Title

Identification of Subtypes of Dry Eye Disease, Including a Candidate Corneal Neuropathic Pain Subtype Through the Use of a Latent Class Analysis.

Journal

Cornea, 42(11)

Authors

Liu, Zijun
Lietman, Tom
Gonzales, John

Publication Date

2023-11-01

DOI

10.1097/ICO.0000000000003222

Peer reviewed

HHS Public Access

Author manuscript

Cornea. Author manuscript; available in PMC 2024 November 01.

Published in final edited form as:

Cornea. 2023 November 01; 42(11): 1422–1425. doi:10.1097/ICO.0000000000003222.

Identification of subtypes of dry eye disease, including a candidate corneal neuropathic pain subtype through the use of a latent class analysis

Zijun Liu, MS[1], **Tom Lietman, MD**[1,2], **John A. Gonzales, MD**[1,2]

[1]Francis I. Proctor Foundation, University of California, San Francisco, San Francisco, CA, USA

[2]Department of Ophthalmology, University of California, San Francisco, San Francisco, CA, USA

Abstract

Purpose: In the absence of a gold standard diagnostic test for different subtypes of dry eye disease, we aimed to identify latent subtypes of dry eye disease within a well-characterized cohort.

Design: Cross-sectional study of participants enrolled in Sjögren's International Collaborative Clinical Alliance (SICCA).

Methods: A latent class analysis was applied to different dry eye-related signs/tests and symptoms of ocular pain (particularly those that aligned with corneal neuropathic pain) giving relative specificities and sensitivities of each diagnostic test or symptom in the SICCA population.

Results: Four subtypes of dry eye disease were identified with putative designations including normal, asymptomatic dry eye, symptomatic dry eye, and corneal neuropathic pain.

Conclusions: More specific classification criteria are needed for dry eye disease. Latent class analysis applied to the signs and symptoms captured in the SICCA cohort may allow for the development and refinement of classification criteria for specific subtypes of dry eye.

Keywords

latent class analysis; dry eye disease; corneal neuropathic pain

Introduction

All dry eye disease (DED) is not the same.[1] DED is a spectrum that broadly includes aqueous sufficient and aqueous deficient dry eye.[2] Some patients complaining of symptoms that align or overlap with dry eye may have no obvious signs of dry eye, but may have significant discomfort or pain.[3,4] Instead, these patients may have corneal neuropathic pain instead.[2] There are a variety of ocular signs and tests used either alone or in combination with each other to identify DED. These measures and tests that may be used to assess dry eye include the assessment of corneal and conjunctival staining with fluorescein (NEI

Corresponding author: John A. Gonzales, MD, Associate Professor, Francis I. Proctor Foundation, Department of Ophthalmology, University of California, San Francisco, 490 Illinois Street, Second Floor, San Francisco, CA 94158, john.gonzales@ucsf.edu.

Conflict of interest statement: None of the authors have conflicts of interest to disclose.

scale), a combination of fluorescein staining of the cornea with conjunctival staining with lissamine green (such as the ocular staining score, OSS, or van Bijsterveld), tear breakup time, Schirmer testing, and tear osmolarity.[5–8] In addition, patient-reported symptoms of dry eye are included in the assessments for identifying patients with DED.[2,5] Because of the marked variation in signs, results of dry eye tests, and symptoms there is significant heterogeneity that amongst those classified with DED.[9] Indeed, different studies may use different reference standards, which can make the classification of patients with dry eye haphazard between different studies. As a result, the quantitative assessment of the performance of different index tests and estimates of disease prevalence may be biased.[10] Moreover, if unknown or latent classes of DED subtypes are included in studies, the overall power of a study may be diminished including the ability to detect meaningful differences with respect to therapeutics. Such issues are not unique to DED classification. Prior to 2016, there was no single, unified consensus for Sjögren's disease classification were at least 15 different classifications for Sjögren's disease, which may have contributed to its underdiagnosis. In fact, there were 11 prior classification systems prior to the introduction of the classification criteria accepted by both the American College of Rheumatology and the European League Against Rheumatism.[11–13] This universally accepted classification criteria for Sjögren's disease was developed in a data-driven manner and was the result of a latent class analysis approach.[11–14]

Since all DED is not the same, the obvious heterogeneity within DED makes it difficult to identify effective and targeted therapy. Analytic algorithms that use multiple variables (such as different DED tests and patient-reported symptoms) to identify homogenous subgroups with a heterogenous population can therefore be helpful. Latent class analysis is one such analytic algorithm, which can identify distinct clinical and biological subtypes of a disease. In some cases, a latent class analysis has identified subtypes of disease that have exhibited different clinical outcomes. A latent class analysis is not a subgroup analysis, since a subgroup analysis splits participant data into subgroups based upon some characteristic. Instead, a latent class analysis is an example of finite mixture modeling, which is a tool that can determine if unmeasured or unobserved groups exist within a population. The unobserved, or "latent" groups are inferred from the patterns of the observed variable or "indicators" (which are categorical) used in the modeling.[15,16]

In this study, we applied a latent class analysis to data from participants in the Sjögren's International Collaborative Clinical Alliance (SICCA) to estimate the probability of testing positive or negative of some of the most commonly used clinical tests and symptoms used to diagnose DED. While we have previously shown that the OSS exhibits both a high sensitivity and specificity for distinguishing between keratoconjunctivitis sicca and dry eye that is not keratoconjunctivitis sicca (or, not aqueous deficient dry eye), we wished to use the SICCA cohort database to determine if additional latent classes could be identified, particularly allowing for the identification of a potential corneal neuropathic pain subtype.[6,17] In the absence of a gold standard corneal neuropathic pain classification, this model-based approach provides a preliminary sense of the relative diagnostic performance of the dry eye tests and ocular pain questions used in SICCA.

Methods

Study Design and Population

SICCA was a cross-sectional study of participants enrolled from 9 international research sites. Participants (≥21 years of age) met at least one of the following conditions: 1) complaint of dry eye or dry mouth, 2) previous diagnosis of primary or secondary Sjögren's disease, 3) abnormal serology (positive anti-SSA, anti-SSB, or elevated ANA and RF), 4) bilateral parotid gland enlargement, or 5) multiple cervical/incisal dental caries. At baseline, participants completed an interview and questionnaires, had oral/ocular/rheumatologic examinations, had blood and saliva samples collected, and had a labial salivary gland biopsy among other procedures.[11–14] Institutional review board approval was obtained at each clinical site and the study adhered to the tenets of the Declaration of Helsinki.

Variables and Measures

Independent variables recorded included OSS (abnormal ≥ 5), Schirmer I (abnormal ≤ 5 mm at 5 minutes), TBUT (abnormal < 10 seconds), light sensitivity (abnormal "some of the time", "half of the time", "most of the time", or "all of the time"), burning or stinging (abnormal "some of the time", "half of the time", "most of the time", or "all of the time"), and pain or burning in the middle of the night or upon waking in the morning (abnormal "some of the time", "half of the time", "most of the time", or "all of the time").

Statistical Analysis

Levels of specificity and sensitivity for each relevant variable (clinical sign/diagnostic test and patient-reported symptom) were estimated using latent class analysis. Using this analysis, model-based clustering of SICCA participants into a specified number of "disease" classes is based on the observed patterns of a series of binary predictor variables representing the presence or absence of important diagnostic-related features. The resulting classes can then be related to disease status based on the class-specific patterns of the diagnostic features. Our modeling was based on 6 predictor variables that relate to DED and corneal neuropathic pain (see "Variables and Measures" section above). Models incorporating different numbers of classes were compared using Bayes information criterion (BIC). In addition, we also fitted latent class analysis models incorporating a random effect to relax the conventional assumption of condition independence of within-class outcomes. Finally, sensitivity and specificity of individual predictors were estimated using the model-based classification with an underlying, unobservable (latent) "gold standard".[12,18,19] Analyses were performed with the R package poLCA (available from the Comprehensive R Archive Network, http://cran.r-project.org).

Results

There were 3,514 participants enrolled into SICCA. The cohort was comprised of 3,185 women (91%) and 329 men (9%). There were 1,541 participants (43.9%) that met the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for Sjögren's disease. Mean age of SICCA participants was 52.9 years +/− 13.3 years (range 21 to 89 years).

Latent class analysis revealed the following estimated class population shares for the following designations: 1) no signs and no symptoms (28%); 2) signs, but no symptoms of dry eye (20%); 3) signs and symptoms of dry eye (25%); and 4) no signs, but symptomatic (26%). When evaluating the latent class analysis outputs, we determined that the specificity of a particular test or symptom was represented by the class that had no evidence of DED and was asymptomatic (essentially, a “normal” or control designation). Table 1 shows the sensitivity for a specific dry eye test or ocular symptom in the SICCA cohort in the other, non-“normal” candidate designations.

Discussion

In the SICCA cohort we found that using a latent class analysis 4 DED-related classes were identified: one class without symptoms or signs of DED (“normal”) and 3 types within the DED spectrum: asymptomatic DED, symptomatic DED, and corneal neuropathic pain. Because latent class analysis is an unsupervised analysis, the designations identified in Table 1 are our putative designations/interpretations of the latent classes. The test negative rate for no signs and asymptomatic (a “normal eye”) could be interpreted as the overall specificity of a diagnostic test for any of the dry eye disease subtypes (Table 1). The sensitivity for a particular entity could be interpreted as the test positivity rate for that class (or subtype of dry eye disease). As an example, for a patient truly without any of the dry eye diseases, we would expect OSS to be normal 87% of the time (specificity of OSS). If a patient truly has asymptomatic or symptomatic dry eye disease, we would expect the OSS to be abnormal 90% and 9!% of the time, respectively(sensitivity of OSS for asymptomatic or symptomatic dry eye disease).

Latent class analysis is able to identify qualitatively different and hidden (or latent) subpopulations (in this case, candidate dry eye designations) within a population (in this case, the SICCA cohort), with each subpopulation sharing specific characteristics with respect to their scores on the different dry eye tests or response to ocular symptoms.[20–22] Our group has used a latent class analysis approaches before: 1) to distinguish Sjögren’s disease from non-Sjögren’s disease participants within the SICCA cohort and 2) to distinguish between aqueous deficient (keratoconjunctivitis sicca) DED from non-aqueous deficient.[11–13,17] The SICCA cohort was established to develop new and universally accepted diagnostic criteria for Sjögren’s disease. Participants were enrolled into SICCA if they had signs or symptoms of dry eye or dry mouth, had dental caries or parotid gland enlargement, had abnormal serologies that could be compatible with Sjögren’s disease, or a prior diagnosis of Sjögren’s disease using older classification criteria. Within the SICCA cohort, then, approximately half of the participants were classified as Sjögren’s disease while the other half were classified as non-Sjögren’s disease. Therefore, the SICCA cohort represents a rich resource with which to characterize Sjögren’s disease as well as DED since it is comprised of participants that share some features that could be compatible with Sjögren’s disease as well as the spectrum of DED, respectively. Remarkably, SICCA participants were divided nearly evenly between the 4 latent classes, which further speaks to the utility of this cohort for future studies.

Prior studies have identified different subtypes of dry eye disease, but this has typically been based upon prespecified parameters of dry eye-related symptoms as well as determining whether there is a predominance of signs that align primarily with an aqueous sufficient/evaporative dry eye or those that align primarily with an aqueous deficient dry eye.[23] The typical algorithm is that patients are categorized based on response to questionnaires and then having an ocular sign of dry eye (tear break-up-time, tear osmolarity, or staining of the ocular surface) present. Therefore, it is possible to classify a patient with dry eye using different types of symptom questionnaires and signs.[23–25]

While prior studies have sought to identify specific tests that may correlate with dry eye disease severity, identifying latent subtypes of dry eye disease based on observed data from symptom and test results has not been performed before prior to the development of the SICCA cohort.[17,26] Since SICCA enrolled participants over 15 years ago and, at that time, ocular pain questionnaires, such as the Ocular Pain Assessment Survey and Neuropathic Pain Symptom Inventory-Eye, had not been introduced yet. It is possible that including such questionnaires in future studies may further refine the DED subtypes that LCA identified in the present study.[27,28]

Conclusion

In the absence of a gold standard dry eye test and without a single set of universally accepted classification criteria, the accurate classification of potentially fundamentally different subtypes of DED is challenging. Appropriately classification of DED spectrum subtypes is important in ensuring fidelity in future randomized controlled trials and identifying more specific and targeted therapeutic targets. A latent class analysis is the first step toward a more refined classification of different DED subtypes. Indeed, in the SICCA cohort, by incorporating participant-reported symptoms, including those that align with corneal neuropathic pain, latent class analysis identified 4 subtypes within the DED spectrum.

References

1. Pflugfelder SC. Prevalence, burden, and pharmacoeconomics of dry eye disease. The American journal of managed care. Apr 2008;14(3 Suppl):S102–6. [PubMed: 18452369]
2. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. The ocular surface. Jul 2017;15(3):276–283. doi:10.1016/j.jtos.2017.05.008 [PubMed: 28736335]
3. Galor A, Zlotcavitch L, Walter SD, et al. Dry eye symptom severity and persistence are associated with symptoms of neuropathic pain. British Journal of Ophthalmology. 2015;99:665–668. [PubMed: 25336572]
4. Rosenthal P, Baran I, Jacobs DS. Corneal pain without stain: is it real? The ocular surface. Jan 2009;7(1):28–40. [PubMed: 19214350]
5. Lemp MA. Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes. The CLAO journal : official publication of the Contact Lens Association of Ophthalmologists, Inc. Oct 1995;21(4):221–32. [PubMed: 8565190]
6. Whitcher JP, Shiboski CH, Shiboski SC, et al. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjogren's Syndrome International Registry. American journal of ophthalmology. Mar 2010;149(3):405–15. doi:10.1016/j.ajo.2009.09.013 [PubMed: 20035924]
7. van Bijsterveld OP. Diagnostic tests in the Sicca syndrome. Archives of ophthalmology (Chicago, Ill : 1960). Jul 1969;82(1):10–4. [PubMed: 4183019]

8. De Roetth A Sr. Lacrimation in normal eyes. AMA Arch Ophthalmol. Feb 1953;49(2):185–9. doi:10.1001/archopht.1953.00920020190008 [PubMed: 13007244]
9. Calvo F, Karras BT, Phillips R, Kimball AM, Wolf F. Diagnoses, syndromes, and diseases: a knowledge representation problem. AMIA Annu Symp Proc. 2003;2003:802.
10. Begg CB. Biases in the assessment of diagnostic tests. Statistics in medicine. Jun 1987;6(4):411–23. [PubMed: 3114858]
11. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjogren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis & rheumatology (Hoboken, NJ). Oct 26 2016;doi:10.1002/art.39859
12. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjogren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. Annals of the rheumatic diseases. Jan 2017;76(1):9–16. doi:10.1136/annrheumdis-2016-210571 [PubMed: 27789466]
13. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis & rheumatology (Hoboken, NJ). Jan 2017;69(1):35–45. doi:10.1002/art.39859
14. Shiboski SC, Shiboski CH, Criswell L, et al. American College of Rheumatology classification criteria for Sjogren's syndrome: a data-driven, expert consensus approach in the Sjogren's International Collaborative Clinical Alliance cohort. Arthritis care & research. Apr 2012;64(4):475–87. [PubMed: 22563590]
15. McLachlan G, Peel D. Finite Fixture Models. John Wiley & Sons; 2000.
16. Sinha P, Calfee CS, Delucchi KL. Practitioner's Guide to Latent Class Analysis: Methodological Considerations and Common Pitfalls. Critical care medicine. Jan 1 2021;49(1):e63–e79. doi:10.1097/ccm.0000000000004710 [PubMed: 33165028]
17. Gonzales JA, Shiboski SC, Bunya VY, et al. Ocular Clinical Signs and Diagnostic Tests Most Compatible With Keratoconjunctivitis Sicca: A Latent Class Approach. Cornea. Aug 2020;39(8):1013–1016. doi:10.1097/ico.0000000000002311 [PubMed: 32251167]
18. Baughman AL, Bisgard KM, Cortese MM, Thompson WW, Sanden GN, Strebel PM. Utility of composite reference standards and latent class analysis in evaluating the clinical accuracy of diagnostic tests for pertussis. Clinical and vaccine immunology : CVI. Jan 2008;15(1):106–14. doi:10.1128/cvi.00223-07 [PubMed: 17989336]
19. See CW, Alemayehu W, Melese M, et al. How reliable are tests for trachoma?--a latent class approach. Investigative ophthalmology & visual science. Aug 03 2011;52(9):6133–7. doi:10.1167/iovs.11-7419 [PubMed: 21685340]
20. Kongsted A, Nielsen AM. Latent Class Analysis in health research. Journal of physiotherapy. Jan 2017;63(1):55–58. doi:10.1016/j.jphys.2016.05.018 [PubMed: 27914733]
21. Lazarsfeld PF, Henry NW. Latent Structure Analysis. Houghton Mifflin; 1968.
22. Dayton CM, MacReady GB. Concomitant-variable latent-class models. Journal of the American Statistical Association. 1988;83(401):173–178.
23. Wolffsohn JS, Arita R, Chalmers R, et al. TFOS DEWS II Diagnostic Methodology report. The ocular surface. Jul 2017;15(3):539–574. doi:10.1016/j.jtos.2017.05.001 [PubMed: 28736342]
24. Akpek EK, Amescua G, Farid M, et al. Dry Eye Syndrome Preferred Practice Pattern®. Ophthalmology. Jan 2019;126(1):P286–p334. doi:10.1016/j.ophtha.2018.10.023 [PubMed: 30366798]
25. Tsubota K, Yokoi N, Shimazaki J, et al. New Perspectives on Dry Eye Definition and Diagnosis: A Consensus Report by the Asia Dry Eye Society. The ocular surface. Jan 2017;15(1):65–76. doi:10.1016/j.jtos.2016.09.003 [PubMed: 27725302]
26. Sullivan BD, Whitmer D, Nichols KK, et al. An objective approach to dry eye disease severity. Investigative ophthalmology & visual science. Dec 2010;51(12):6125–30. doi:10.1167/iovs.10-5390 [PubMed: 20631232]
27. Qazi Y, Hurwitz S, Khan S, Jurkunas UV, Dana R, Hamrah P. Validity and Reliability of a Novel Ocular Pain Assessment Survey (OPAS) in Quantifying and Monitoring Corneal and

Ocular Surface Pain. Ophthalmology. Jul 2016;123(7):1458–68. doi:10.1016/j.ophtha.2016.03.006 [PubMed: 27089999]

28. Farhangi M, Feuer W, Galor A, et al. Modification of the Neuropathic Pain Symptom Inventory for use in eye pain (NPSI-Eye). Pain. Jul 2019;160(7):1541–1550. doi:10.1097/j.pain.0000000000001552 [PubMed: 30883524]

Table 1.

Latent classes with putative candidate designations and probability of testing negative or positive for each ocular test or symptom.

Schirmer I (positive test is < 5 mm in 5 seconds)		
Class	Candidate designation	Test statistic (95% CI)
No signs and no symptoms	Normal	0.89 (0.84, 0.93) specificity for no disease state
Signs, but no symptoms	Asymptomatic dry eye *	0.48 (0.44, 0.53) sensitivity for this disease state
Signs and symptoms	Symptomatic dry eye *	0.47 (0.42, 0.51) sensitivity for this disease state
No signs, but symptomatic	Corneal neuropathic pain	0.11 (0.06, 0.15) sensitivity for this disease state
Ocular Staining Score (positive test is ≥ 5)		
Class	Candidate designation	Test statistic (95% CI)
No signs and no symptoms	Normal	0.87 (0.81, 0.95) specificity for no disease state
Signs, but no symptoms	Asymptomatic dry eye *	0.90 (0.83, 1.00) sensitivity for this disease state
Signs and symptoms	Symptomatic dry eye *	0.91 (0.85, 1.00) sensitivity for this disease state
No signs, but symptomatic	Corneal neuropathic pain	0.20 (0.13, 0.26) sensitivity for this disease state
Tear-break-up time (positive test is < 10 seconds)		
Class	Candidate designation	Test statistic (95% CI)
No signs and no symptoms	Normal	0.33 (0.28, 0.38) specificity for no disease state
Signs, but no symptoms	Asymptomatic dry eye *	0.99 (0.97, 1.00) sensitivity for this disease state
Signs and symptoms	Symptomatic dry eye *	1.00 (0.99, 1.00) sensitivity for this disease state
No signs, but symptomatic	Corneal neuropathic pain	0.69 (0.63, 0.74) sensitivity for this disease state
Burning or pain awaking one at night (positive test is “yes” response)		
Class	Candidate designation	Test statistic (95% CI)
No signs and no symptoms	Normal	0.91 (0.88, 0.95) specificity for no disease state
Signs, but no symptoms	Asymptomatic dry eye *	0.09 (0.05, 0.12) sensitivity for this disease state
Signs and symptoms	Symptomatic dry eye *	0.79 (0.74, 0.84) sensitivity for this disease state
No signs, but symptomatic	Corneal neuropathic pain	0.76 (0.69, 0.83) sensitivity for this disease state
Light sensitivity (positive test is “yes” response)		
Class	Candidate designation	Test statistic (95% CI)
No signs and no symptoms	Normal	0.83 (0.80, 0.87) specificity for no disease state
Signs, but no symptoms	Asymptomatic dry eye *	0.12 (0.09, 0.15) sensitivity for this disease state
Signs and symptoms	Symptomatic dry eye *	0.58 (0.53, 0.62) sensitivity for this disease state
No signs, but symptomatic	Corneal neuropathic pain	0.58 (0.53, 0.63) sensitivity for this disease state
Burning or stinging (positive test is “yes” response)		
Class	Candidate designation	Test statistic (95% CI)
No signs and no symptoms	Normal	0.75 (0.07, 0.82) specificity for no disease state
Signs, but no symptoms	Asymptomatic dry eye *	0.20 (0.15, 0.25) sensitivity for this disease state
Signs and symptoms	Symptomatic dry eye *	0.94 (0.91, 0.97) sensitivity for this disease state

No signs, but symptomatic	Corneal neuropathic pain	0.98 (0.95, 1.00) sensitivity for this disease state

*This candidate designation could represent either aqueous sufficient or aqueous deficient (keratoconjunctivitis sicca) dry eye. The population share within the SICCA cohort for each candidate designation are as follows: Normal, 28%; Asymptomatic dry eye, 20%; Symptomatic dry eye, 26%; Corneal neuropathic pain, 26%.