve your eyes and mouth.

- Dental cavities. Because saliva helps protect the teeth from the bacteria that cause cavities, you're more prone to developing cavities if your mouth is dry.
- Yeast infections. People with Sjogren's syndrome are much more likely to develop oral thrush, a yeast infection in the mouth.
- Vision problems. Dry eyes can lead to light sensitivity, blurred vision and corneal damage.

Less common complications might affect:

- Lungs, kidneys or liver. Inflammation can cause pneumonia, bronchitis or other problems in your lungs; lead to problems with kidney function; and cause hepatitis or cirrhosis in your liver.
- Lymph nodes. A small percentage of people with Sjogren's syndrome develop cancer of the lymph nodes (lymphoma).
- Nerves. You might develop numbness, tingling and burning in your hands and feet (peripheral neuropathy).

Literature Review:

1. **Evaluation of patients with dry eye for presence of underlying Sjögren syndrome.[23]**

Esen Karamursel Akpek, Alena Klimava, Jennifer E Thorne, Don Martin, Kaevalin Lekhanont, Ann Ostrovsky. Cornea. 2009 Jun;28(5):493-7. doi: 10.1097/ICO.0b013e31818d3846

Abstract

Purpose: To evaluate the rate of Sjögren syndrome (SS) in a cohort of patients with dry eye syndrome.

Methods: Medical records of patients with a primary diagnosis of dry eye syndrome (International Classification of Diseases [ICD] code 375.15 or 370.33) were reviewed retrospectively. Patients who had 2 or more visits to a single dry eye center during a 2-year period (January 2004 to January 2006) were considered.

Results: Two hundred twenty patients with dry eye syndrome were identified. A total of 57 patients (25.9%) had an underlying rheumatic condition: 25 patients (11.4%) had rheumatoid arthritis and 24 (10.9%) had primary Sjögren syndrome (PSS). Majority of the patients with rheumatoid arthritis (96%) carried the diagnosis at the time of presentation. Of all patients with PSS, only 33.3% (8/24) carried the diagnosis at the time of presentation. Fifty percent (12/24) were diagnosed as a result of the initial evaluation. Among those, only 66.6% (8/12) tested SSA (anti-Ro antibodies) or SSB (anti-La antibodies) positive. One third of patients (4/12) tested only antinuclear antibody positive at a titer of <1/320 and required minor salivary gland biopsy for definitive diagnosis. Additional 16.7% (4/24), who were initially serologically negative, eventually underwent minor salivary gland biopsy and became diagnosed with SS.

Conclusions: PSS seems to be underdiagnosed in patients with dry eye syndrome and should be the focus of diagnostic evaluations. A minor salivary gland biopsy might be required for a definitive diagnosis in a significant proportion of the patients with SS.

2. The Prevalence of Dry Eye Syndrome and the Likelihood to Develop Sjögren's Syndrome in Taiwan: A Population-Based Study.[26]

Ju-Chuan Yen, Chia-An Hsu, Yu-Chuan Li, Min-Huei Hsu, . Int J Environ Res Public Health. 2015 Jul; 12(7): 7647–7655. doi: 10.3390/ijerph120707647

Abstract

***Background*:** Dry eye syndrome (DES) is one of the key clinical features and possibly an early clinical presentation of Sjögren's syndrome (SS). We explore DES prevalence and assess the likelihood of DES patients to develop SS in Taiwan through the National Health Insurance Research Database (NHIRD). ***Methods*:** Through a cohort comparison study, longitudinal data from the NHIRD (2000 to 2008) in Taiwan was used to probe the prevalence of DES and the odds that DES patients would later develop SS. ***Results*:** The prevalence of DES in the present study is 4.87%. The incidence rates of developing SS were 4.8% for the DES group and 1.5% for the comparison group. The median age and interquartile range of DES and comparison patients was 49.8 (10) and 48.7 (15) years old, respectively. The crude hazard ratio (with 95% confidence interval) for DES patients to develop SS was 3.13 (3.10–3.50) for the DES group, and the adjusted hazard ratio (with 95% confidence interval) was 3.64 (3.43–3.87). The observation period and interquartile range for DES and comparison patients to develop SS later were 1418 (781–2316) *versus* 1641 (971–2512) days respectively. ***Conclusions*:** DES patients carried a higher risk for developing SS (hazard ratio 3.13) and presented for SS 3.88 years earlier than comparison group patients in this study.

Keywords: prevalence, dry eye syndrome (DES), Sjögren's syndrome (SS), National Health Insurance Research Database (NHIRD)

3. **Factors associated with severe dry eye in primary Sjögren's syndrome diagnosed patients.[27]**

Mónica Fernandez Castro, Carlos Sánchez-Piedra, Jose Luis Andreu, Víctor Martínez Taboada, Alejandro Olivé, Jose Rosas, and On behalf of SJOGRENSER Group, part of the Spanish Society of Rheumatology Systemic Autoimmune Diseases Study Group (EASSER)

Rheumatol Int. 2018; 38(6): 1075–1082. doi: 10.1007/s00296-018-4013-5

Abstract:

Introduction: Primary Sjögren's syndrome (pSS) is an autoimmune disease, characterized by lymphocytic infiltration of exocrine glands and other organs, resulting in dry eye, dry mouth and extraglandular systemic findings.

Objective: To explore the association of severe or very severe dry eye with extraocular involvement in patients diagnosed with primary Sjögren's syndrome.

Methods: SJOGRENSER registry is a multicenter cross-sectional study of pSS patients. For the construction of our main variable, severe/very severe dry eye, we used those variables that represented a degree 3–4 of severity according to the 2007 Dry Eye Workshop classification. First, bivariate logistic regression models were used to identify the effect of each independent variable on severe/very severe dry eye. Secondly, multivariate analysis using a regression model was used to establish the independent effect of patient characteristics.

Results: Four hundred and thirty-seven patients were included in SJOGRENSER registry; 94% of the patients complained of dry eye and 16% developed corneal ulcer. Schirmer's test was pathological in 92% of the patients; 378 patients presented severe/very severe dry eye. Inflammatory articular involvement was significantly more frequent in patients with severe/very severe dry eye than in those without severe/very severe dry eye (82.5 vs 69.5%, $p = 0{,}028$). Inflammatory joint involvement was associated with severe/very severe dry eye in the multivariate analysis, OR 2.079 (95% CI 1.096–3.941).

Conclusion: Severe or very severe dry eye is associated with the presence of inflammatory joint involvement in patients with pSS. These results suggest that a directed anamnesis including systemic comorbidities, such as the presence of inflammatory joint involvement or dry mouth in patients with dry eye, would be useful to suspect a pSS.

Keywords: Dry eye syndromes, Sjögren's syndrome, Joints, Schirmer's test

4. **Prevalence of Dry Eye Syndrome and Sjogren's Syndrome in Patients with Rheumatoid Arthritis [28]**

Panida Kosrirukvongs, Panotsom Ngowyutagon, Pawana Pusuwan, Ajchara Koolvisoot, Surasak Nilganuwong .J Med Assoc Thai 2012; 95 (Suppl. 4): S61-S69 Full text. e-Journal: http://www.jmat.mat.or.th

Abstract:

Background: Rheumatoid arthritis has manifestations in various organs including ophthalmic involvement. The present study evaluates prevalence of dry eye and secondary Sjogren's syndrome using salivary scintigraphy which has not been used in previous reports.

Objective: To evaluate the prevalence of secondary Sjogren's syndrome in patients with rheumatoid arthritis, including clinical characteristics and dry eye, compared with non-Sjogren's syndrome. Design: Descriptive cross-sectional study. Material and Method: Sixty-one patients with rheumatoid arthritis were recruited at Siriraj Hospital during March 2009- September 2010 and filled in the questionnaires about dry eye for Ocular Surface Disease Index (OSDI) with a history taking of associated diseases, medications, duration of symptoms of dry eyes and dry mouth. The Schirmer I test without anesthesia, tear break-up time, rose bengal staining score, severity of keratitis and salivary scintigraphy were measured and analyzed.

Results: Prevalence of secondary Sjogren's syndrome and dry eye were 22.2% (95% CI 15.4 to 30.9) and 46.7% (95% CI 38.0 to 55.6), respectively. Dry eye interpreted from OSDI, Schirmer I test, tear break-up time and rose bengal staining was16.4%, 46.7%, 82% and 3.3% respectively. Fifty-two percent of patients had a history of dry eye and dry mouth with mean duration 27.4 and 29.8 months, respectively. Superficial punctate keratitis and abnormal salivary scintigraphy were found in 58.2% and 77.8%. Duration of rheumatoid arthritis, erythrocyte sedimentation rate was not correlated with secondary Sjogren's syndrome. Dry eye from OSDI with secondary Sjogren's syndrome (33.3%) compared with non-Sjogren's syndrome (9.5%) was a significant difference ($p = 0.008$). Adjusted odds ratio for secondary Sjogren's syndrome in

OSDI score > 25 was 13.8 (95% CI 2.6 to 73.8, p = 0.002) compared to OSDI score < 25.

Conclusion: Awareness and detection of dry eye syndrome and secondary Sjogren's syndrome in rheumatoid arthritis was crucial for evaluation of their severity and proper management. Keywords: Dry eye, Sjogren's syndrome, Rheumatoid arthritis, Ocular Surface Disease Index (OSDI

5.**Diagnostic performance of dry eye tests, serology and labial salivary gland biopsy in primary Sjogren's syndrome in an Indian setting.[29]**

Roma Johria, Jayanthi Petera, Vishali Peravalib, Pulukool Sandhyac, Debashish Dandac, Sarada Davida. Clinical Epidemiology and Global Health. 2020; 8(1) :301-304. https://doi.org/10.1016/j.cegh.2019.03.007

Abstract:

Purpose: To evaluate the diagnostic performance of dry eye tests, serology and labial salivary gland biopsy in Primary Sjogren's syndrome (pSS).

Methods: Prospective cross-sectional study spanning 7-months of patients referred from rheumatology for evaluation of dry eyes. Severity of ocular symptoms was assessed using the Ocular Surface Disease Index (OSDI) questionnaire. The sensitivity, specificity and positive likelihood ratio (+LR) of Schirmer-I (Sch-I) test, Tear Break-up time (TBUT) and Ocular Staining Score (OSS) were assessed and Receiver Operating characteristic (ROC) curves were analysed. The American College of Rheumatology (ACR) criteria was used to diagnose pSS.

Results: Of the 95 patients, 31 (32.6%) fulfilled the ACR criteria for pSS. OSDI score was significantly ($p < 0.001$) higher (24.6 ± 9.4) in pSS than non-pSS (17.8 ± 5.4) patients. The sensitivity and specificity were 3.2% and 100% for Sch-I ≤5 mm and 61.3% and 90.6% for OSS ≥3 respectively. TBUT of < 10 s had poor specificity (12.5%); however, at lower threshold (< 8 s), sensitivity (80.6%) and specificity (60.9%) were optimal. The + LR was 2.07 for TBUT < 8 s and 6.54 for OSS ≥3. Twenty-six (83.9%) patients diagnosed as pSS had anti-SSA or anti-SSB antibodies. Anti-SSA, when compared with anti-SSB, had better sensitivity (76.7% vs. 52.4%)

than specificity (88.7% vs. 100%). Labial biopsy had the best diagnostic performance (sensitivity 96.8%; specificity 88.9%; +LR 8.71).

Conclusion: In patients with high OSDI scores, dry eye tests in combination with serology will identify the subset of patients with a high probability of pSS. Labial biopsy may be considered in patients with negative serology.

Keywords: dry eye labial biopsy Serology Sjogren's syndrome Tests

6. **Primary Sjögren's syndrome and the eye - Major Review.[30]**

Oddbjørn Bjordal, Katrine Brække Norheim, Eyvind Rødahl, Roland Jonsson DDS,Roald Omdal. Survey Ophthalmology 65, (2020) 119-132.https://doi.org/10.1016/j.survophthal.2019.10.004

Abstract:

Primary Sjögren syndrome is an autoimmune disease that mainly affects exocrine glands such as the salivary and lacrimal glands. In addition, systemic involvement is common. Primary Sjögren syndrome is of particular interest to ophthalmologists as it constitutes an important differential diagnosis in conditions with dry eye disease. In addition, ocular tests for more precisely diagnosing and monitoring primary Sjögren syndrome have become increasingly important, and new therapeutics for local and systemic treatment evolve as a result of increased understanding of immunological mechanisms and molecular pathways in the pathogenesis of primary Sjögren syndrome. We provide an update of interest to ophthalmologists regarding pathogenesis, diagnosis, investigative procedures, and treatment options.

Keywords

primary Sjögren syndrome dry eye disease treatment lacrimal gland inflammation

7. **Long-Term Ocular Outcomes of Sjogren's Syndrome vs Non-Sjogren's Dry Eye Disease.[31]**

David Cui, Priya Mathews, W.L. Gore, Sezen Karakus, Esen Akpek. Investigative Ophthalmology & Visual Science June 2020, Vol.61, 118.

Abstract:

Purpose: To compare the longitudinal clinical treatments and ocular findings in primary Sjogren's Syndrome (SS) and non-Sjogren's Syndrome dry eye patients.

Methods: All patients were evaluated and followed at the Johns Hopkins Hospital, a tertiary academic medical center between 2004-2019, and had one clinic visit per calendar year for a minimum of 5 years. Primary SS patients were identified through an existing database from the Johns Hopkins Sjogren's Syndrome Center, and non-Sjogren's patients were identified using ICD codes for dry eye syndrome/keratoconjunctivitis sicca. Primary SS patients fulfilled the American College of Rheumatology's 2012 criteria, requiring 2 of the following: positive serum anti-SSA and/or anti-SSB, ocular staining score ≥3, and presence of focal lymphocytic sialadenitis in labial salivary gland biopsy. A retrospective chart review was performed of each patient from their initial visit to all subsequent follow-ups.

Results: One hundred randomly selected patients were included, with 50 Sjogren's and 50 non-Sjogren's patients with dry eyes caused by all other etiologies. The average patient age at initial presentation was 53.1 +/- 13.8 years, with an average follow-up period of 7.4 +/- 3.0 years. Sjogren's patients used on average 6.9 separate dry eye treatments, compared to non-Sjogren's patients with 5.8 treatments and 4.7 on follow-up. Eighty-two percent (41/50) of SS patients received additional treatment for Sjogren's either as systemic medication or saliva production stimulator.Average Ocular Staining Score for Sjogren's and non-Sjogren's patients on presentation was 5.1 and 4.9 respectively for the worse eye on presentation, with the score decreasing/improving by 2.0 for both groups by their most recent visit. During the follow-up period, eighteen (36%) of Sjogren's patients and 10 (20%) non-Sjogren's patients had a dry eye related ocular complication.

Conclusions: Patients with chronic dry eye disease require the utilization and trial of multiple treatments, eventually helping improve objective measurements of dry eye over time. Response to treatment was similar between the two groups, however Sjogren's patients may have marginally worse findings such as a worse staining score at baseline, utilizing more dry eye treatments, and a greater prevalence of dry eye complication on follow-up.

c. Research objectives and hypothesis

Dry eye disease (DED) is a multifactorial disease of the ocular surface with loss of homeostasis of the tear film and ocular symptoms with the prevalence ranging from 5 to 50 percent. Sjögren's syndrome (SS) is a chronic autoimmune inflammatory disorder characterized by diminished lacrimal and salivary gland function with resultant dryness of the eyes and mouth. SS can be primary when it is not associated with other diseases and secondary when it complicates or overlaps with other rheumatic conditions. The incidence rates of developing SS were 4.8% for the DES group in a study in Taiwan. Autoimmune diseases are on a rise worldwide and with clear diagnostic criteria more cases of Sjogrens are being identified. Proper and timely identification of the disease not only helps in preventing blinding eye complications but also prevents systemic morbidity which requires oral medications unlike the other conventional DES treatment. Hence our primary objective is to identify SS among patients with DES.

c. Objectives:

General Objective:

To study the prevalence of Sjogren's syndrome in Dry eye patients in a tertiary hospital in Nepal.

Specific objectives:

1. To determine the demographic characteristics of patients presenting with the various grades of dry eye
2. To determine the prevalence of Sjogren's syndrome (SS) among patients with dry eye syndrome (DES)
3. To describe the demographic characteristics of patients diagnosed with SS.
4. To correlate the severity of DES with duration of diagnosis of systemic disease and the severity of systemic disease.
5. To study positive predictive value of the various signs of DES in diagnosing SS

d. Hypothesis:

A subset of patients presenting with dry eye have Sjogrens syndrome which unlike other types of dry eye are not adequately treated with conventional dry eye therapy. They require systemic immunosuppression to prevent blinding eye complications and systemic morbidity

CHAPTER 2

METHODOLOGY

a. **Study Design:** Hospital based Prospective non-randomized cross-sectional observational study.

Research Method - Quantitative

Types of study- Cross-sectional, Observational

b. Study Area: This study was conducted at the Rheumatology department of Tribhuvan University teaching hospital (TUTH) and B. P. Koirala Lions Centre for Ophthalmic Studies (BPKLCOS), Institute of Medicine, Maharajgunj. Kathmandu.

Study Units:

1. B.P. Koirala Lions Center for Ophthalmic Studies
2. Rheumatology Department of Tribhuvan University Teaching Hospital
3. Pathology department of Tribhuvan University Teaching Hospital
4. Dental department of MMC
5. Investigative units

Investigative Units:

1. Procedure unit (room no.18), Dry eye workup unit (room no. 23) of BPKLCOS OPD
2. TUTH Hematological & biochemistry laboratory
3. TUTH Pathology Laboratory
4. Dental OPD of MMC

c. Duration of the Study- 6 months (Oct 2021- Apr 2022)

Study population/sampling frame

DES subjects were recruited from individuals above 18 years consulting the ophthalmology department in our hospital with symptoms of dry eyes. Approval of the institutional ethical committee was obtained. Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

A detailed medical history, including information about duration and severity symptoms, history of systemic diseases, and a detailed drug history was taken. All participants underwent a comprehensive ophthalmic examination, including anterior and posterior segment examination along with the Schirmer test I (without anesthesia), the non -invasive tear break up time, and grading the corneal fluorescein staining pattern.

Contact lens wearers were asked to discontinue CL wear for 7 days before the dry eye examination. In chronological order the test was performed as follows: the Schirmer test I (without anesthesia) was done first, followed by instillation of fluorescein dye, determining the tear break up time, and grading the corneal fluorescein staining pattern. After fluorescein grading of the cornea, lissamine green dye was applied and the conjunctiva quickly examined and graded before the dye diffuses or the intensity of staining diminishes.

DES diagnosis was performed by a cornea specialist using the diagnostic criteria specified above. Patients with a high suspicion for SS were further evaluated by a rheumatologist, a cornea specialist, and an oral medicine specialist to confirm the diagnosis of SS. The diagnosis of SS was made based on the following criteria:

ACR-EULAR Classification Criteria for primary Sjögren's syndrome (pSS)*

The classification of SS applies to any individual who meets the *inclusion criteria,* [1] *does not have any condition listed as exclusion criteria,* [2] *and who has a score ≥ 4 when summing the weights from the following items:*

Item	**Weight / Score**
Labial salivary gland with focal lymphocytic sialadenitis and focus score ≥ 1	3
Anti-SSA (Ro) +	3
Ocular staining score ≥ 5 (or van Bijsterfeld score ≥ 4) on at least one eye	1
Schirmer ≤ 5 mm/5min on at least one eye	1
Unstimulated whole saliva flow rate ≤ 0.1 ml/min	1

**Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, Rasmussen A, Scofield H, Vitali C, Bowman SJ, Mariette X. 2016 ACR-EULAR classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Arthritis & rheumatology (Hoboken, NJ). 2017 Jan;69(1):35.*

Sampling Method- Non probability sampling

d. Sample Size Calculation

The incidence rates of developing SS were 4.8% for the DES group in a study in Taiwan. Hence, taking the prevalence of SS as 5 % N = 4PQ/L2 Where N is the sample size, P is the prevalence (5%) Q=95 L is allowable error (taken as 5%), N= 4x 5x95/ 5x5 N=76 For 6 months sample collection duration, N/2 = 76/2= 38 Considering for 10% error, 38 + 10%= 41.8= 42 So the sample size of 42 was considered for the study.

Number of participants and Justification:

The incidence rates of developing SS were 4.8% for the DES group in a study in Taiwan.

N = 4PQ/L2

Where N is the sample size,

P is the prevalence (5%)

Q=95

L is allowable error (taken as 5%),

N= 4x 5x95/ 5x5

N=76

For 6 months sample collection duration, N/2 = 76/2= 38

Considering for 10% error, 38 + 10%= 41.8= 42

So, the sample size of 42 was considered for the study.

Data collection tools

Data collections tools include: 1. Schirmer test I (without anesthesia) -Whatman's filter paper

2. Tear break up time (TBUT), NIBUT- Corneal topographer BON SIRRUS machine

3. Ocular staining - Rose Bengal dye / Lissamine green stain.

4. Slit lamp Biomicroscopy

5. ENA panel

6. Labial salivary gland Biopsy

7.Unstimulated whole saliva flow rate

8. Proforma was used for data collection

1. Clinical Evaluation: DES subjects were recruited from individuals above 18 years consulting the ophthalmology department in our hospital with symptoms of dry eyes. All participants underwent a comprehensive ophthalmic examination, including anterior and posterior segment examination.

2. Investigations: Schirmer test I (without anesthesia), the tear break up time, and grading the corneal fluorescein staining pattern was done. Contact lens wearers were asked to discontinue CL wear for 7 days before the dry eye examination. The chronological order of the test performed was as follows: the Schirmer test I (without anesthesia) was done first, followed by instillation of fluorescein dye, determining the tear break up time, and grading the corneal fluorescein staining pattern. After fluorescein grading of the cornea, lissamine green dye was applied and the conjunctiva quickly examined and graded before the dye diffuses or the intensity of staining diminishes. DES diagnosis was performed by a cornea specialist using the diagnostic criteria specified above. Patients with a high suspicion for SS were further evaluated by a rheumatologist, a cornea specialist, and an oral medicine specialist to confirm the diagnosis of SS.

3. ENA panel blood investigations were done if Schirmer's test & NIBUT was positive.

4. If the ENA panel was Negative Labial salivary gland biopsy was done and sent for Histopathological examination, Unstimulated outflow rate of saliva was also done by the Rheumatologist.

Pretesting: NA

Validity and reliability of tool:

Tests and investigations are done routinely for dry eye disease patients & accepted internationally and nationally. Hence, these are reliable and valid tools for the study.

Potential Biases:

As TUTH & BPKLCOS are tertiary level referral hospitals there is a very high chance of having dry patients to be diagnosed more frequently as Sjogren's syndrome.

e. Inclusion criteria

The inclusion criteria for the DES group were as follows: (presence of any 2)

- subjects with complaints of dry eyes who have an Ocular Surface Disease Index (OSDI) questionnaire score of >25,
- positive Schirmer I test (without anesthesia, <5 mm in 5 min), or
- break of fluorescein corneal dye in less than 5 sec in tear breakup time (TBUT), in at least one eye or NIBUT less than 5 seconds
- Rose bengal/Lissamine score ≥4 according to van Bijsterveld's scoring system, or other ocular dye scores

Exclusion criteria included known diagnoses of:

- Infectious conditions like hepatitis C infection, HIV infection, active tuberculosis
- Inflammatory conditions like sarcoidosis, graft versus host disease, IgG4-related disease
- 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 the last 5 years;
- Physical or mental condition interfering with successful participation in the study.

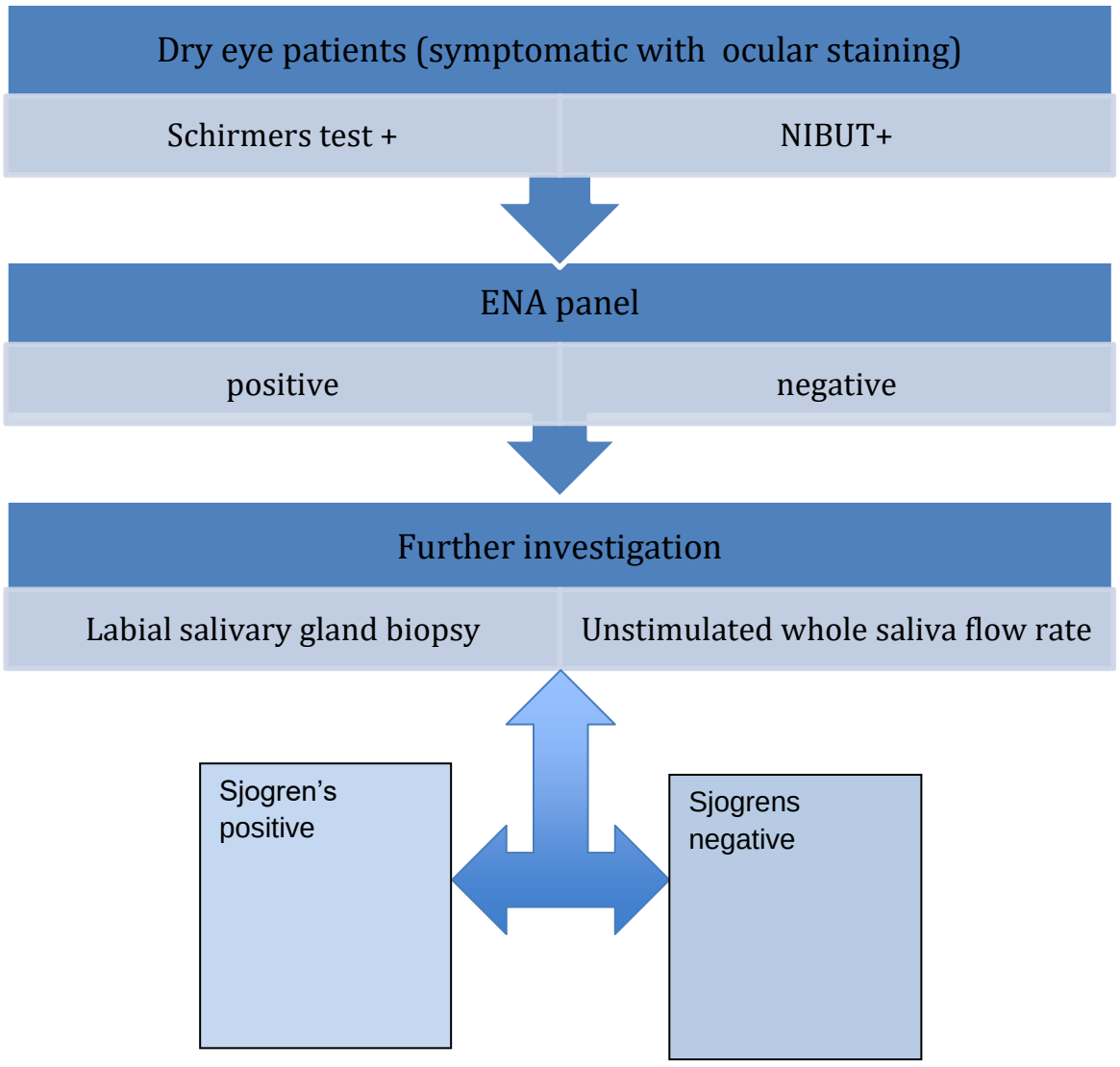
Data Management and Statistical Analysis:

Data entry and analysis was done using statistical tools in the statistical package for social science (SPSS) version 20.0. Parametric tests were used for comparison of homogeneously distributed data, whereas nonparametric tests were used for comparison of non-homogeneously distributed data. Multistep regression formula was applied for correlation analysis. Confidence interval was considered at 95% level. P-value was considered significant for less than 0.05.

Plan for Supervision and Monitoring:

The study was conducted under the supervision and monitoring of Prof Ananda Kumar Sharma, previous Executive Director of BPKLCOS.

Conceptual framework:



Work plan

Activity	August 21	September 21	Oct 21	Nov 21	Dec 21	Jan 22	Feb 22	Mar 22	Apr 22
Research Protocol									
Receive Approval									
Data Collection									
Data Entry									
Literature Review									
Data Analysis									
Discussion									
Proofreading And Correction									
Print and Submission									

CHAPTER 3

RESULTS & ANALYSIS

Total number of patients with dry eye disease included in this study according to the sample size was 42 during a study duration of 6 months. Table 1 below gives the demography of patients who presented with dry eye disease to our hospital . The number of females presenting with dry eye disease was 31 (71.80%) compared to males which was 11 (26.19%) in number. This shows that female patients presented with more dry eye disease compared to males.

Table 1: Demography of patients presenting with Dry Eye Disease

Age group (years)	Female Number(N)	Female (%)	Male Number (N)	Male (%)	Total
20-30	6	14.28	0	0	6
30-40	6	14.28	4	9.52	10
40-50	7	16.66	3	7.14	10
50-60	5	11.90	2	4.76	7
60-70	7	16.66	2	4.76	9
Total	31	73.80%	11	26.19%	42

Table 1 shows that more females presented with dry eye disease, 31 (73.80%) in comparison to male patients which was 11 (26.19%) in number. This data shows that females suffer from Dry eye disease more frequently in comparison to males.

Graph 1: Demographic Characteristics of Patients Presenting with Dry Eye Disease

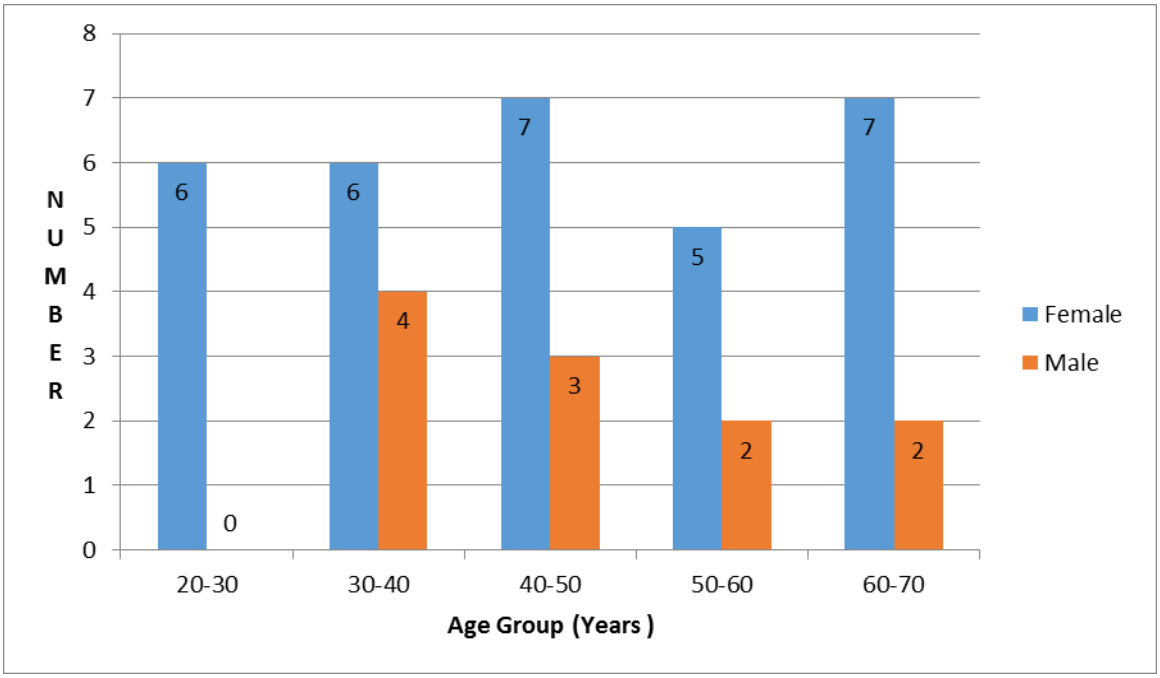


Table 2: Demographic Characteristics of Primary Sjogren's syndrome

Age group (Years)	Female Number (N)	Male Number (N)	Total Number (N)	Total (%)
20-30	0	0	0	0
30-40	1	0	1	2.38%
40-50	1	1	2	4.76%
50-60	1	1	2	4.76%
60-70	3	0	3	7.14%
Total	6 (14.28%)	2(4.76%)	8	19.04%

Table 2 shows the demographic characteristics of Primary Sjogren's syndrome. It is seen that primary Sjogren's Syndrome was seen more commonly in female patients which was 6 (14.28%) in number in comparison to males, where only 2 patients (4.76%) were found to suffer from Primary Sjogren's syndrome. Thus, this data showed females to be more frequently affected with Primary Sjogren's syndrome. 60-70 years age group females were found to be affected more with Primary Sjogren's syndrome, 3 (7.14%) out of the study sample of 42 patients suffering from Dry Eye Disease. Thus, Dry eye patients suffering from Primary Sjogren's was 19.04%.

Graph 2: Demographic Characteristics of Patients with Primary Sjogren's Syndrome

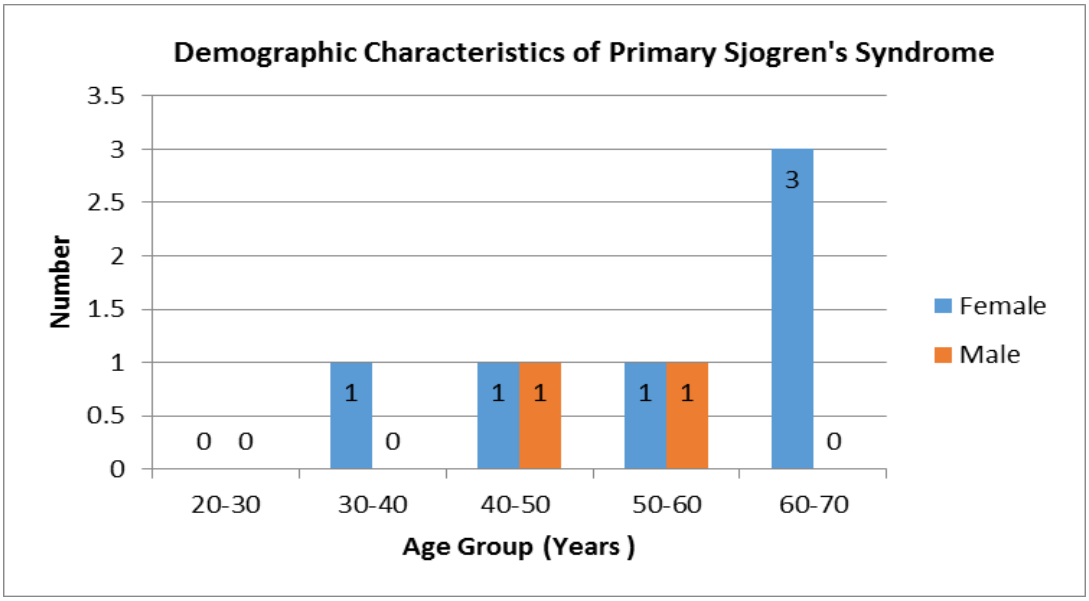
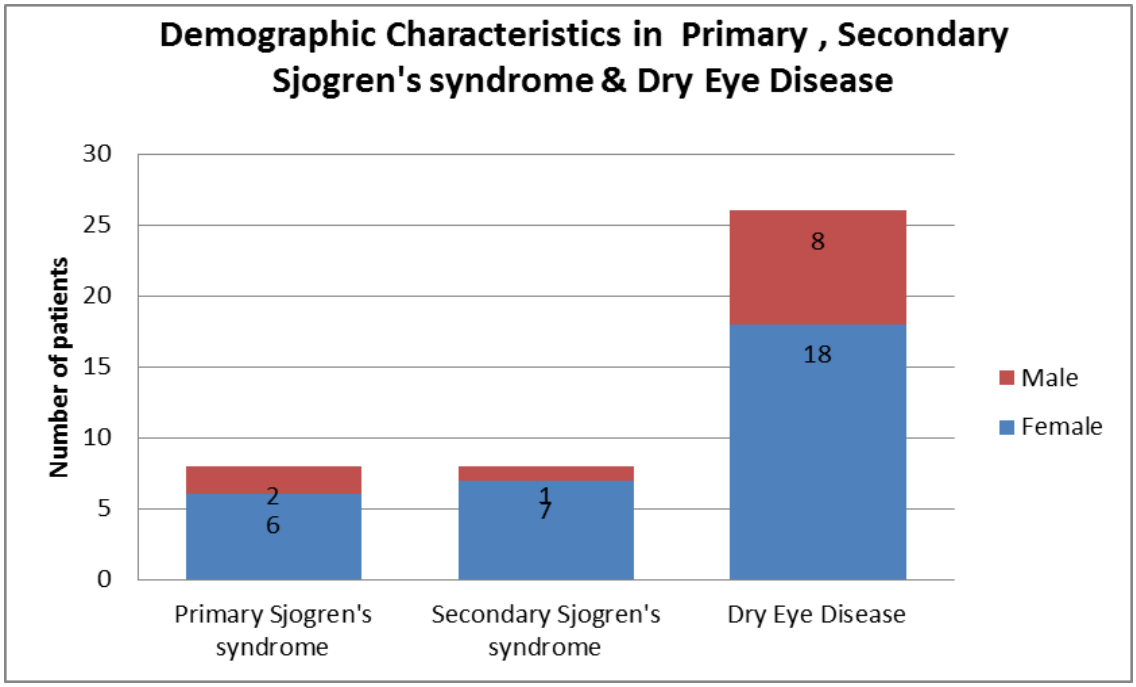


Table 3: Demographic Characteristics of Secondary Sjogren's syndrome

Age group (Years)	Female Number (N)	Male Number (N)	Total Number	Total (%)
20-30	**2**	**0**	**2**	**4.76%**
30-40	**2**	**0**	**2**	**4.76%**
40-50	**0**	**0**	**0**	**0**
50-60	**2**	**0**	**2**	**4.76%**
60-70	**1**	**1**	**2**	**4.76%**
Total	**7(16.66%)**	**1(2.38%)**	**8**	**19.04%**

Table 3 demonstrates the demographic Characteristics of Secondary Sjogren's syndrome. This table also shows preponderance of female patients, 7 (16.66%). Secondary Sjogren's syndrome was found to be related to Rheumatoid Arthritis leading to secondary Sjogren's syndrome. Only one (2.38%) male patient suffering from dry eye disease was diagnosed as secondary Sjogren's syndrome due to Rheumatoid arthritis.

Graph 3: Demographic Characteristics of Primary & Secondary Sjogren's syndrome in patients of Dry Eye Disease



Graph 4: Pie Chart showing the distribution of Primary & Secondary Sjogren's syndrome in Dry Eye patients

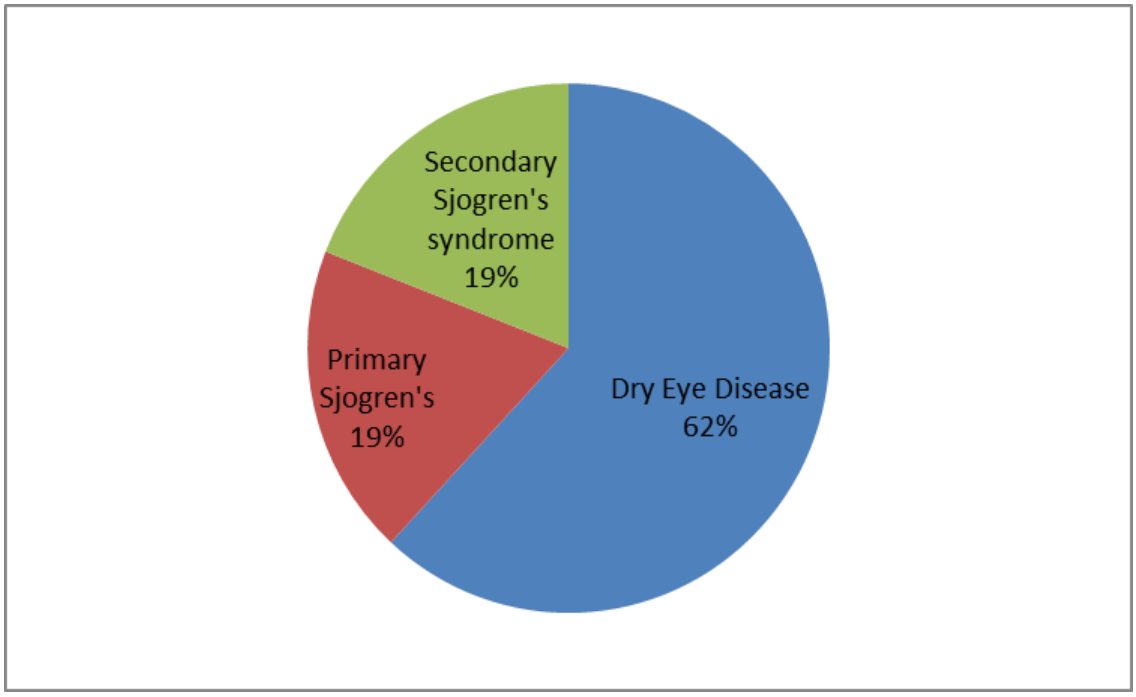


Table 4: Investigations done in relation to ENA Profile, RA Factor, Anti-CCP Antibody, ANA & Labial gland salivary Biopsy

Investigations	Positive (N)	Negative (N)
ENA Profile	**8**	**34**
RA factor	**4**	**27**
ANA	**1**	
Anti–CCP Antibody	**2**	
Labial Salivary Gland Biopsy	**1**	**26**

Table 4 shows that patients with dry eye disease (DED) showed ENA profile blood investigations positive in 8 cases and 34 had negative ENA profile. Out of these ENA negative test reports, 8 patients showed positive RA factor (4), ANA (1) & Anti CCP (3) investigations. Patients with negative ENA profile & Rheumatologic investigations, who underwent labial salivary gland biopsy, only 1 case was confirmed to have Primary Sjogren's syndrome based on the pathology report of Focus score which was more than 2 (F> 2).

Graph 5: Demonstrating Positivity of Labial Salivary Gland Biopsy, ENA Profile, RA factor, ANA & Anti- CCP Antibody in Patients' Blood Investigations

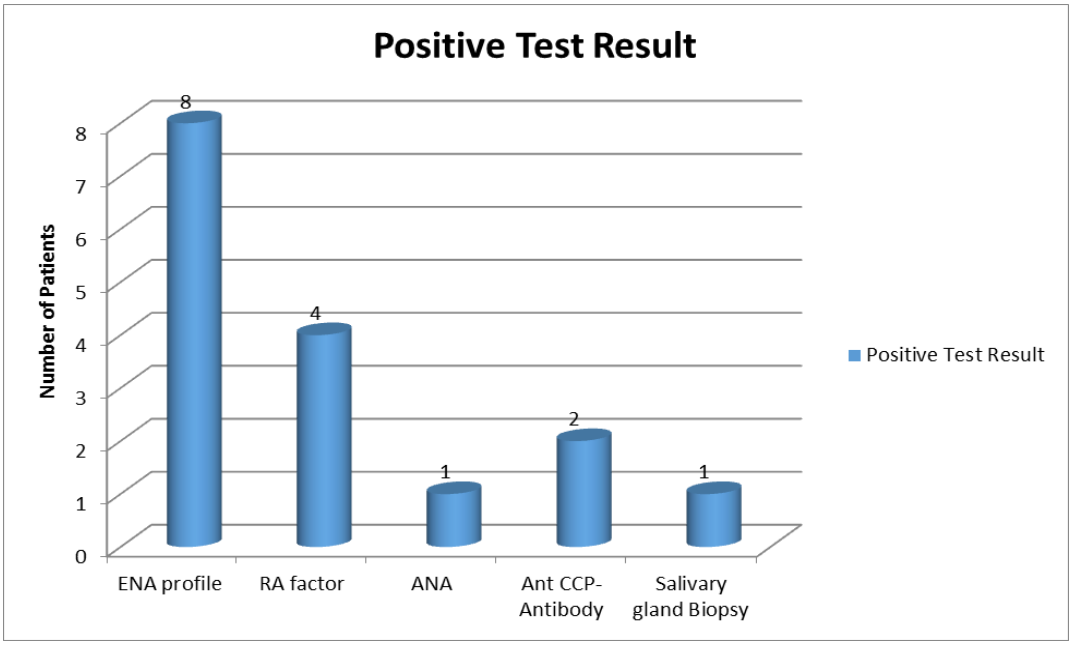


Table 5 (a): Relationship between Duration of Dry Eye Disease with Various Signs of Diagnosis of Dry eye syndrome (DES)

S.No	Duration of DED	Schirmer's test RE (mm)	Schirmer's Test LE (mm)	NIBUT RE secs)	NIBUT LE (secs)	Ocular Staining RE	Ocular Staining LE	Speed Score
1.	1 month	6	5	3.2	6.4	0	0	10
2.	1 month	0	0	6.45	6.45	0	0	14
3.	3 months	2	2	8	9	0	0	12
4.	3 months	4	7	1.6	12	0	0	3
5.	2 months	0	2	9.3	7.2	0	0	8
6.	5 months	10	2	9	6	2	2	22
7.	6 months	10	8	9	8	0	0	11
8.	6 months	0	0	4	3.3	0	4	23
9.	6 months	4	6	10	12	0	0	8
10.	8 months	5	2	10	8	1	1	12
11.	8 months	0	0	12	12	1	1	9
12.	10 months	0	1	1.35	2.5	0	0	6
13.	1year	5	12	3.2	2.5	2	2	15
14.	1 year	0	0	10	10	0	0	6
15.	1 year	3	3	5.2	5.2	2	2	6
16.	1 year	2	1	10	6	0	0	21
17.	1 year	5	5	3.65	6.5	1	1	11
18.	1 year	0	0	2.65	3.65	2	2	8
19.	1 year	0	0	4	4	0	0	18
20.	1 year	10	5	6	10	0	0	6
21.	2 years	2	2	3.76	3.8	1	1	10

22.	2 years	5	2	6.8	5.4	0	4	9
23.	3 years	2	4	4	10	0	0	17
24.	3 years	0	2	8	9	1	1	17
25.	3 years	4	8	5.5	5.9	3	3	14
26.	3.5 years	0	0	6	4	2	2	15
27.	3 years	10	9	5.25	4.35	0	0	14
28.	4 years	2	3	8	10	0	0	14
29.	4 years	0	0	5.8	4.8	3	3	20
30.	4 years	2	0	3.9	4	0	0	20
31.	5 years	5	2	8.2	6.2	1	1	11
32.	5 years	5	12	1.45	4.15	0	0	8
33.	6 years	0	0	5.65	5.65	1	1	12
34.	8 years	0	2	3	3	1	1	6
35.	8 years	2	4	8	10	0	3	16
36.	9 years	0	3	5.5	3.8	0	0	9
37.	10 years	10	12	14	12	0	0	4
38.	10 years	0	0	3.8	4.8	2	2	14
39.	12 years	0	0	4	2	2	1	16
40.	12 years	0	0	2.9	3.35	3	5	12
41.	14 years	10	23	17	5.75	0	0	24
42.	14 years	7	7	12.5	13	1	1	20

Table 5(b): Relationship between Duration of Dry Eye Disease with Various Signs of Diagnosis of Dry eye syndrome (DES)

S.No	Duration of DED	Schirmer's test RE (mm)	Schirmer's Test LE (mm)	NIBUT RE (secs)	NIBUT LE (secs)	Ocular Staining RE	Ocular Staining LE	Speed Score	Diagnosis
1.	1 month	6	5	3.2	6.4	0	0	10	Severe dry eyes
2.	1 month	0	0	6.45	6.45	0	0	14	Dry eyes
3.	3 months	2	2	8	9	0	0	12	SJS-Dry eyes
4.	3 months	4	7	1.6	12	0	0	3	Dry Eyes
5.	2 months	0	2	9.3	7.2	0	0	8	Severe Dry eyes
6.	5 months	10	2	9	6	2	2	22	Dry eyes
7.	6 months	10	8	9	8	0	0	11	Dry eyes
8.	6 months	0	0	4	3.3	0	4	23	Primary SS
9.	6 months	4	6	10	12	0	0	8	Dry eyes
10.	8 months	5	2	10	8	1	1	12	Severe Dry eyes
11.	8 months	0	0	12	12	1	1	9	Severe dry eyes
12.	10 months	0	1	1.35	2.5	0	0	6	Severe dry eyes
13.	1 year	5	12	3.2	2.5	2	2	15	Inflammatory Arthritis
14.	1 year	0	0	10	10	0	0	6	Severe Dry eyes
15.	1 year	3	3	5.2	5.2	2	2	6	Secondary SS (RA)
16.	1 year	2	1	10	6	0	0	21	Severe dry eyes

17.	1 year	5	5	3.65	6.5	1	1	11	Primary SS
18.	1 year	0	0	2.65	3.65	2	2	8	Severe Dry Eyes
19.	1 year	0	0	4	4	0	0	18	Secondary SS(RA)
20.	1 year	10	5	6	10	0	0	6	Primary SS
21.	2 years	2	2	3.76	3.8	1	1	10	Severe dry eyes
22.	2 years	5	2	6.8	5.4	0	4	9	Severe Dry eyes
23.	3 years	2	4	4	10	0	0	17	Secondary SS(Mixed connective tissue disorder)
24.	3 years	0	2	8	9	1	1	17	Inflammatory Arthritis
25.	3 years	4	8	5.5	5.9	3	3	14	SLE
26.	3.5 years	0	0	6	4	2	2	15	Primary SS
27.	3 years	10	9	5.25	4.35	0	0	14	Severe dry eyes
28.	4 years	2	3	8	10	0	0	14	Dry Eyes
29.	4 years	0	0	5.8	4.8	3	3	20	Primary SS
30.	4 years	2	0	3.9	4	0	0	20	Severe Dry Eyes
31.	5 years	5	2	8.2	6.2	1	1	11	Secondary SS
32.	5 years	5	12	1.45	4.15	0	0	8	Dry Eyes
33.	6 years	0	0	5.65	5.65	1	1	12	Severe Dry Eyes
34.	8 years	0	2	3	3	1	1	6	Secondary SS (RA)
35.	8 years	2	4	8	10	0	3	16	Severe dry eyes

36.	9 years	0	3	5.5	3.8	0	0	9	Secondary SS
37.	10 years	10	12	14	12	0	0	4	SJS-Dry Eyes
38.	10 years	0	0	3.8	4.8	2	2	14	Primary SS
39.	12 years	0	0	4	2	2	1	16	Primary SS
40.	12 years	0	0	2.9	3.35	3	5	12	Primary SS
41.	14 years	10	23	17	5.75	0	0	24	Dry Eyes
42.	14 years	7	7	12.5	13	1	1	20	Dry Eyes - AIDS

The SPEED score ranged between 12-23 in Primary SS in 8 patients.

Table 6: Correlates severity of Dry eye syndrome (DES) with duration of diagnosis of systemic disease & severity of systemic disease

S.No	Duration of DED	Duration & type of systemic disease	Schirmer test RE (mm)	Schirmer' Test LE (mm)	NIBUT RE (secs)	NIBUT LE (secs)	Ocular Staining RE	Ocular Staining LE	Speed Score	Ocular Diagnosis
1.	1 month	1-month HTN	6	5	3.2	6.4	0	0	10	Severe dry eyes
2.	1 month	1 yr Hypothyroidism	0	0	6.45	6.45	0	0	14	Dry eyes
3.	3 months	1-month SJS	2	2	8	9	0	0	12	SJS-Dry eyes
4.	3 months	3 months Hypothyroidism	4	7	1.6	12	0	0	3	Dry Eyes
5.	2 months	1 yr Back pain	0	2	9.3	7.2	0	0	8	Severe Dry eyes
6.	5 months	3 yrs HTN	10	2	9	6	2	2	22	Dry eyes
7.	6 months	0	10	8	9	8	0	0	11	Dry eyes
8.	6 months	1 yr Dry mouth	0	0	4	3.3	0	4	23	Primary SS
9.	6 months	0	4	6	10	12	0	0	8	Dry eyes
10.	8 months	0	5	2	10	8	1	1	12	Severe Dry eyes
11.	8 months	9 yrs dry mouth	0	0	12	12	1	1	9	Severe dry eyes
12.	10 months	2 yrs Hypothyroidism + DM	0	1	1.35	2.5	0	0	6	Severe dry eyes
13.	1 year	1 yr Arthritis	5	12	3.2	2.5	2	2	15	Inflammatory Arthritis
14.	1 year	2 yrs Hypothyroidism	0	0	10	10	0	0	6	Severe Dry eyes
15.	1 year	2 yrs RA	3	3	5.2	5.2	2	2	6	Secondary SS (RA)
16.	1 year	2 yrs HTN	2	1	10	6	0	0	21	Severe dry eyes
17.	1 year	6 yrs RA	5	5	3.65	6.5	1	1	11	Primary SS
18.	1 year	0	0	0	2.65	3.65	2	2	8	Severe Dry Eyes
19.	1 year	2 yrs RA	0	0	4	4	0	0	18	Secondary SS(RA)
20.	1 year	5 months Hypothyroidism	10	5	6	10	0	0	6	Primary SS

21.	2 years	0	2	2	3.76	3.8	1	1	10	Severe dry eyes
22.	2 years	0	5	2	6.8	5.4	0	4	9	Severe Dry eyes
23.	3 years	2 yrs arthralgia	2	4	4	10	0	0	17	Secondary SS(Mixed connective tissue disorder)
24.	3 years	3 yrs arthritis	0	2	8	9	1	1	17	Inflammatory Arthritis
25.	3 years	3 yrs, SLE	4	8	5.5	5.9	3	3	14	SLE
26.	3.5 years	1 yr Hypothyroidism	0	0	6	4	2	2	15	Primary SS
27.	3 years	1 yr Hypothyroidism	10	9	5.25	4.35	0	0	14	Severe dry eyes
28.	4 years	0	2	3	8	10	0	0	14	Dry Eyes
29.	4 years	3 yrs Hypothyroidism	0	0	5.8	4.8	3	3	20	Primary SS
30.	4 years	0	2	0	3.9	4	0	0	20	Severe Dry Eyes
31.	5 years	6 yrs arthritis	5	2	8.2	6.2	1	1	11	Secondary SS
32.	5 years	2 yrs arthralgia	5	12	1.45	4.15	0	0	8	Dry Eyes
33.	6 years	6 yrs HTN	0	0	5.65	5.65	1	1	12	Severe Dry Eyes
34.	8 years	5 yrs RA	0	2	3	3	1	1	6	Secondary SS (RA)
35.	8 years	1 yr Hypothyroidism	2	4	8	10	0	3	16	Severe dry eyes
36.	9 years	9 yrs Arthritis	0	3	5.5	3.8	0	0	9	Secondary SS
37.	10 years	0	10	12	14	12	0	0	4	SJS-Dry Eyes
38.	10 years	8 yrs HTN + DM	0	0	3.8	4.8	2	2	14	Primary SS
39.	12 years	9 yrs Dry mouth	0	0	4	2	2	1	16	Primary SS
40.	12 years	0	0	0	2.9	3.35	3	5	12	Primary SS
41.	14 years	0	10	23	17	5.75	0	0	24	Dry Eyes
42.	14 years	16 yrs AIDS	7	7	12.5	13	1	1	20	Dry Eyes - AIDS

Table 7: Descriptive analysis

The measures of central tendency, standard deviation and range of various continuous variables are presented in the table below.

	DED duration	Schirmer's test RE mm	Schirmer's test LE mm	"NIBUT RE (secs)"	"NIBUT LE (secs)"	"Ocular Staining RE"	"Ocular Staining LE"	"Speed Score"	"Age (years)"	"Duration of Systemic Disease "
N	42	42	42	42	42	42	42	42	42	42
Missing	0	0	0	0	0	0	0	0	0	0
Mean	3.90	3.14	3.71	6.19	6.31	0.762	1.05	12.6	44.9	1.48
Median	2.00	2.00	2.00	5.00	5.50	0.00	1.00	12.0	42.5	0.00
Standard Deviation	4.00	3.51	4.68	3.69	3.24	0.983	1.32	5.42	13.3	3.43
Minimum	1	0	0	1	2	0	0	3	22	0
Maximum	14	10	23	17	13	3	5	24	64	16

N, mean, SD and range of continuous variables.

A correlation matrix was drawn to identify any association between these continuous variables. The matrix reveals a statistically significant correlation between Duration of DED and Duration of systemic disease. As one of our objectives was to test this hypothesis, we performed a paired t-test with power analysis to evaluate if the results are reliable or not.

Table 8: Paired Samples T-Test

			Statistic	df	p	Mean difference	SE difference		Effect Size
DED duration	"Duration of Systemic Disease "	Student's t	4.42	41.0	< .001	2.43	0.550	Cohen's d	0.682
		Wilcoxon W	647		< .001	2.00	0.550	Rank biserial correlation	0.839

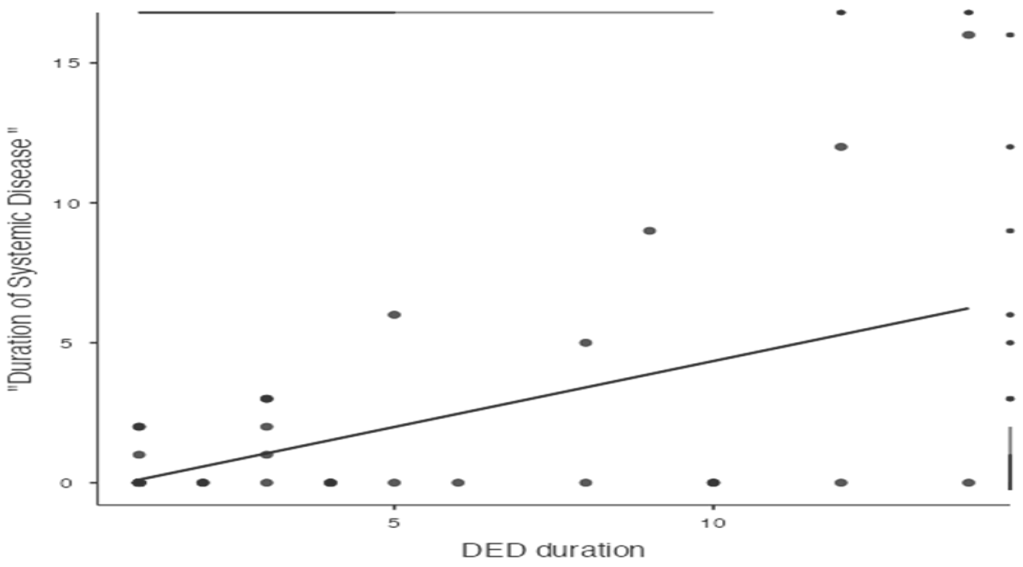
*5 pair(s) of values were tied

Although, there is a statistically significant association between the two variables, the test is underpowered as we would need a sample size of 44 to reliably (with probability greater than 0.9) detect an effect size of $\delta \geq 0.5$, assuming a two-sided criterion for detection that allows for a maximum Type I error rate of $\alpha = 0.05$.

To test if there exists a predictive pattern between duration of DED and Duration of systemic disease, we performed a linear regression. The linear regression model is statistically significant as shown in the table below and in the scatter plot with fitted regression line in the figure below.

Model Fit Measures

			Overall Model Test			
Model	R	R^2	F	df1	df2	p
1	0.549	0.302	17.3	1	40	< .001



Graph 6: Scatter plot of Duration of DED against duration of Systemic disease.

We performed a multinomial logistic regression analysis to reveal any association between duration of DED and other severity of clinical markers of DED with the severity of Sjogren syndrome diagnosis (which has more than two levels). None of the predictors, including the duration of DED and severity of clinical markers of DED were able to predict the diagnosis. The results of multinomial logistic regression are presented in the table below.

Table 9: Model Coefficients - "Diagnosis "

"Diagnosis "	Predictor	Estimate	SE	Z	p
Dry Eye Disease - SJS-Dry Eye Disease	Intercept	5.547	2.756	2.0129	0.044
	DED duration	-0.403	0.271	-1.4891	0.136
	"Duration of Systemic Disease "	-8.001	291.302	-0.0275	0.978
Dry Eye Disease - AIDS - SJS-Dry Eye Disease	Intercept	-18.622	167.513	-0.1112	0.911
	DED duration	-8.081	81.396	-0.0993	0.921
	"Duration of Systemic Disease "	14.122	95.496	0.1479	0.882
Inflammatory arthritis - SJS-Dry Eye Disease	Intercept	3.407	3.024	1.1269	0.260
	DED duration	-1.544	1.066	-1.4487	0.147
	"Duration of Systemic Disease "	6.172	50.618	0.1219	0.903
Primary Sjogren's Syndrome - SJS-Dry Eye Disease	Intercept	3.175	2.802	1.1331	0.257
	DED duration	-0.203	0.270	-0.7492	0.454
	"Duration of Systemic Disease "	5.062	50.609	0.1000	0.920
SLE - SJS-Dry Eye Disease	Intercept	2.288	3.175	0.7208	0.471
	DED duration	-1.364	1.282	-1.0641	0.287
	"Duration of Systemic Disease "	6.169	50.623	0.1219	0.903
Secondary Sjogren's Syndrome - SJS-Dry Eye Disease	Intercept	3.868	2.886	1.3404	0.180
	DED duration	-0.966	0.612	-1.5792	0.114
	"Duration of Systemic Disease "	5.864	50.612	0.1159	0.908

CHAPTER 4

DISCUSSION

The total number of patients with dry eye disease (DED) included in this study according to the sample size was 42 during a study duration of 6 months. The number of females presenting with dry eye disease was 31 (71.80%) compared to males which was 11 (26.19%) in number. This shows that female patients presented with more dry eye disease compared to the males' Female patients with dry eye Disease (DED) commonly presented in the age group ranging from 20 years to 70 years. This data is similar to studies done by Ju-Chuan Yen etal (26) in a population-based study in Taiwan which reported a sex ratio as females, 70.1% and males, 29.9% in the DES group. Studies done by Alpek EK et al [23] have also shown similar results to our study where the majority of the patients (75.9%) were females with a median age of 59 years (range 10 to 91 years). The sex ratio difference showing female dominance is believed to be due to estrogen overproduction or androgen underproduction.[26]

Prevalence of Primary Sjogren's syndrome was 19.04% in our study with predominance of primary SS in 14.28% of females in comparision to males who were affected only in 4.76% case. Study done by Akpek etal (23) in two hundred twenty patients with dry eye syndrome found that total of 57 patients (25.9%) had an underlying rheumatic condition: 25 patients (11.4%) had rheumatoid arthritis and 24 (10.9%) had primary Sjögren syndrome (pSS). In our study the prevalence of Secondary sjogren's syndrome was 19.04%. [23] The prevalence rate of both Primary & Secondary SS was high in our study as the sample size included only patients suffering from moderate to severe dry eyes were included which could have led to selection bias of the DED cases. Also, the sample size in our study was small. Study done by Panida Kosrirukvongs etal [28] and Matsuo's etal [32] have also reported a prevalence of secondary Sjogren's syndrome to be 22.2% with 95% CI 13.2 to 34.9, and (17.1%) [32] respectively, which is very similar to our study (19.04%).

Female preponderance was seen in our study both in Primary SS (14.28%) as well as in secondary SS (16.66%). Study done by Mónica Fernandez Castro et al [27] on factors affecting severe dry eyes in diagnosed patients of primary SS included four

hundred and thirty-seven patients from SJOGRENSER registry & reported that female gender was affected in 95%; median age 58 (50.02–67.98) years.

Thus, we found that the prevalence of Primary SS in our study was 19.04%, secondary SS was 19.04% and patients suffering from only Dry eye Disease which is non- sjogren's was 62%.

In our study 2 cases had Dry eye disease due to Steven Johnson Syndrome (SJS) and 2 cases suffered from AIDS. Dry eyes due to SJS have also been reported by Kohanim S et al [33] & Jain et al [34] in their studies on SJS.

In our study ENA profile was positive in 8 (19.04%) patients, RA factor was positive in 4, ANA in 1and Anti CCP Antibody in 2 patients. R Johri et al [29], Versura P et al [35], Kessel A et al [36] & Giovelli RA et al [37] have also reported a positive pSS in 39% and 10-39 % patients suffering from DES. Only 1 patient out of 27 ENA profile & Rheumatic test negative showed a focus score of >2 on labial salivary gland biopsy. Similar reports have been given by studies done by R Johri et al. [29] They have shown in their study that out of 95 patients, five patients with negative anti-SSA and anti-SSB had a positive biopsy.[29] Hence, these results strengthen the recommendation that salivary gland biopsy may be reserved for those patients who have a positive ocular test and negative anti-SSA and antiSSB.

In our study 24 (57.14%) patients presented with severe dry eyes, 11 (26.19%) with moderate dry eyes and 7 (16.67%) patients presented with mild dry eyes. These are the patients who were confirmed by Schirmer's test and hence were aqueous deficient dry eye patients. Evaporative deficiency was seen in 34 (80.95%) patients with DED. 8 patients (19.04%) did not have any evaporative deficiency. The SPEED score was high in patients with Primary & Secondary Sjogren's Syndrome, but was not found to have any statistical significance as patients with severe to moderate dry eye disease also had high SPEED score values. The SPEED score ranged from 12-23 in 8 patients suffering from Primary SS. R Johri et al [29] have also reported a high-SPEED score in patients with pSS.

In our study, Schirmer's test was positive in 83.33% whereas NIBUT was positive in 80.95% of patients suffering from DED. Study done by Versura P etal [35] showed a poor diagnostic performance of Schirmer test I (sensitivity 0.42; specificity 0.76;

LR+1.75) and BUT (sensitivity 0.92; specificity 0.17; LR+1.11) (area under the curve in ROC analysis <0.58). Our data needs to be further analyzed for statistical association and significance.

Descriptive analysis done in our study revealed a statistically significant correlation between duration of DED and duration of systemic disease. Although, there was a statistically significant association between the two variables, the test is underpowered as we would need a sample size of 44 to reliably (with probability greater than 0.9) detect an effect size of $\delta \geq 0.5$, assuming a two-sided criterion for detection that allows for a maximum Type I error rate of $\alpha=0.05$. Thus, in our study the sample size of 42 could not give a conclusive statistical association.

In our study we performed a multinomial logistic regression analysis to reveal any association between duration of DED and other severity of clinical markers of DED with the severity of Sjogren syndrome diagnosis (which has more than two levels). None of the predictors, including the duration of DED and severity of clinical markers of DED were able to predict the diagnosis.

The diagnostic performance of tear functions tests has been assessed in an earlier publication by Versura P et al [35] involving 177 patients that included 66 patients with pSS. The authors observed that the diagnostic performance of the Sch-I test was poor (sensitivity 42%; specificity 76%). R Johri et al [29] observed that TBUT had a high sensitivity (92%) and very low specificity (17%). R Johri et al [29] reported in their study that in patients with high OSDI scores, dry eye tests in combination with serology will identify the subset of patients with a high probability of Primary Sjogren's syndrome (pSS). Labial biopsy may be considered in patients with negative serology.

But these results need to be further studied and analyzed in our study.

CHAPTER 5

CONCLUSION

A total of 42 patients suffering from Dry Eye Disease were included in this study who presented with the symptoms of dry eyes in a tertiary hospital in Kathmandu, Nepal. The prevalence of Primary Sjogren's syndrome was 19.04%. Similarly, the prevalence of Secondary Sjogren's syndrome was also found to be 19.04 % in our study. Patients with Dry eye disease without systemic involvement were seen in 62% of patients. Sex ratio showed a female preponderance in both Primary (14.28%) & secondary Sjogren's syndrome (16.66%). Labial salivary gland biopsy was positive only in one case, but the results strengthen the recommendation that salivary gland biopsy should be reserved for those patients who have a positive ocular test and negative anti-SSA and antiSSB (ENA profile). The duration of DED and duration of systemic disease showed a statistically significant association in our study. In our study, none of the predictors, including duration of DED and the severity of clinical markers of DED, were able to predict the diagnosis of Sjogren's syndrome. Hence, we can conclude that further larger, multicentric or population-based cohort studies need be undertaken to have a better understanding of Sjogren's syndrome in Nepal.

CHAPTER 6

LIMITATION OF THE STUDY

1. Time period of the study was only 6 months.

2. Small sample size.

3. Hospital, single centric study.

CHAPTER 7

RECOMMENDATION

1.Community based study with larger sample size, population-based studies need to be undertaken for better understanding of prevalence of Sjogren's syndrome.

2.Prospective cohort studies should be done to find out the long-term effects of dry eyes & Sjogren's syndrome in the eye as well as on other systems of the body.

3. Every patient of moderate to severe dry eyes should be evaluated by the Rheumatologist to rule out Sjogren's Syndrome.

CHAPTER 8

REFERENCES

1. Moss S.E., Klein R., Klein B.E. Prevalence of and risk factors for dry eye syndrome. *JAMA Ophthalmol.* 2000;**118**:1264–1268. doi: 10.1001/archopht.118.9.1264.

2. Schein O.D., Munoz B., Tielsch J.M., Bandeen-Roche K., West S. Prevalence of dry eye among the elderly. *Am. J. Ophthalmol.* 1997;124:723–728. doi: 10.1016/S0002-9394(14)71688-5.

3. Uchino M., Nishwaki Y., Michikawa T., Shirakawa K., Kuwahara E., Yamada M., Dogru M., Schaumberg D.A., Kawakita T., Takebayashi T., et al. Prevalence and risk factors of dry eye disease in Japan: Koumi study. *Ophthalmology.* 2011;**118**:2361–2367. doi: 10.1016/j.ophtha.2011.05.029.

4. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007)," The Ocular Surface, vol. 5, no. 2, pp. 75–92, 2007.

5. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007)," The Ocular Surface, vol. 5, no. 2, pp. 163–178, 2007.

6. Z. Liu, "Diagnosis of dry eye," Chinese Journal of Ophthal- mology, vol. 38, no. 5, pp. 318–320, 2001

7. Dafni UG, Tzioufas AG, Staikos P, et al. Prevalence of Sjogren's syndrome in a closed rural community. Ann Rheum Dis. 1997; 56:521-525)

8. Thomas E, Hay EM, Hajeer A, Silman AJ. Sjögren's syndrome: a community-based study of prevalence and impact. Br J Rheumatol 1998; 37:1069–76.

9. Birlik M, Akar S, Gurler O, et al. Prevalence of primary Sjogren's syndrome in Turkey: a population-based epidemiological study. Int J Clin Pract 2009;63:954–61.

10. Anderson L.A., Gadalla S., Morton L.M., Landgren O., Pfeiffer R., Warren J.L., Berndt S.I., Ricker W., Parsons R., Engels E.A. Population-based study of autoimmune conditions and the risk of specific lymphoid malignancies. *Int. J. Cancer.* 2009;**125**:398–405. doi: 10.1002/ijc.24287.

11. Sjögren H. Zur Kenntnis der Keratoconjunctivitis Sicca (Keratitis filiformis bei Hypofunktion der Tranendrusen) [dissertation]. Acta Ophthalmol Suppl 1933;2:1–151.

12. Fox RI. Sjögren's syndrome. Lancet 2005;366:321–31.

13. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. Arch Intern Med 2004;164:1275–84.

14. Kruszka P, O'Brian RJ. Diagnosis and management of Sjögren syndrome. Am Fam Physician 2009;79:465–70.

15. Manthorpe R, Asmussen K, Oxholm P. Primary Sjögren's syndrome: diagnostic criteria, clinical features, and disease activity. J Rheumatol Suppl 1997;50:8–11.

16. Sánchez-Guerrero J, Pérez-Dosal MR, Cárdenas- Velázquez F, et al. Prevalence of Sjögren's syndrome in ambulatory patients according to the American-European Consensus Group criteria. Rheumatology (Oxford) 2005;44:235–40.

17. Segal B, Bowman SJ, Fox PC, et al. Primary Sjogren's syndrome: health experiences and predictors of health quality among patients in the United States. Health Qual Life Outcomes [serial online] 2009;7:46. Available at: http://www.hqlo.com/content/7/1/46. Accessed July 14, 2014.

18. Garcia-Carrasco M, Ramos-Casals M, Rosas J, et al. Primary Sjogren syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. Medicine (Baltimore) 2002;81: 270–80.

19. Voulgarelis M, Skopouli FN. Clinical, immunologic, and molecular factors predicting lymphoma development in Sjögren's syndrome. Clin Rev Allergy Immunol 2007;32: 265–74.

20. Tzioufas AG, Voulgarelis M. Update on Sjogren's syndrome autoimmune epithelitis: from classification to increased neoplasias. Best Pract Res Clin Rheumatol 2007;21: 989–1010.

21. Smedby KE, Hjalgrim H, Askling J, et al. Autoimmune and chronic inflammatory disorders and risk of non- Hodgkin lymphoma by subtype. J Natl Cancer Inst 2006;98:51–60.

22. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta- analysis. Arch Intern Med 2005;165:2337–44.

23. Akpek EK, Klimava A, Thorne JE, et al. Evaluation of patients with dry eye for presence of underlying Sjögren syndrome. Cornea 2009;28:493–7

24. Ahmadi-Simab K, Lamprecht P, Nölle B, et al. Successful treatment of refractory anterior scleritis in primary Sjogren's syndrome with rituximab [letter]. Ann Rheum Dis 2005;64: 1087–8.

25. Basnet, P, Basnet A, Karki P. Demographic Profile and Risk Factors for Dry Eye. Nepalese Medical Journal. vol.1, No. 1, 2018, page: 9-11.

26. Ju-Chuan Yen , Chia-An Hsu , Yu-Chuan (Jack) Li, Min-Huei Hsu .The prevalence of dry eye syndrome and the likelihood to develop Sjögren's syndrome in Taiwan: A population-based study. Int. J. Environ. Res. Public Health 2015, 12, 7647-7655; doi:10.3390/ijerph120707647.

27. Mónica Fernandez Castro, Carlos Sánchez-Piedra, Jose Luis Andreu, Víctor Martínez Taboada, Alejandro Olivé, Jose Rosas, on behalf of SJOGRENSER Group, part of the Spanish Society of Rheumatology Systemic Autoimmune Diseases Study Group (EASSER). Factors associated with severe dry eye in primary Sjögren's syndrome diagnosed patients. Rheumatology International (2018) 38:1075–1082 https://doi.org/10.1007/s00296-018-4013-5.

28. Panida Kosrirukvongs, Panotsom Ngowyutagon , Pawana Pusuwan , Ajchara Koolvisoot, Surasak Nilganuwong. Prevalence of Dry Eye Syndrome and Sjogren's Syndrome in Patients with Rheumatoid Arthritis .J Med Assoc Thai 2012; 95 (Suppl. 4): S61-S69 .

29. Roma Johria , Jayanthi Petera, Vishali Peravalib , Pulukool Sandhyac , Debashish Dandac , Sarada Davida. Diagnostic performance of dry eye tests, serology and labial salivary gland biopsy in primary Sjogren's syndrome in an Indian setting.Clinical Epidemiology and Global Health.2020; 8(1): 301-304.https://doi.org/10.1016/j.cegh.2019.03.007

30. Bjordal, Oddbjørn, Norheim, Katrine Brække,Rødahl, Eyvind, Jonsson, Roland Omdal, Roald Omdal . Primary Sjögren's syndrome and the eye. Survey of Ophthalmology 2020 ;65(2):119-132 .

31. David Cui, Priya Mathews, W.L. Gore ,Sezen Karakus, Esen AkpekLong-Term Ocular Outcomes of Sjogren's Syndrome vs Non-Sjogren's Dry Eye Disease**.** Investigative Ophthalmology & Visual Science June 2020, Vol.61, 118.

32. Matsuo T, Kono R, Matsuo N, Ezawa K, Natsumeda M, Soda K, et al. Incidence of ocular complications in rheumatoid arthritis and the relation of keratoconjunctivitis sicca with its systemic activity. Scand J Rheumatol 1997; 26: 113-6.

33. Kohanim S, Palioura S, Saeed HN. Acute and Chronic Ophthalmic Involvement in Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis - A Comprehensive Review and Guide to Therapy. II. Ophthalmic Disease. Ocul Surf. 2016;14(2):168–88.

34. Jain R, Sharma N, BasuS, IyerG, UetaM, SotozonoC. Stevens Johnson syndrome:The role of an ophthalmologist.SurvOphthalmol.2016;61(4):369–99. doi:10.1016/j.survophthal.2016.01.004.

35. Versura P, Frigato M, Cellini M, Mule R, Malavolta N, Campos EC. Diagnostic per- formance of tear function tests in Sjogren's syndrome patients. Eye. 2007;21:229–237.

36. Kessel A, Toubi E, Rozenbaum M, Zisman D, Sabo E, Rosner I. Sjogren's syndrome in the community: can serology replace salivary gland biopsy? Rheumatol Int. 2006;26:337–339.

37. Giovelli RA, Santos MC, Serrano EV, Valim V. Clinical characteristics and biopsy accuracy in suspected cases of Sjogren's syndrome referred to labial salivary gland biopsy. BMC Muscoskelet Disord. 2015;16:30

APPENDICES

FINANCE

Budget breakdown		
Expenditure Category	**Proportion**	**Total**
Human Resource (investigators) **Cornea specialist (2)** **Rheumatologist (1)** **Pathologist (1)**	**10,000 each x 4**	**Rs.40,000**
Research work		
Stationary/photocopies	**Rs. 5,000**	**Rs. 5,000**
Remuneration to research assistant	**Rs.5,000/month x 4months x 2 person**	**Rs.40,000**
Statistician Consultation Charge	**Rs 10,000**	**Rs. 10,000**
Investigations		
1. ENA panel	**3000×20=60,000**	**60,000**
2. Schirmer's test	**200×76=15,200**	**15,200**
3. NIBUT	**300×76=22,800**	**22,800**
4. Histopathology	**10,000**	**10,000**
Unforeseen cost	**Rs.10,000**	**Rs.10,000**
Total		**Rs. 213,000**

FORMS:

1. Proforma
2. Consent in Nepali
3. Consent in English

PROFORMA

"Prevalence of Sjogren's syndrome in patients with Dry Eye disease in a tertiary hospital in Nepal"

1. PATIENT DETAILS **Date of registration:**

Study ID: **Hospital Registration number:**

Name **Age/sex:**

Address: **Biopsy no:**

Telephone no:

- **Duration of symptoms:**
- **Time lag of seeking medical help since onset of symptoms:**

2. Any History of

contact lens wear history- Yes / No,

If Yes specify: type of lens_____

duration of use _____hrs/day; usage since _____years/months

Medical history (i.e., presence of systemic diseases other than SS)

Ocular health history-

Ocular Surgery –None / cataract / pterygium / LASIK / lid surgery / others_____

Antiglaucoma drugs	Topical NSAIDS	Others
Beta blockers (timolol, betaxolol) **Alpha agonist (brimonidine)** **CA inhibitors (dorzolamide)** **PG analogues (latanoprost/ bimatoprost)**	**Ketorolac** **Diclofenac**	**BAK** **Olapatadine** **Naphazoline** **Acyclovir** **Tropicamide** **Cyclopentolate**

Systemic medications:

a. **Drugs with known association with dry eyes: Please circle**

Antihypertensives	Antihistamine and decongestants	Antidepressants	Antipsychotic	Others
Beta blockers **Thiazides** **Furosemide**	**diphenhydramine** **chlorpheniramine** **loratadine**	**Sertraline** **Paroxetine** **Amitriptyline** **doxepin**	**thioridazine, chlorpromazine**	**PPI** **Estrogen/HRT** **NSAIDs** **Cyclophosphamide**

b. Other systemic medications:

Current DED treatments: including lid care, goggles, punctal plugs

Artificial tears _____ frequency

3. **DED symptoms: Standard Patient Evaluation of Eye Dryness II (SPEED II) [6]:**

Speed II Questionnaire for Dry Eye Disease/Ocular Surface Disease

1. Report the FREQUENCY of the dry eye symptoms. How many times are you experiencing the symptoms?

SYMPTOMS	Never 0	Sometimes 1	Often 2	Constant 3
Dryness, Grittiness or Scratchiness				
Soreness or Irritation				
Burning or Watering				
Eye Fatigue				

2. Report the SEVERITY of the dry eye symptoms

Never = No problems

Tolerable= not perfect but not uncomfortable

Uncomfortable = irritating but does not interfere with my day

Bothersome = irritating and interferes with my day

Intolerable= unable to perform my daily tasks

SYMPTOMS	Never 0	Tolerable 1	Uncomfortable 2	Bothersome 3	Intolerable 4
Dryness, Grittiness or Scratchiness					
Soreness or Irritation					
Burning or Watering					
Eye Fatigue					

Please mark and X if you have experienced these symptoms"

Today _____ Within the past 72 hours _____ Within past 3 months _____

Do you use eye drops and/or ointments? YES NO

Have you used them today? YES NO

Name of drops:_____ How long are they effective?_____

Do the drops last 4 hours? YES NO Do any gels last 12 hours? YES NO

Did you use Moisturizer, lotions or creams around eyes today? YES NO

Did you use makeup today? YES NO

Have you touched/rubbed your eye(s) today? YES NO If yes, when? _____ , How?_____

Have you ever been told you have BLEPHARITIS? YES NO STYE? YES NO

Do you have fluctuating vision problems (that's gets better with BLINKING)

Never, Sometimes, Frequently, A lot/always

Total Speed Score

(Frequency + Severity) =

4. Clinical features at presentation

- SS related symptoms
- Dry mouth
- Dry eyes
- Both dry mouth and eyes
- Dental cavities and mouth infections
- Difficulty swallowing or chewing
- Parotid enlargement
    - § Unilateral Bilateral

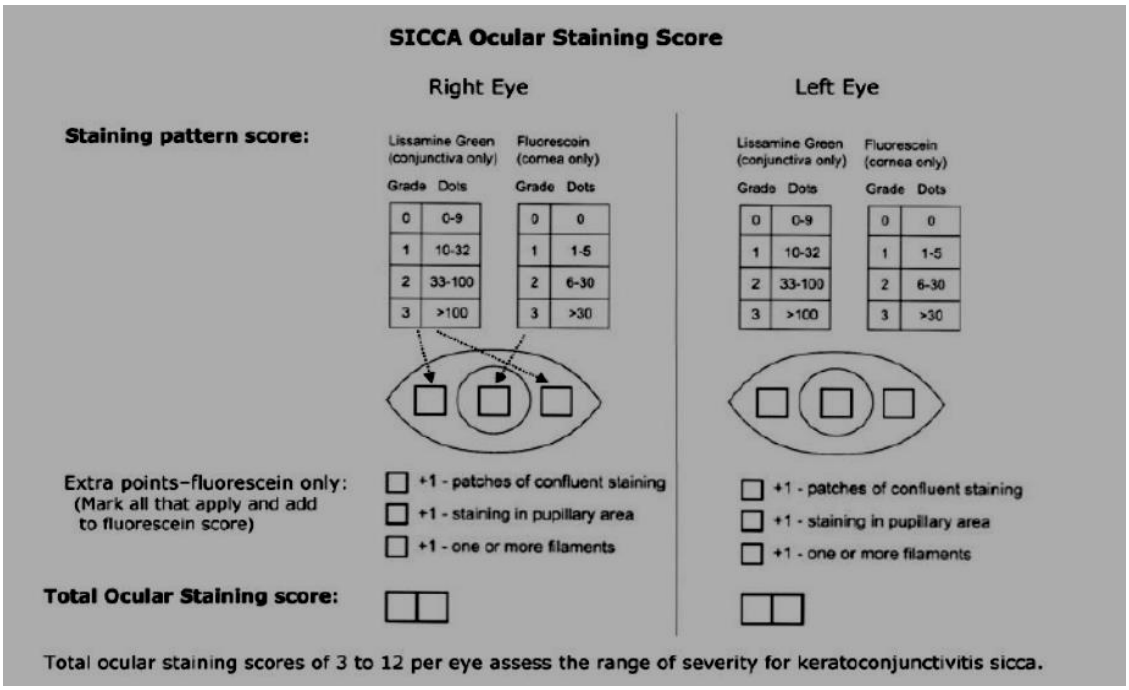
5. Ocular findings:

	RE	LE
Visual acuity		
Lid margin (MGD, blepharitis, Demodex and telangiectasia)		
Conjunctival congestion/ Papillae/ concretions		
Corneal – SPK/ abrasions/ ulcer		
Others		

The presence of superior limbic keratoconjunctivitis (SLK)

6. Investigative procedures

Investigations	RE	LE
NIBUT		
Unanesthetized Schirmer's test		
Tear meniscus height		
SICCA ocular staining score		



1. Blood investigations

Positive serum:

anti-SSA (Ro)

anti-SSB (La)

anti-SSA and B

rheumatoid factor

ANA ELISA:

ANA ≥ 1:40

ANA ≥ 1:320

ANA pattern

ENA Profile:

2. Unstimulated salivary outflow: Unstimulated whole salivary flow < 0.1 ml/ min

3. Salivary gland scintigraphy

4. labial salivary gland Labial salivary gland biopsy diagnosis:

- Non-specific/sclerosing chronic sialadenitis
- Granulomatous inflammation / within normal limits
- MALT (mucosa-associated lymphoid tissue) lymphoma
- Inadequate specimen 28 (2)
- Focal lymphocytic sialadenitis (focus scores (FS)

  FS > 1

  FS = 1

  FS < 1

5. Diagnosis:

Rheumatologic history / Examination:

1. Any History of

· Head and neck radiation treatment

· Hepatitis C infection

· Acquired Immunodeficiency Syndrome

· Sarcoidosis

· Amyloidosis

· Graft versus host disease

· IgG4-related disease

· Currently using daily eye drops for glaucoma

· Had corneal surgery or cosmetic eyelid surgery in the last 5 years

2. Extra glandular manifestations of SS

Cutaneous

- Skin dryness, hair loss (telo-effluvium), and scarring alopecia
- Maculopapular rashes
- Leukocytoclastic vasculitis
- Urticaria and urticarial vasculitis
- Raynaud's phenomena, digital ulceration, and acrocyanosis
- Infectious (including Herpes zoster)
- Embolic and thrombotic lesions

Joints and muscles

- Arthralgia/arthritis including overlap syndromes with rheumatoid arthritis, SLE, Jaccoud's arthritis, osteoarthritis, erosive osteoarthritis, and seronegative spondyloarthropathies
- Myalgia's and myositis including overlap with SLE, polymyositis, inclusion body myositis, metabolic myopathies, and neuropathic myopathies; overlaps with myositis
- Fibromyalgia

Endocrine

- Thyroiditis, diabetes
- Adrenal insufficiency including autoimmune and catastrophic cardiolipin syndrome
- Androgen/estrogen replacement
- Autonomic neuropathy

Pulmonary

- Interstitial pneumonitis
- Pleurisy and pleural effusions including lymphomatous
- Pulmonary hypertension and occult pulmonary emboli
- Lymphoproliferative manifestations [BALT (bronchial MALT lymphoma)
- Laryngotracheal reflux and motility disorders
- Infections including tuberculosis that may mimic Sjögren's syndrome
- Infections including atypical mycobacterial pneumonitis
- Aspiration pneumonia in the SS patient with dysphagia

Cardiovascular

- Pericarditis and cardiomyopathy
- Anti-coagulant antibody
- Accelerated atherosclerosis including "precocious" carotid intimal thickening
- Autonomic neuropathy

Gastrointestinal

- Gastro esophageal reflux and duodenal ulcer
- Motility disorders including laryngotracheal reflux will be covered in 10.1007/978-1-60327-957-4_16
- Celiac sprue, atrophic gastritis, and malabsorptive disorders
- Mesenteric vasculitis and ischemic colitis
- Irritable bowel syndrome and inflammatory bowel syndromes

Hepatic and pancreatic

• Autoimmune hepatitis and biliary cirrhosis

• Pancreatitis

Sclerosing cholangitis

• Occult presentation of hepatitis C virus

Renal–urological

• Interstitial nephritis

• Hypertensive crisis include “microvasculitis” with anti-cardiolipin antibody

• Hypertensive crisis due to pre-renal cause

• Glomerulonephritis due to mixed cryoglobulinemia and amyloid

Hematological

• Leukopenia, agranulocytosis

• Thrombocytopenia and thrombocytosis

• Hemolytic anemia and pernicious anemia

• Cryoglobulinemia

• Lymphoma

Obstetrical/gynecological

• Neonatal heart block

• Issues of estrogen/androgen replacement

• Potential problems of pregnancy

• Vaginal dryness/dyspareunia

Associated clinical manifestations and complications

Systemic

- Fatigue:
- Malaise:
- Fever:
- Anorexia:
- Weight loss:
- Others

Musculoskeletal

- Arthralgia's/myalgia's:
- Arthritis
- Hand deformities:
- Myopathy
- Others
- X ray and findings:

Cutaneous

- Photosensitivity:
- Malar Rash:
- Oral ulcer:
- Alopecia:
- Vasculitis rash:
- Histopathology details if any:

Pulmonary

- Interstitial fibrosis:
- Pneumonitis:
- ARDS:

- Pulmonary hemorrhage:
- Pleuritis
- Effusion
- Imaging Findings:

Cardiovascular

- Myocarditis :
- Pericarditis :
- Effusion
- ECHO Findings

CNS

- Neuropathy
- NCS/EMG details:
- Cognitive disorder:
- Seizure:
- Stroke/TIA:y/myositis:
- Imaging Findings

Hematological

- Anemia (Hb<12 mg/dl)
- Leucopenia (TLC<4000)
- Thrombocytopenia (Platelett<1 laks)

Renal

- Frothuria
- Proteinuria
- Distal Renal Tubular Acidosis

3. Positive serum for

a. Hepatitis C

b. Hepatitis B

c. HIV

d. Serum IgG

· Salivary Scintigraphy

4. Clinical Details (At Baseline)

- Blood Pressure
- Pallor:
- Icterus:
- Clubbing:
- Cyanosis:
- Edema:
- Lymphnodes:

5. Lab Parameters (At Baseline):

- Hemoglobin:
- TLC:
- DLC:
- Platelets:
- Reticulocyte count:
- Peripheral smear:
- Coomb's test:
- ESR:
- Urea:
- Creatinine:
- Na+:
- K+:
- Urine active sediments:
    - RBC:
    - WBC:
    - Granular cast:
    - Protein:
- 24 hour urinary protein:
- Renal Biopsy:
- ds DNA:
- C3/C4:
- APLA :
    - LAC
    - acl IgG
    - acl IgM
    - Anti B_2 GP1

Imaging findings:

X-ray

MRI

CT Scan

Biopsy Findings:

Diagnosis:

-

CONSENT FORM IN NEPALI

अनुसन्धान अध्ययनमा भाग लिन नेपालीमा सहमति फारम

बि.पी.कोईराला लायन्स नेत्र अधय्यन केन्द्र, चिकित्सा शास्त्र अध्ययन संस्थान ,

महाराजगंज चिकित्सा क्याम्पस, त्रि.वि. विश्वविध.लय,

महाराजगंज, काठमाडौं , नेपाल

अध्ययनको शीर्षक: "Prevalence of Sjogren's syndrome in patients with Dry Eye disease in a tertiary hospital in Nepal"

प्रमुख अन्वेषक	प्रा.डा.मीनु चौधरी
सहअन्वेषक	डा.सञ्जिता सिटौला
सहअन्वेषक	डा.साकेत झा
सहअन्वेषक	डा.अनिलदेव पन्त

यो अनुसन्धान अध्ययन हो, तपाईको अध्ययन डाक्टर(हरू), डा. मीनु चौधरी, डा. सञ्जिता सिटौला, डा. साकेत झा र डा. अनिल देव पन्त नेत्ररोग विभाग, बी.पी.कोइराला लायन्स नेत्र अधय्यन केन्द्र, चिकित्सा संस्थान , महाराजगञ्ज मेडिकल क्याम्पस, त्रिभुवन विश्वविद्यालय र त्रिभुवन विश्वविद्यालय शिक्षण अस्पताल, काठमाडौं नेपालको वातविज्ञान तथा प्याथोलोजी विभागले तपाईलाई अनुसन्धानको व्याख्या गर्नेछ।

अध्ययन सारांश

यो अध्ययन व्यापकता जान्न को लागी एक क्लिनिकल अध्ययन हो । यो अध्ययन हाम्रो अस्पतालमा आउने सुख्खा आँखा रोगका बिरामीहरूमा Sjogren's syndrome को व्यापकता जान्नको लागि एक क्लिनिकल अध्ययन हो। यस अध्ययनमा भाग लिन छनौट गर्ने व्यक्तिहरू मात्र समावेश हुन्छन्। कृपया सहभागी हुने बारे आफ्नो निर्णय लिनको लागि आफ्नो समय लिनुहोस्। तपाईंले आफ्नो निर्णय आफ्नो परिवार र साथीहरूसँग र आफ्नो स्वास्थ्य हेरचाह टोलीसँग छलफल गर्न सक्नुहुन्छ। यदि तपाईंसँग कुनै प्रश्नहरू छन् भने, तपाईंले आफ्नो अध्ययन चिकित्सक वा अनुसन्धान सहायकहरूलाई सोध्न सक्नुहुन्छ।

परिचय: बि.पी.कोइराला लायन्स नेत्र अधय्यन केन्द्र विभागका डा मीनु चौधरी, डा सञ्जिता सिटौला, र त्रिभुवन विश्वविद्यालय शिक्षण अस्पताल, बाथ रोग विज्ञान र प्याथोलोजी विभाग को डा साकेत झा र डा अनिल देव पन्तले गरिरहेको अनुसन्धान अध्ययनमा सहभागी हुन आग्रह गरिरहेका छौं। सहमतिको पहिलो भागले तपाईंलाई व्याख्या गरेको अध्ययनको विवरण दिन्छ।

• उद्देश्य:

यो अध्ययन सञ्चालन गर्नुको उद्देश्य सुख्खा आँखा रोग भएका बिरामीहरूमा Sjogren's syndrome को व्यापकता अध्ययन गर्नु हो। हामी सुख्खा आँखा, सुख्खा मुख र शरीरको अन्य भागमा सुख्खापन, जोर्नी दुख्ने वा तपाइँसँग भएको कुनै अन्य प्रतिरक्षा सम्बन्धी रोगको सम्बन्धमा तपाइँको कुनै प्रणालीगत समस्याहरूको इतिहास लिनेछौं। यो रोगमा तपाईको प्रतिरक्षा प्रणालीले तपाईको शरीरका स्वस्थ कोशिकाहरुलाई गल्तीले आक्रमण गर्न सक्छ र यसरी तपाईको जोर्नी, फोक्सो लगायत शरीरका अन्य अंगहरु पनि संलग्न हुन सक्छन् । हामी फिल्टर पेपर प्रयोग गरेर आँसु परीक्षण गर्नेछौं जुन तपाईंको आँखामा 5 मिनेटको लागि राखिनेछ, आँसुको लागि कम्प्युटर परीक्षण (NIBUT परीक्षण) जसले हामीलाई तपाईंको आँखामा आँसुको मात्रा र प्रकार थाहा पाउन मद्दत गर्नेछ। हामी तपाईंको आँखामा सुक्खापनको प्रभाव अध्ययन गर्न स्ट्रिप (लिसामाइन ग्रीन) ले तपाईंको आँखालाई दाग गर्नेछौं। यो सबै डाटा यस अध्ययनको लागि तयार गरिएको प्रोफार्मामा प्रविष्ट गरिनेछ र तपाईंको नामको गोपनीयता कायम गरिनेछ। यी आँखा परीक्षण गरिसकेपछि र आँखा सुख्खा भएको पाइयो भने ,तपाईंको रगत परीक्षण (ANA immunoblotting/ ENA panel) गर्नेछौं। रगत परीक्षण नेगेटिभ आयो भने मात्र हामीले तपाईंको मुखमा र्याल स्राव गर्ने तपाईंको लार ग्रन्थीबाट बायोप्सी गर्नेछौं, र तपाईंको लारको प्रवाह पनि जाँच गर्नेछौं। यो तन्तुको नमूना Sjogren's syndrome को निदान पुष्टि गर्न हिस्टोपाथोलोजिकल परीक्षणको लागि पठाइनेछ। तसर्थ, तपाईलाई यस अध्ययनमा भाग लिन भनिएको छ किनभने तपाईका आँखा सुख्खा छन् र त्यसैले तपाईलाई Sjogren's syndrome हुन सक्छ जसले कोर्नियल अन्धोपन जस्ता गम्भीर जटिलता निम्त्याउन सक्छ।

• ६ महिनासम्म सञ्चालन हुने यस अध्ययनमा करिब ४२ जना सहभागीहरूले स्वयम्सेवा गर्नेछन्। एक अध्ययन सहभागीको रूपमा तपाईंले आँखा सुख्खा भएको निदान गरेपछि मात्र एक पटक अस्पताल जानुपर्नेछ।

• एक अध्ययन सहभागीको रूपमा हामी तपाईंलाई अनुसन्धानको नैतिकताको पालना गरून् र हामीलाई आवश्यक आँखा र प्रणालीगत परीक्षण र अनुसन्धान गर्न अनुमति दिन चाहन्छौं।

- तपाईं यस अनुसन्धानमा (स्वैच्छिक रूपमा) र अध्ययनमा सहभागी हुन सक्नुहुन्छ। तपाईको व्यक्तिगत जानकारी गोप्य राखिनेछ।
- तपाईंले कुनै पनि समय अध्ययन सहभागी हुनबाट फिर्ता लिन वा रोक्न सक्नुहुन्छ र यसका लागि तपाईंले अध्ययन गर्ने डाक्टरलाई जानकारी दिनुपर्छ, यदि तपाईंले त्यसो गर्ने योजना बनाउनुभएको छ भने। यदि तपाइँ अध्ययन छोड्न चाहनुहुन्छ भने त्यहाँ कुनै जरिवाना हुनेछैन र यो तपाइँको व्यक्तिगत निर्णय हो। यदि तपाइँ अध्ययनबाट फिर्ता लिन चाहनुहुन्छ भने त्यहाँ कुनै कानुनी प्रभाव हुनेछैन। अध्ययन छाड्दा तपाईलाई तपाईको रोगको व्यवस्थापनसँग सम्बन्धित कुनै असर पर्दैन।
- अध्ययन डाक्टरले तपाईंलाई कुनै पनि समयमा यो अध्ययनमा भाग लिनबाट रोक्न सक्छ, यदि उसले/उनलाई यो सबैभन्दा राम्रो हित हो भन्ने लाग्छ वा तपाईंले अध्ययन नियमहरू पालना गर्नुभएन भने, वा अध्ययन रोकियो भने।
- यदि तपाईंले अध्ययनमा भाग लिनुभयो भने, हामी आँखा र प्रणालीगत परीक्षण र अनुसन्धान गर्नेछौं । यसरी तपाईलाई Sjogren's syndrome छ कि छैन भनी पुष्टि गरेर पनि लाभ प्राप्त गर्नुहुनेछ । Sjogren's syndrome सुरुमा सुख्खा आँखाको रूपमा मात्र उपचार गर्दै छुटेको हुन सक्छ । यदि तपाइँ यस अध्ययनमा सहभागी हुनुहुन्न भने पनि, तपाइँलाई उपचार गरिनेछ।
- आँखा वा मुखमा केही असुविधा बाहेक (बायोप्सी आवश्यक भएमा र गर्नु पर्ने भएमा मात्र) यस अध्ययनमा भाग लिएर र अनुसन्धान गरेर तपाईलाई कुनै जोखिम वा सम्भावित खतराहरू हुनेछैनन्।
- वास्तवमा अध्ययनमा सहभागी (स्वैच्छिक रूपमा) हुन गरेर तपाईंले Sjogren's syndrome को निदानको पुष्टि गरेर लाभ उठाउनुहुनेछ ,जुन पहिले सामान्य सुख्खा आँखा रोगको रूपमा छुटेको हुन सक्छ। निदानको यो पुष्टिले तपाईंलाई उचित उपचार प्राप्त गर्न मद्दत गर्नेछ।
- तपाईंको रगत र तन्तु (रगत परीक्षण नेगेटिभ छ भने मा) नमूनाहरू भण्डारण गरिने छैन। तपाईको परीक्षणले निदान पुष्टि नभएसम्म तपाईको नमूनाहरू मात्र राखिनेछ। ANA Immunoblottting/ENA प्यानल समावेश भएको रगत परीक्षणको लागि प्रयोगशालाले तपाईको रगतको 5ml संकलन गर्नेछ। तपाईको मुखबाट टिस्यु नमूना (लाल ग्रंथि) - लगभग ०.४ सेमी x ०.४ सेन्टिमिटर लिइनेछ, यदि तपाईको रगत परीक्षण नेगेटिभ आयो भने मात्र

हिस्टोपाथोलोजिकल जाँचको लागि पठाइन्छ। रगत परीक्षणको रिपोर्ट २ दिनपछि र बायोप्सीको नतिजा १ हप्ता पछि आउनेछ।

- अनुसन्धान पूरा गरेपछि - सुख्खा आँखा रोगका बिरामीहरूमा Sjogren's syndrome को व्यापकता अध्ययन गर्न मात्र तपाईंको डाटा प्रयोग गरिनेछ। तिम्रो रगत र तन्तु निदानको पुष्टिको लागि मात्र प्रयोग गरिनेछ र अध्ययन पूरा भएपछि थप प्रयोग गरिने छैन। निदान पुष्टि भएपछि तिनीहरूलाई खारेज गरिनेछ। तपाईंको अध्ययन नमूनाहरू माध्यमिक अनुसन्धान वा अध्ययन उद्देश्यको लागि भण्डारण गरिने छैन।
- यसरी, Sjogren's syndrome बहुप्रणाली अटोइम्यून रोग हो जसले आँखा र शरीरका अन्य अंगहरूलाई असर गर्छ। यसले आँखा सुख्खा हुन सक्छ जसले दृष्टि, कोर्नियल अन्धोपन र जीवनको गुणस्तर लाई असर गर्न सक्छ। यसले फोक्सो, मिर्गौला, कलेजो जस्ता अन्य अंगहरूलाई पनि असर गर्न सक्छ। तपाईंले यस अध्ययनमा भाग लिएर थप लाभ उठाउनुहुनेछ जसले तपाईंको निदान पुष्टि गर्नेछ ।

  तसर्थ, यस अध्ययनले हामीलाई सुख्खा आँखा रोगीहरूमा Sjogren's syndrome को व्यापकता बुझ्न मद्दत गर्नेछ।
- तपाईंले यस अध्ययनको बारेमा कुनै पनि प्रश्न, चिन्ता र गुनासोहरूको बारेमा आफ्नो अध्ययन चिकित्सकसँग कुरा गर्न सक्नुहुन्छ। आफ्नो अध्ययन चिकित्सक (हरू) डा. मीनु चौधरीलाई ९७७-९८४१२५०८०२ वा drmeenu67@gmail.com मा सम्पर्क गर्नुहोस्।

सुसूचित मन्जुरीनामा

यसरी, यो ज्ञान पछि, मेरो अध्ययन डाक्टरहरूबाट मैले बुझेको छु र सुख्खा आँखा रोगका बिरामीहरूमा यो अध्ययनमा सहभागी हुन स्वयम्सेवा गर्न चाहन्छु , जसले मलाई यो रोगबाट पीडित भएमा Sjogren's syndrome को निदान पुष्टि गर्नेछ।

मैले बुझेको छु कि Sjogren's Syndrome एक अटोइम्यून रोग हो जसले आँखा र मुख सुख्खा हुन्छ। यो रोगमा हाम्रो इम्युन सिस्टमले हाम्रो शरीरका स्वस्थ कोशिकाहरूमा गल्तीले आक्रमण गर्छ र यसरी शरीरका अन्य अंगहरू पनि संलग्न हुन्छन् जसमा जोर्नीको समस्या पनि हुन सक्छ। आँखा र मुख सुख्खा हुनु सबैभन्दा सामान्य लक्षण हो। Sjögren's Syndrome ले हाम्रो शरीरमा आर्द्रता उत्पादन गर्ने ग्रन्थीहरूलाई असर गर्छ, जस्तै ग्रन्थी जसले लार र आँसु सिर्जना गर्छ। यसले सामान्यतया पीडादायी सुख्खा, तपाईंको आँखामा जलन, र सुक्खा मुख निम्त्याउँछ जसले बोल्न र चपाउन गाह्रो बनाउन सक्छ, र दाँत सम्बन्धी समस्याहरू निम्त्याउन सक्छ। सुख्खा आँखाको रोगको कारण तिनीहरूको कोर्नियामा धेरै समस्याहरू हुन सक्छ जसले अन्धोपन निम्त्याउँछ। तसर्थ, यस अध्ययनमा हामी सुक्खा आँखाका बिरामीहरूमा एसको व्यापकतालाई बिरामीहरूमा यसको गम्भीरता बारे जान्नको लागि अध्ययन गर्नेछौं। तसर्थ, " Sjogren's syndrome को व्यापकता बुझ्नको लागि गरिएको सुक्खा आँखा रोगीहरू" सम्बन्धी यस अध्ययनमा म सहभागी हुन चाहन्छु।

म ..... उमेर ..... वर्षको पुरुष/महिलाले 8f= मीनु चौधरी, 8f=सन्जीता सितौला (बि.पी.कोईराला लायन्स नेत्र अधय्यन केन्द्र, चिकित्सा शास्त्र अध्ययन संस्थान, महाराजगंज चिकित्सा क्याम्पस, त्रि.वि. विश्वविधलय, महाराजगंज, काठमाडौं, नेपाल) / 8f=साकेत झा, 8f=अनिल देवपन्त (त्रि.विशिक्षण अस्पताल, महाराजगंज, काठमाडौं, नेपाल) ले गर्न लाग्नु भएको यस अनुसन्धान सम्बन्धि संलग्न जानकारी सुनेर र प्रश्नोत्तर समेत गरेर यो अध्ययन-अनुसन्धान सम्बन्धमा जानकारी प्राप्त भयो।

- यो अनुसन्धान कार्यमा मेरो सहभागिता मेरो व्यक्तिगत इच्छामा भर पर्ने र मैले चाहेको खण्डमा कुनै पनि बेला यो अनुसन्धान प्रक्रियाबाट बाहिरिन पाउने भन्ने कुरा मैले बुझेको छु। यसको

लागि मैले कुनै कारण दिनु नपर्ने र त्यसबाट मैले पाउने सेवा र मेरो कानुनी अधिकारमा असर नपर्ने समेत मलाई बुझाईएकोछ।

- यस अनुसन्धानको प्रतिवेदन वा सम्बन्धित प्रकाशित कृतिहरुमा मेरो कुनै व्यक्तिगत परिचय खुल्ने जानकारी प्रकाशित हुने छैन भन्ने कुरा मैले बुझेकोछु।
- यी सबै कुराहरु जानी-बुझी, म यस अध्ययन-अनुसन्धानमा सहभागी हुन स्वेच्छाले राजी भई यो सुसूचित मन्जुरीनामामा सहिछाप गरेको छु।

सहभागी/सहभागीको अभिभावकको सही : .....

दाँया	बाँया

नाम-थर : .....

मिति : ----------

सहमति प्राप्त गर्ने व्यक्ति: ----------

मिति:----------

CONSENT FORM IN ENGLISH

Consent form in English to participate in a research study

B.P. Koirala Lions Center for Ophthalmic Studies, Institute of Medicine, Maharajgunj Medical Campus, Tribhuvan University, Kathmandu, Nepal

Study Title: "Prevalence of Sjogren's syndrome in patients with Dry Eye disease in a tertiary hospital in Nepal "

Principal Investigator	**Prof. Dr. Meenu Chaudhary**
Co-Investigators	**Dr. Sanjeeta Sitaula**
Co-Investigators	**Dr. Saket Jha**
Co-Investigators	**Dr. Anil Dev Panta**

This is a research study, your study doctor(s), Dr.Meenu Chaudhary, Dr. Sanjeeta Sitaula, Dr. Saket Jha and Dr. Anil Dev Panta from the department of Ophthalmology, B.P.Koirala Lions Center for Ophthalmic Studies, Institute of Medicine, Maharajgunj Medical campus, Tribhuvan University and Department of Rheumatology and Pathology of Tribhuvan University Teaching hospital, Kathmandu Nepal will explain the research to you.

Study Summary:

This study is a clinical study about knowing the prevalence of Sjogren's syndrome in dry eye disease patients attending our hospital. This study includes only people who choose to take part. Please take your time to make your decision about participating.

You may discuss your decision with your family, friends and your health care team. If you have any questions, you may ask your study doctor or the research assistants.

Introduction: We are asking you to take part in a research study being done by Dr. Meenu Chaudhary, Dr. Sanjeeta Sitaula, Dr. Saket Jha and Dr. Anil Dev Panta from the department of Ophthalmology, B.P.Koirala Lions Center for Ophthalmic Studies, Institute of Medicine, Maharajgunj Medical campus, Tribhuvan University and Department of Rheumatology and Pathology of Tribhuvan University Teaching hospital, Kathmandu Nepal. The first part of the consent gives you the details of the study explained by the study team and you can ask questions if you have, which will be answered.

- Purpose & Methods used for the study: The purpose of conducting this study is to study the prevalence of Sjogren's syndrome in patients with dry eye disease. We will be taking history of dry eyes, dry mouth and any systemic problems you may have. In this disease your immune system is dysregulated and may attack healthy cells in your body. This may result in involvement of other organs of the body like your joints, lungs and kidneys. We will do tear test using a filter paper which will be put in your eyes for 5 minutes , a computer test for tear (NIBUT test) which will help us to know the amount and type of tear you have in your eyes. We will also stain your eyes with a strip (Lissamine green) to study the effect of dryness in your eyes. All this data will be entered in a proforma prepared for this study and the confidentiality will be maintained. After doing these eye tests and if you are found to have dry eyes, you will be sent for evaluation by rheumatologist to look for any systemic involvement and immune related problems. Patients will also need to undergo blood work up. This blood test will include ANA Immunoblotting (ENA panel) for which 5.0 ml of your blood will be drawn in a serum vial and will be sent to the laboratory for investigation. If your blood test comes negative/ inconclusive, you may be required to undergo minor salivary gland biopsy from the inner surface of your lips, and also check the flow of your saliva. This tissue sample will be sent for histopathological examination to confirm the diagnosis of Sjogren's syndrome. Thus, you are being asked to

participate in this study because you have dry eyes and hence you can have Sjogren's syndrome which can cause serious complication like corneal blindness & affect your joints, lungs, kidneys, pancreas & liver.

- About 42 participants will volunteer for this study which will be conducted for 6 months. As a study participant you will have to attend the hospital only once after you have been diagnosed to have dry eyes.
- As a study participant we want you to follow the ethics of research and allow us to do the necessary eye & systemic examination and the investigations required for the study according to the protocol.
- You can be a study participant if you want (voluntarily) in this research. Your personal information will be kept confidential & information of the study tests will only be used for research. If information from this study is published or presented at scientific meetings your name & other personal information will not be used & confidentiality will be maintained.
- You can withdraw or stop from being a study participant anytime and for this you have to inform the study doctor, if you are planning to do so. There will be no penalty if you want to leave the study and this is your personal decision. There will be no legal implications if you want to withdraw from the study. By leaving the study you will also have no effect related to management of your disease.
- The study doctor may stop you from taking part in this study at any time, if he/she believes it is in their best interest, if you do not follow the study rules, or if the study is stopped.
- If you participate in the study, we will be doing eye & systemic examination and investigations for which you do not have to pay. In this way you will also get benefitted by confirming whether you have Sjogren's syndrome which could have been missed or treated initially only as dry eyes. Even if you do not participate in this study, you will still be treated & you can decide later to participate in this study.
- You will have no risks or potential hazards by participating and doing investigations for this study except for some discomfort in eyes or mouth (only if biopsy is necessary and has to be done).

- In fact by volunteering to be a study participant you will benefit by confirmation of the diagnosis of Sjogren's syndrome which may have been previously missed as simple dry eye disease. This confirmation of diagnosis will help you get proper treatment & prevent systemic complications & corneal blindness. This confirmation of your diagnosis will also help you to decrease the economic burden caused due to use of unnecessary medications in the past.
- Your blood and tissue (done only if the blood test is negative) samples will not be stored. Your samples will be only kept till your test confirms the diagnosis. For a blood test which includes an ENA panel the laboratory will collect 5.0 ml of your blood. Tissue sample from your mouth (labial salivary gland) – about 0.4cm x 0.4 cm will be taken, only if your blood test is negative and then sent for Histopathological examination. The report of the blood test will be available after 2days and biopsy results after 1 week. Your tests will be done free of cost and will be borne by the study. You do not have to pay for the tests.
- Post research – only your data will be used to study the prevalence of Sjogren's syndrome in dry eye disease patients. Your blood & tissue samples will be used only for confirmation of diagnosis and will not be used further after the study has been completed. They will be discarded after the diagnosis has been confirmed. Your study samples will not be stored for secondary research or study purposes.
- Thus, Sjogren's syndrome is a multisystem autoimmune disease which affects the eyes and other organs of the body. This can lead to dry eyes which can affect vision, quality of life and corneal blindness. It can also affect other organs like lungs, kidneys, liver & pancreas leading to life threatening complications. You will benefit more by participating in this study which will confirm your diagnosis & better management. Thus, this study will help us in understanding the prevalence of Sjogren's syndrome in dry eye disease patients.
- You can talk to your study doctor about any questions, concerns and complaints you have about this study. Contact your study doctor(s) Dr. Meenu Chaudhary at 977-9841250802 or drmeenu67@gmail.com.

Consent:

Thus, after this knowledge & explanation from my study doctors I have understood & thus would like to volunteer to participate in this study on dry eye disease patients which will confirm my diagnosis of Sjogren's syndrome if I am suffering from that disease.

I have understood that Sjogren's syndrome is an autoimmune disease which causes dry eyes and dry mouth. In this disease our immune system mistakenly attacks healthy cells in our body and thus other organs of the body also get involved which may include joint problems also. Dry eyes and mouth are the most common symptoms. Sjögren's syndrome affects the glands in our body that produce moisture, such as the glands that create saliva and tears. This typically causes a painful dry, burning sensation in your eyes, and dry mouth that can make it difficult to talk and chew, and can cause dental issues. Along with symptoms of extensive dryness, complications may get more serious as time goes on and can include vision problems due to involvement of the cornea. Therefore, I would like to participate in this study on "Dry eye disease patients which is being undertaken to understand the prevalence of Sjogren's syndrome in Nepal".

I ---------- years ----------male / female have been explained by Dr. Meenu Chaudhary, Dr. Sanjeeta Sitaula (B.P.Koirala Lions Center for Ophthalmic Studies, Institute of Medicine , Maharajgunj Medical campus , Tribhuvan University) & Dr. Saket Jha & Dr. Anil Dev Pant (Tribhuvan University Teaching hospital) about this research. I have also come to know about this research by reading & information given to me about Sjogren's syndrome & dry eye disease by the study doctor(s). I have understood that there is no harm to me by participating in this study and in fact I will benefit by participating in the study, which will help in confirming my diagnosis and better management of my disease.

I have also understood that I can quit the study if I want & this will have no legal implication on me.

My identity will also be kept confidential in the data files and during the process of publication Thus, I would like to volunteer to participate in this study and give my consent of participation.

Participant/ Relative / Next of Kin of the participant:

Name of the Participant: ----------

Signature: ---------- Date: ----------

Right	Left

Person obtaining the consent: ----------

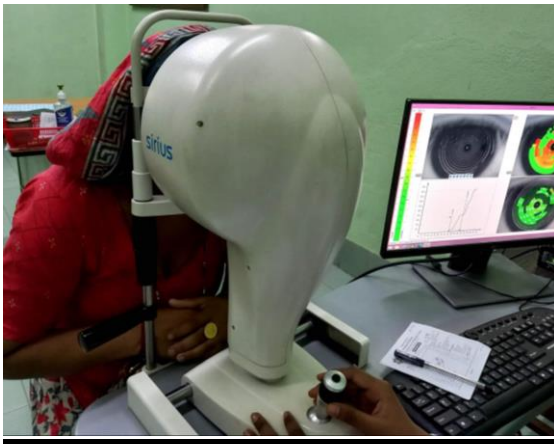
Date: ----------

PHOTOGRAPHS

Photo 1: Unanesthetized Schirmer's test being done in the patients of DED

Photo 2: Schirmer's Test Strip (Whatman No 41 filter paper)

Photo 3: Non Invasive Tear Break Up Time (NIBUT) being done in DED patient



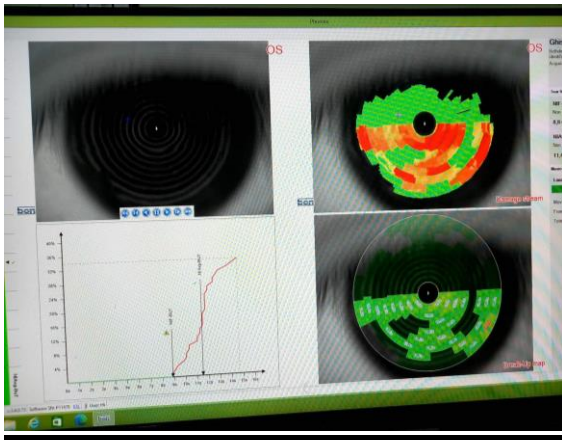


Photo 4: Lissamine green dye staining of conjunctiva in dry eye patient

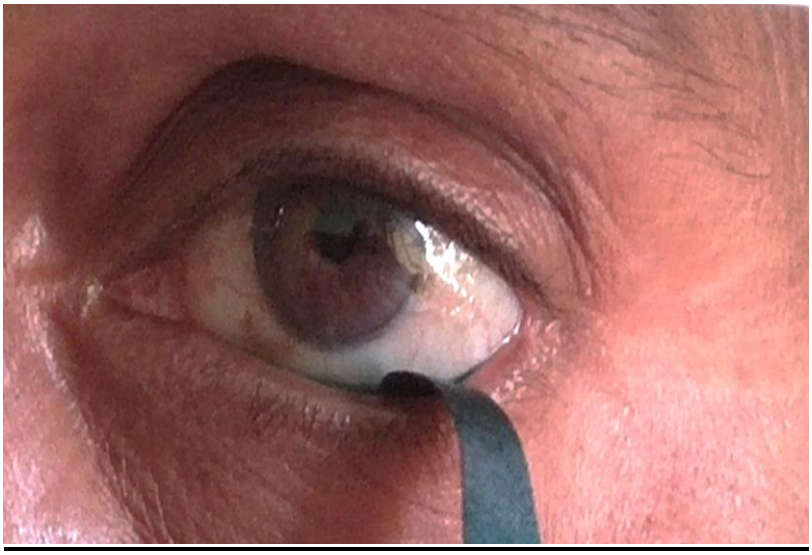


Photo 5: Fluorescein staining of Cornea in dry eye patient