RELATIONSHIP BETWEEN SYMPTOMS AND DIAGNOSTIC TEST OF DRY EYE: A CLUSTER ANALYSIS APPROACH

CRISTINA-IOANA ROTH[1], ADRIANA STĂNILĂ[2], DAN STĂNILĂ[3], GEORGE CONSTANTIN MANIU[4]

[1, 2, 3, 4] *"Lucian Blaga" University of Sibiu*

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Abstract: *The current study aim is to analyse the relationship between symptoms (Schirmer test, tear film breakup time tests, ocular surface staining) and diagnostic test of dry eye (ocular surface disease index questionnaire - OSDI) using a cluster analysis approach. The research was performed among the patients (32 with dry eye disease and 15 control subjects) admitted to the Ophthalmology Clinic of Clinical County Emergency Hospital of Sibiu, Romania. For all performed tests, the differences between dry-eye group and control group were statistically significant (OSDI 47.03±19.86 vs. 8.53±3.72, BUT 3.86±1.43 vs. 17.83±1.87, SCHL 4.47±3.25 vs. 20.37±2.79, OXF 0.88±0.87 vs. 0±0.86). The cluster analysis procedure, in the context of our patient's data, estimates the following hierarchical discriminative importance of the tests results: BUT (100%), Schirmer I Test (67%), OSDI (29%), OXF (12%). Tear film instability is a common link for all types of dry eyes and its evaluation can be crucial when there is no ocular staining and the tear volume is normal or abundant.*

INTRODUCTION

The prevalence of dry eye disease ranges from 7.8% to 29% and this values depends on the inclusion criteria in the study cohort.(1) Dry eye remains a under-recognized disease, despite its high prevalence, because there are various test and non-invasive instruments, but there is no specific test for the diagnostic.(2) The most used diagnostic tests in clinical practice are Schirmer test, tear film breakup time (TBUT) tests and ocular surface staining by using fluorescein, rose bengal and lissamine green, as well as the use of dry eye questionnaires (OSDI questionnaire).(2)

All diagnostic tests have their contribution in the diagnosis of dry eye disease, but there is no single golden test for dry eye diagnosis, therefore a combination of minimal-invasive, objective and clinical applicable tests are preferable in medical practice.(3)

The battery of tests are different from practitioner to practitioner and depends on the availability of the equipment.(4,5)

The ocular surface disease index (OSDI questionnaire) is a useful tool and one of the most frequently used instruments to assess dry eye symptoms.(6) OSDI has 12 questions and evaluates the frequency of symptoms over the preceding week. The questionnaire requires approximately 5 minutes for the patient to be filled out and the points range is from 0 to 100, a higher score representing a higher disability.(6) Depending on the outcome of the OSDI score, the patients can be divided in normal: 0-12 points, mild dry eye: 13-22 points, moderate dry eye: 23-32 points, severe dry eye: 33-100 points.(6,7)

Tear film break-up time is a clinical test to determinate the tear film stability.(8) The method is assed using sodium fluorescein dye and the tear film is examined under the slit lamp until the disruption of the tear film develop (tiny dry spots).(8)

TBUT test is measured in seconds: greater than 10 seconds is normal, between 5 and 10 is marginal and less than 5 seconds is considered low.(8)

Schirmer described (one hundred and eleven years ago) three methods to measure the tear secretion: Schirmer I: without anesthesia and the length of wetting is measured after five minutes, Schirmer II: with anesthesia and stimulation of the nasal mucosa, the length of wetting is measured after five minutes and Schirmer III with topical anesthesia and the patient look at the sun, the wetting is measured after five minutes.(9) Schirmer I is the most used in clinical practice.(9) Schirmer I values are variable and differ from study to study: normal, greater than 15 mm and abnormal, less than 6 mm(10) or greater than 13 mm, normal (after five minutes) and greater than 10 mm, normal (after two minutes).(11) Several diagnostic values have been suggested, from ≤5 mm/5 min to ≤ 10 mm/5 min.(12)

Oxford Schema is a validated procedure to evaluate under a cobalt blue light filter the cornea and the conjunctiva. Staining is classified in a series of panels from 0 to 5.(8)

AIM

This study aims at analysing the relationship between symptoms and diagnostic test of dry eye (Schirmer test, tear film breakup time tests, ocular surface staining and ocular surface disease index questionnaire) using a cluster analysis approach.

MATERIALS AND METHODS

The research was performed prospectively among the patients admitted to the Ophthalmology Clinic of the Clinical County Emergency Emergency Hospital of Sibiu, Romania. The study was conducted in accordance with the tenets of the Declaration of Helsinki, and verbal informed consent was obtained from all participants.

All 47 patients had a complete ophthalmic evaluation to exclude condition that can mimic dry eye. Dry eye diagnosis was based on the methodologies of TFOS DEWS Report 2017.(12)

The severity of dry eye-associated symptoms was evaluated using Ocular Surface Disease Index (OSDI).(13) The

[1]Corresponding author: Roth Cristina-Ioana, Str. Regele Ferdinand, Nr 7, Bl B4, Şelimbăr, Sibiu, România, E-mail: cristinatrihenea@gmail.com, Phone: +40746 963451
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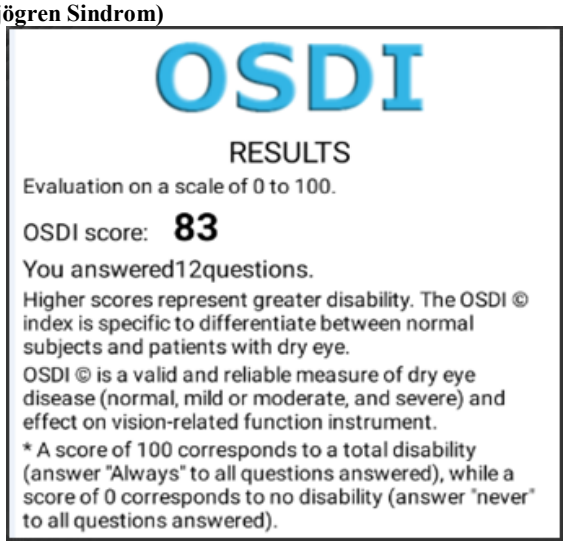
OSDI score was obtained using OSDI application, available in Magazin Play for Android Smartphone. This application is very useful and helped us to save time in evaluating the symptomatology of patients with dry eye syndrome. The examiner addressed the questions and checked the answers in the application. At the end of the questionnaire the application generated a score for each patient. In the classic version the OSDI score is calculated for each subject based on the formula: the sum of scores of all items answered multiplied by twenty-five divided by the total number of items answered.(13)

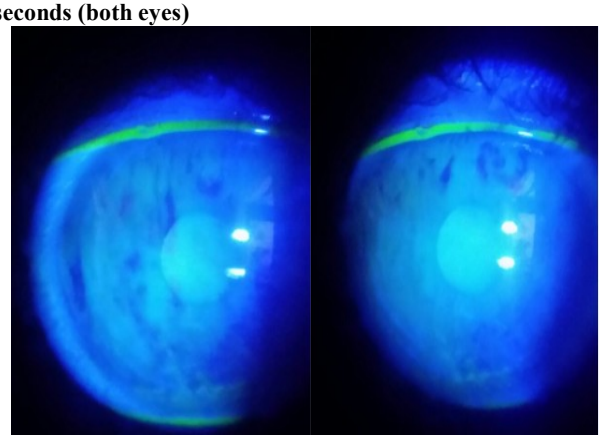
Figure no. 1. OSDI Questionnaire application

Figure no. 2. OSDI Questionnaire application results of a 59 years old patient diagnosed with aqueous deficient dry eye (Sjögren Sindrom)



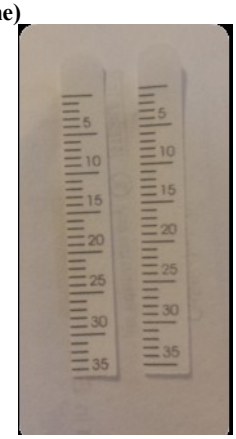
Tear breakup time (BUT) was measured using a fluorescein-impregnated strip wetted with a single drop of normal saline. The patients blink for few times then the time - from normal blinking to the first appearance of a dry eye spot in the tear film - was measured. The mean value of the tree measurements was used.(3)

Figure no. 3. Tear break-up time of the same patient with aqueous deficient dry eye (Sjögren syndrome) after 2 seconds (both eyes)



The Schirmer I Test (SCHL) was performed with the help of filter paper strips (Visual Med, Tear Touch Schirmer Strips) placed at the temporal third of the lower eyelid and the patients with closed eyes. 5 minutes later, the wetted length was measured.(3)

Figure no. 4. Tear Touch Schirmer Strips with 0 lacrimal secretion of the same patient with aqueous deficient dry eye (Sjögren Syndrome)



Ocular surface staining was graded using the Oxford staining schema (0-5). Corneal fluorescein staining was performed using fluorescein sodium strips followed by slit-lamp examination with cobalt-blue light.

Patients were selected on the basis of the following criteria at the initial visit: subjects between 20-70 years old, symptoms of dry eye (e.g. tearing, foreign body sensation, grittiness, dryness, redness, transient blurring of vision, burning sensation) (14) with OSDI more than 13 points, Schirmer I Test values less/equal than 10 mm, Tear breakup time (TBUT) less/equal than 5 seconds, visual acuity AO=1 (corrected or uncorrected), spherical equivalent less/equal +/-4 D, no other ocular disease (except dry eye). All patients were new cases without a history of dry eye medication.

Control group inclusion criteria: age above 20 years and below 70 years, OSDI score less or equal than 10 points, Schirmer I test values greater or equal than 15 seconds, tear film breakup time >/= 15 seconds, negative corneal fluorescein staining, best visual acuity measured with ETDRS Chart (the spherical equivalent +/-4Dsf) 1 and without any ocular disease. Patients with contact lens, herpetic disease, penetrating

keratoplasty and active infection were excluded.

For the data analysis we considered:

- OSDI scores as: (1) absolute values, (2) categories according to (2, 7, 15, 16): normal (0-12), mild(13-22), moderate(23-32), severe (33-100)
- TBUT scores as: (1) absolute values, (2) categories according to (8): normal (>10 seconds), marginal(5-10 seconds), low(<5 seconds)
- Schirmer I Test (SCHL) scores as: (1) absolute values, (2) categories according to (10): normal (>=15 mm), moderate (6-15mm), abnormal (<6mm)
- OXF scores as: (1) absolute values, (2) categories: normal (0), abnormal (>0)

Descriptive statistics for continuous and categorical variables was performed and analysed using parametric and non-parametric tests, as appropriate. Comparisons between study and control groups were performed using Mann-Whitney test. A p-value of 0.05 was considered significant.(17,18)

Cluster analysis, an unsupervised learning technique, was used in order to:

(i) identify different groups of patients based on results of the performed test for dry-eye disease,

(ii) describe the profile of the identified groups in terms of tests scores,

(iii) identify the hierarchical structure of tests in terms of their importance for between-groups discrimination,

(iv) analyse/identify correlations between the tests.

RESULTS

The patients enrolled in this research were 32 with dry eye disease (study group) and 15 control subjects (control group). The mean ages were 52 (M=52.21, SD=11.95, range: 20-69) for the study group and 46 (M=45.80, SD=11.99, range: 28-64) for the control, majority female patients (84% study, 67% control).

For all performed tests the differences between dry-eye group and control group were statistically significant (table no.1). For the dry eye patients group, the correlation between signs (Schirmer test I, tear break up time, Oxford staining) and symptoms (OSDI) was described in a previous research (19), using Spearmen's correlation coefficient:

- a significant negative correlation was observed between OSDI and TBUT (r = -0.501, p = 0.003) - dry eye symptomatology is associated with tear film instability;
- a significant negative correlation was observed between OSDI scores and Schirmer test I (r = -0.271, p = 0.134) - greater disability is associated with low amount of tears;
- a marginal significant positive correlation was observed between OSDI and Oxford staining scale (r = 0.317, p = 0.077) - increased OSDI score are associated with increased Oxford grades.

Table no. 1. Differences between dry-eye group and control group in case of OSDI, BUT, Schirmer I Test, OXF scores

Test	Study M±SD (Min-Max; Median)	Control M±SD (Min-Max;Median)	p
OSDI	47.03±19.86 (12-95; 49,00)	8.53±3.72 (3-16; 9.00)	0.000
BUT (s)	3.86±1.43 (1-7; 3.75)	17.83±1.87 (16-22; 16.50)	0.000
SCHL (mm)	4.47±3.25 (0-11; 4.25)	20.37±2.79 (16-26; 20.00)	0.000
OXF	0.88±0.87 (0-3; 1)	0±0.86 (0-0; 0)	0.000

The cluster analysis procedure (TwoSteps cluster method) automatically identifies two segments/clusters - 2 groups of patients, corresponding to the dry-eye and control group, with an average measure of cohesion and separation (silhouette average – cluster quality measure) of 70%.

The hierarchical importance of the tests results – used as attributes upon which clusters construction is based – is the following: BUT (100%), Schirmer I Test (67%), OSDI (29%), OXF (12%).

Figure no. 5. Cluster analysis groups profile, in case of OSDI, BUT, Schirmer I Test, OXF, scores considered as pure values

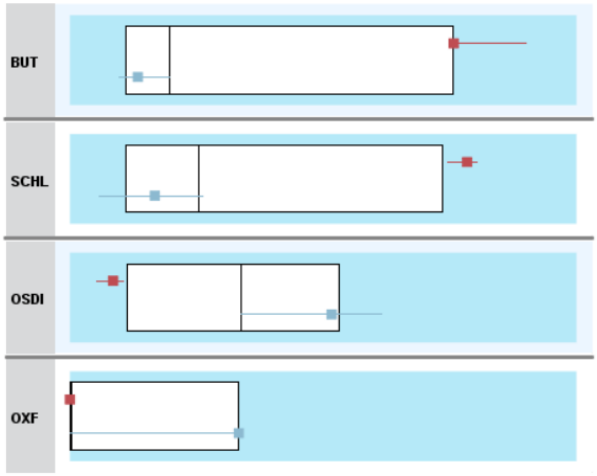
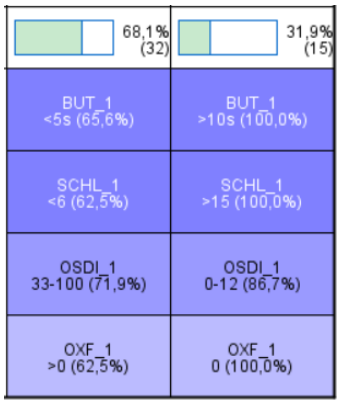


Figure no. 5 is representing the two identified cluster profile (blue – dry eye group – first cluster, red – control group – second cluster). The dry eye group has high values for BUT and Schirmer I test and small values for OSDI and OXF in comparation with the control group. A negative correlation between OSDI and BUT, respectively between OSDI and Schirmer I Test is suggested.

Considering OSDI, BUT, Schirmer I Test, OXF scores as categories (new variables OSDI_1, BUT_1, SCHL_1, OXF_1, as specified in the methods section of this research), we obtained the following hierarchical importance of the tests results: BUT (100%), Schirmer I Test (100%), OSDI (74%), OXF (42%), with a silhouette average of 60% for the cluster analysis procedure (figure no. 6).

Figure no. 6. Cluster analysis groups profile, in case of OSDI, BUT, Schirmer I Test, OXF, scores considered as categories

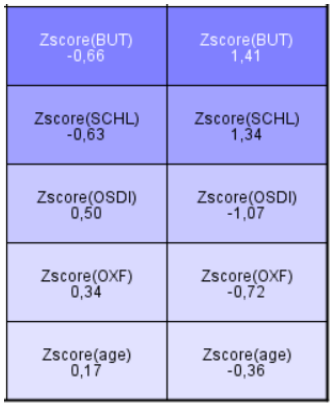


Changes in importance hierarchy did not occur (figure no. 7, silhouette average 70%) if:

- normalized version of (continuous) variables were used

- age variable was added, but her importance was only 3%

Figure no. 7. Cluster analysis groups profile, in case of OSDI, BUT, Schirmer I Test, OXF, scores considered as categories



DISCUSSIONS

Tear break up time (TBUT) is a clinical test for dry eye that has the potential to capture the combined contributions of aqueous deficiencies, lipid and mucin to tear instability.(20) Koh S et. al. (21) and Lee KW et al (22) compared the mean fluorescein tear break-up time (FTBUT) of the normal patients (7.1 seconds) with the mean fluorescein tear break-up time in patients with aqueous deficient dry eye (2.1 seconds) (21) and non-invasive tear break-up time was found to be 3.3 seconds for patients with aqueous deficient dry eye compared to 6.6 seconds for patients with Meibomian gland dysfunction.(22) The evaporation rate is an important factor in cases of evaporative dry eye and even a normal evaporation can lead to important dry eye symptoms in patients with aqueous deficient dry eye (due to the very thin tear layers).(1)

In our study group we observed results comparable to those of the studies mentioned above. Also, there are two patients diagnosed with aqueous deficient dry eye (Sjögren Sindrom) and the values of TBUT were 1 second, respectively 2 seconds.

Short tear break-up time was found to indicate tear hyperosmolarity, which is also a core mechanism for dry eye symptoms.(20) Kaido et al suggest that visual function is also affected in dry eye patients and is associated with short tear break-up time, due to unstable tear film.(23) All these results highlight the important contribution of tear break-up time assessment in dry eye evaluation and diagnosis.

According to the literature results, short tear break-up time and subjective symptoms are the two key components for the diagnosis of dry eye and the results of vital staining and Schirmer test are not mandatory for dry eye diagnosis.(24)

This study has potential limitations: one of these limitations can be the small number of cases in both groups (study group and control group). We aim in the future at: (i) the analysis of these tests on a larger study population and possibly the use of other tests, (ii) the analysis of the results of these tests taking into account the associated comorbidities.

CONCLUSIONS

The stability of tear film is a core pathological mechanism in dry eye and is compromised when the aqueous components are reduced in volume.(25) Fluorescein tear break-up time could be the most used clinical test of tear function (20) and can give important information about tear film stability but its evaluation and clinical application vary widely.(20) Schirmer test values and methods can also vary from study to study, but this test is less invasive and could give valuable information in clinical practice.

Two-Step cluster analysis procedure has the advantage that it is able to automatically identify the optimal number of clusters/groups using categorical or continuous data.(26) In the context of our patient's data, the cluster analysis considered the results of BUT test and Schirmer I Test as the most important in group separation (dry eye disease group vs. control group). However, this result must be interpreted with caution since the model quality is moderate (60-70%).

Understanding the tear break-up time function in dry eye diagnosis and evaluation is especially important because tear film instability is a common link for all types of dry eyes and its evaluation can be crucial when there is no ocular staining and the tear volume is normal or abundant.

REFERENCES

1. Prokopich CL, Bitton E, Barbara Caffery B, Michaud L, Cunningham DN et al Screening. Diagnosis and management of dry eye disease: practical guidelines for Canadian optometrists. Canadian Journal of Optometry Revue Canadienne d'Optométrie. 2014;76 Suppl 1, ISSN 0045-5075.
2. Özcura F, Aydin S, Helvaci MR. Ocular surface disease iIndex for the diagnosis of dry eye syndrome. Ocular Immunology and Inflammation. 2007;15(5):389-393.
3. Craig JP, Nichols KK., Akpek EK, Caffery B, Dua HS, Joo CK, Liu Z, Nelson JD, Nichols JJ, Tsubota K, Stapleton F, (2017) TFOS DEWS II definition and classification report , Ocul Surf. 2017;15:(3) 276–283.
4. Mzumara T, Afonne J.Assessing the relationship between non-invasive tear break-up time and maximum blink interval values among young adults at Mzuzu University, Clinical Optometry. 2018:10 87–91.
5. Henderson R, Madden L. Dry-eye management. Optom Pract. 2013;14:137–146.
6. Amparo F, Schaumberg DA, Reza D. Comparison of Two questionnaires for dry eye symptom assessment the ocular surface disease index and the symptom assessment in dry eye, American Academy of Ophthalmology, July 2015;122(7):1498-1503.
7. Miller KL, Walt JG, Mink DR, Satram-Hoang S, Wilson SE, Perry HD, Asbell PA, Pflugfelder SC, Minimal clinically important difference for the ocular surface disease index, Arch Ophthalmol. 2010 Jan;128(1):94-101.
8. Dibajnia P, Mohammadinia M, Moghadasin M, Aghazade MA, Tear film break-up time in bipolar disorder, Iran J Psychiatry. 2012 Fall; 7(4):191–193.
9. Savini G, Prabhawasat P, Kojima T, Grueterich M, Espana E, Goto E. The challenge of dry eye diagnosis. Clin Ophthalmol. 2008 March;2(1):31-55.
10. Leão Gabbay Serruya L, Cruz Nogueira D, Yudi Hida R. Schirmer test performed with open and closed eyes: variations in normal individuals, Arq. Bras. Oftalmol. 2009;72(1).
11. Karampatakis V, Karamitsos A, Skriapa A, Pastiadis G. Comparison between normal values of 2- and 5-minute Schirmer test without anesthesia. Cornea. 2010 May;29(5):497-501.
12. Wolffsohn JS, Arita R, Chalmers R et al TFOS DEWS II - Diagnostic Methodology Report, The Ocular Surface (2017) 544-579.
13. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the ocular surface

disease. Arch Ophthalmol. 2000;118(5):615-621.
14. Miller KL, Walt JG, Mink DR, et al. Minimal clinically important difference for the ocular surface disease index. Arch Ophthalmol. 2010;128:94.
15. Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, Gupta PK, Karpecki P, Lazreg S, Pult H, Sullivan BD, Tomlinson A, Tong L, Villani E, Yoon KC, Jones L, Craig JP. TFOS DEWS II diagnostic methodology report. Ocul Surf. 2017;15:539-574.
16. Köksoy Vayısoğlu S, Öncü E, Dursun Ö, Dinç E. Investigation of dry eye symptoms in lecturers by ocular surface disease index. Turk J Ophthalmol. 2019;49(3):142–148.
17. Maniu I. Tehnici de analiză a datelor: statistica (Data analysis techniques: Statistics), Ed. Univ. Lucian Blaga Sibiu; 2014.
18. Mocan I. SPSS Introducere în analiza datelor (SPSS Introduction in data analysis), Ed. Univ. Lucian Blaga Sibiu; 2005.
19. Roth CI, Stanila A, Maniu I, Muntean AC. Dry eye: the relation between symptoms and diagnostic tests. SEA Practical Application of Science. 2019;VII(20).
20. Charles W. Mcmonnies. Tear instability importance, mechanisms, validity and reliability of assessment, J Optom. 2018 Oct-Dec;11(4):203–210.
21. Koh S, Ikeda C, Fujimoto H, et al. Regional differences in tear film stability and Meibomian glands in patients with aqueous-deficient dry eye. Eye Cont Lens. 2016;42:250-255.
22. Lee KW, Kim JY, Chin HS, et al. Assessment of tear meniscus by strip meniscometry and eratography in patients with dry eye disease according to the presence of Meibomian gland dysfunction. Cornea. 2017;36:189-195.
23. Kaido M, Ishida R, Dogru M, Tsubota K. Visual function changes after punctal occlusion with the treatment of short BUT type of dry eye. Cornea. 2012;31:1009-1013.
24. Tsubota K. Short Tear Film Breakup Time–Type Dry Eye, Invest Ophthalmol Vis Sci. 2018 Nov1;59(14):DES64-DES70.doi: 10.1167/iovs.17-23746.
25. Yokoi N, Georgiev GA, Kato H, et al. Classification of fluorescein breakup patterns: a novel method of differential diagnosis for dry eye.Am J Ophthalmol. 2017;180:72-85
26. IBM Knowledge Center, https://www.ibm.com/support/knowledgecenter/en/SSLVMB_23.0.0/spss/base/idh_twostep_main.html#idh_twostep_main. Accessed on 05.07.2019.