

Sex Differences and Discordance Between Symptoms and Signs of Dry Eye Disease



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- **PURPOSE:** To examine the initial presenting symptoms in relation to sex and identify predictors of discordance between symptoms and signs of dry eye disease (DED) in Taiwan.
- **DESIGN:** Retrospective cross-sectional study.
- **METHODS:** This clinic-based cohort from a tertiary referral center in Taiwan included 1229 patients diagnosed with DED at Keelung Chang Gung Memorial Hospital in Taiwan between August 1, 2011, and July 31, 2018. Initial presenting symptoms were cross-sectionally and retrospectively collected. The composite score, indicating the discordance between symptoms and signs, was derived from the difference between the DED symptom severity score and the DED sign severity score.
- **RESULTS:** Of 1229 patients, 975 (79.3%) were female, with a mean age of 56.7 ± 14.9 years. Initial presenting symptoms didn't show significant sex differences (all $P > .05$). In multivariate analysis, predictors of higher symptom severity score than sign severity score included being female ($P = .011$) and having a surgical history of cataract ($P = .037$), pterygium, or conjunctivochalasis ($P = .014$). Conversely, older age ($P < .001$) and artificial tear use ($P < .001$) were significant predictors of a lower symptom severity score than sign severity score.
- **CONCLUSIONS:** Strong predictors of incongruity between DED symptoms and signs include age, gender, surgical history for cataract, pterygium or conjunctivochalasis, and artificial tear use. Ophthalmologists should prioritize symptoms for female patients and postsurgery cases. In addition, the absence of symptoms should not dismiss DED possibility in older adult patients and those using artificial tears. Notably, early recognition and enhancement of postoperative care can improve patient satisfaction and quality of life. (Am J Ophthalmol 2024;260: 14–20. © 2023 Published by Elsevier Inc.)

ACCORDING TO THE 2017 INTERNATIONAL DRY EYE Workshop II Report (DEWS II), dry eye disease (DED) is a multifactorial disease. Loss of homeostasis of the tear film plays a key role in DED, which affects approximately 5% to 50% of adults worldwide.^{1,2} In Taiwan, the overall prevalence of DED is 7.85%, and the prevalence among patients ≥ 65 years of age is 20.72%.³ Although not sight-threatening, damage of the ocular surface can cause symptoms of eye irritation or fluctuating visual disturbance,⁴ leading to difficulties performing daily activities, such as watching television, driving, and using a computer. Consequently, DED can have significant adverse effects on patients' quality of life and productivity.^{5,6}

The lack of a universal and accurate test that can establish a diagnosis of DED poses a challenge to the assessment and classification of DED. In clinical practice, a diagnosis of DED is determined by applying a combination of subjective symptoms and objective signs and may involve a screening questionnaire and diagnostic tests (eg, for non-invasive breakup time, osmolarity, and ocular surface staining).⁷ However, the symptoms and signs of DED are poorly associated and inconsistent^{8,9}; DED-related neurosensory dysfunction may be responsible for this phenomenon.⁴ Vehofo and associates¹⁰ investigated the predictors of discordance between DED symptoms and signs in a clinic-based cohort of patients with DED in the Netherlands comprised predominantly of a female population and containing a high proportion of patients with Sjögren disease. No studies have yet investigated the factors influencing the dissociation between symptoms and signs of DED in an Asian population. Furthermore, no studies have investigated sex differences in the initial ocular complaints of patients with DED. Thus, the present study examined whether surgical history, especially cataract surgical history, has an effect on the dissociation between symptoms and signs of DED.

In summary, this study investigated possible associations between symptoms and signs of DED and assessed sex differences in the initial presenting symptoms of DED by analyzing a large cohort from Keelung Chang Gung Memorial Hospital in Taiwan.

METHODS

- **STUDY SAMPLE:** This study was approved by the Ethics Institutional Review Board of Chang Gung Memorial

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Hospital (approval 202100786B0) and adhered to the spirit of the Declaration of Helsinki.

This study was a retrospective, longitudinal, clinic-based study. Patients with DED were enrolled from the tertiary dry eye clinic at Keelung Chang Gung Memorial Hospital in Taiwan. DED was defined based on an Ocular Surface Disease Index (OSDI) score >12 combined with a tear breakup time (TBUT) <5 seconds or positive corneal staining with fluorescein. Assessment was performed by an ophthalmologist (C-C.S.). Cross-sectional data related to general medical history, ophthalmic medical history inclusive of cataract and ocular surgical history, date at DED diagnosis, and initial DED symptoms and signs at the first visit were collected from August 2011 to July 2018.

- **ASSESSMENT OF DRY EYE SYMPTOMS:** The patients were asked to complete the OSDI questionnaire at their first visit. The OSDI is used to quantify ocular surface symptoms and was created by the Outcomes Research Group at Allergan Inc as a method of rapidly assessing the frequency of ocular irritation symptoms and how these symptoms affect vision-related functioning.¹¹ Patients rate their responses on a 5-point Likert scale with endpoints ranging from 0 (none of the time) to 4 (all of the time) according to the frequency of symptoms across 3 subscales: ocular symptoms, vision-related functioning, and environmental triggers. The total score is calculated by summing all the responses and ranges from 0 (no symptoms) to 100 (worst symptoms).

- **ASSESSMENT OF DRY EYE SIGNS:** Assessments of dry eyes were made in both eyes and included the Schirmer test (without topical anesthesia), TBUT, fluorescein corneal staining, and analysis of meibomian gland dysfunction. A Schirmer test without anesthesia was performed to provide an estimation of reflex tear flow.⁷ A Schirmer strip was placed into the inferior fornix for 5 minutes; subsequently, wetness was measured. TBUT was measured by inserting an impregnated fluorescein strip into the inferior fornix and then counting the time between a complete blink and the first appearance of a dry spot or break in the tear film.⁷ TBUT was then determined by averaging the results of 3 measurements. The cornea was stained with fluorescein sodium strips, and a score 0 or 1 was given according to the presence of punctate dot staining in the interpalpebral cornea.⁷ Finally, meibomian gland dysfunction was diagnosed on the basis of meibum quantity, quality, and expressibility, all of which were assessed by applying gentle digital pressure. A score of 0 or 1 was given depending on whether meibomian gland dysfunction was present.⁷

- **STATISTICAL ANALYSIS:** First, we divided the total OSDI score by 100 to obtain a DED symptom severity score, which ranged from 0 (minimal symptoms) to 1 (maximal symptoms). Then, each of the 4 dry eye tests was converted to a common unit severity score, which ranged from

0 (fewest DED signs) to 1 (most DED signs), based on the data in [Table 1](#). The eye with the higher score then underwent further analysis. Test scores between the quartile points were transformed through linear interpolation. We subsequently calculated the mean value of the 4 independent severity scores to obtain a DED sign severity score.

The primary outcome variable was a modified version of that from a previous study.¹⁰ The composite score, indicating the discordance between symptoms and signs, was derived from the difference between the DED symptom severity score and the DED sign severity score and ranged from 1 (maximal symptoms and minimal signs) to -1 (minimal symptoms and maximal signs).

Data were cross-sectionally analyzed with SPSS software version 20.0 for Windows (SPSS, Inc, Chicago, Illinois, USA). Descriptive statistics were generated, and continuous variables were presented as means with standard deviations (SDs). A multivariate linear regression model was used to identify predictors that were independently associated with a discordance between DED signs and DED symptoms. A Pearson χ^2 test was conducted to determine associations and differences between variables. $P < .05$ was considered statistically significant.

RESULTS

A total of 1229 patients were enrolled. Data were retrospectively and cross-sectionally collected starting from the first visit of each patient. Most of the patients were female ($n = 975$, 79.3%), and the mean age was 56.7 years (SD 14.9 years).

The symptoms reported in initial visits are listed in [Table 2](#). The most common symptom was dryness sensation (43.5%), which was reported by 38.9% of male patients and 44.7% of female patients. The second most common symptom was blurred vision (24.2%), followed by foreign body sensation (18.1%) and tearing (12.4%). No significant differences were observed between the sexes for initial presenting symptoms (all $P > .05$; [Table 2](#)).

The results of univariate and multivariate analysis regarding the association between predictors and discordance between symptoms and signs are detailed in [Table 3](#). In the univariate analysis, several factors were found to significantly predict higher symptom severity scores compared with sign severity scores. These factors included female sex ($P = .004$), having ocular allergies ($P = .037$), a history of previous cataract surgery ($P = .015$), and a history of surgery for pterygium or conjunctivochalasis ($P = .039$).

On the other hand, certain factors were identified as significant predictors of lower symptom severity scores compared with sign severity scores. These factors encompassed advanced age ($P < .001$), the presence of type 2 diabetes mellitus ($P = .015$), having cataracts ($P = .001$), and the use of artificial tears ($P < .001$).

TABLE 1. Transformation of Dry Eye Test Measurement Into Common Unit System

	Severity Grade			
	0	0.33	0.67	1
TBUT (sec)	10	5	3	0
Schirmer test (mm/5 min)	10	5	2	0
Corneal fluorescein staining	Absence of SPK	N/A	N/A	Presence of SPK
MGD	Absence of MGD	N/A	N/A	Presence of MGD

DED = dry eye disease; MGD = meibomian gland dysfunction; SPK = superficial punctate keratitis; TBUT = tear breakup time.

TABLE 2. Initial Presenting Symptoms in Patients With Dry Eye Disease

Symptoms, n (%)	Total (N = 1229)	Female (n = 975)	Male (n = 254)	P Value
Dryness	535 (43.5)	436 (44.7)	99 (38.9)	.100
Blurred vision	298 (24.2)	247 (25.3)	51 (20.1)	.082
Foreign body sensation	223 (18.1)	183 (18.8)	40 (15.7)	.266
Tearing	152 (12.4)	118 (12.1)	34 (13.4)	.580
Itchiness	141 (11.4)	115 (11.8)	26 (10.2)	.293
Ocular pain	135 (10.9)	110 (11.3)	25 (9.8)	.636
Soreness	131 (10.6)	107 (10.9)	24 (9.4)	.604
Redness	124 (10.1)	104 (10.7)	20 (7.9)	.188
Irritation	100 (8.1)	82 (8.4)	18 (7.1)	.492
Discharge	72 (5.9)	56 (5.7)	16 (6.3)	.737
Gritty sensation	51 (4.1)	38 (3.9)	13 (5.1)	.385
Photophobia	47 (3.8)	38 (3.9)	9 (3.5)	.793
Sticky sensation	25 (2.0)	17 (1.7)	8 (3.1)	.157
Eye strain	5 (0.4)	5 (0.5)	0 (0.0)	.253
Fullness	4 (0.3)	4 (0.4)	0 (0.0)	.307
Burning sensation	3 (0.2)	2 (0.2)	1 (0.3)	.588

P value = χ^2 test, comparing the difference between the sexes.

In the multivariate model, independent associations were observed between discordance in symptoms and signs and the following factors: age ($P < .001$), gender ($P = .011$), history of cataract surgery ($P = .037$), history of surgery for pterygium or conjunctivochalasis ($P = .014$), and the use of artificial tears ($P < .001$).

DISCUSSION

This study investigated sex differences in DED presentation and predictors of discordance between symptoms and signs of DED. No significant differences between the sexes in initial presenting symptoms were observed. Significant predictors of a greater symptom severity score than sign severity score were female sex and surgical history of cataract, pterygium, or conjunctivochalasis. A significant predictor of a lower symptom severity score than sign severity score was advanced age and the use of artificial tears.

Among the symptoms reported in initial visits, the most common was dryness sensation, which was consistent with other studies.^{4,9} In patients with DED, decreased tear secretion and tear film instability causes inflammation and peripheral nerve damage on the ocular surface.^{1,4} In addition, inflammation causes sensitization of the corneal nociceptors and thus evokes a dryness sensation and ocular pain.⁴ Change in the dryness of the ocular surface may lead to ocular irritation and elicit a reflex that contributes to overflow tearing.⁴ Uneven tear film disruption results in irregular tear film thickness, which hinders visual acuity and leads to fluctuating visual disturbance.^{12,13}

Advanced age is one of the most well-established risk factors for DED.^{2,14} Older adults are susceptible to decreased tear production and a gradual reduction in corneal sensitivity.¹⁵ We found that advanced age was associated with lower symptom severity scores than sign severity scores; this finding was consistent with those of previous studies.^{10,16,17} Profound molecular, biochemical, and immune system changes and inflammation on the ocular surface play

TABLE 3. Univariable and Multivariable Linear Regression Analysis of Predictors of Discordance in Symptoms and Signs in Patients With Dry Eye

Predictor	Patients, n (%) or Value (Mean ± SD)	Univariate		Multivariate	
		β	P Value	β	P Value
Age (yrs)	56.7 ± 14.9	-0.175	<.001	-0.205	<.001
Female	975 (79.3)	0.083	.004	0.084	.011
Sjögren disease	195 (15.9)	0.041	.153	0.001	.986
Rheumatoid arthritis	77 (6.3)	0.015	.601	0.003	.922
Systemic lupus erythematosus	28 (2.3)	0.051	.074	0.021	.530
Type 2 diabetes mellitus	140 (11.4)	-0.069	.017	-0.005	.880
Ocular allergy	87 (7.1)	0.077	.007	0.038	.252
Cataract	433 (35.2)	-0.077	.007	-0.002	.969
Pterygium	67 (5.5)	-0.018	.531	-0.036	.220
Conjunctivochalasis	176 (14.3)	-0.043	.134	-0.016	.574
Cataract surgery history	276 (22.5)	0.032	.015	0.103	.037
Refractive surgery history	37 (3.0)	0.031	.275	0.027	.335
Pterygium or conjunctivochalasis surgery history	54 (4.4)	0.050	.039	0.074	.014
Contact lens user	41 (3.3)	0.007	.815	0.001	.973
Depression	75 (6.1)	0.108	.119	0.429	.405
Anxiety	85 (6.9)	0.015	.609	0.117	.316
Use of antidepressants	77 (6.1)	0.039	.170	0.057	.086
Use of anxiolytics	84 (6.8)	0.023	.417	0.132	.261
Use of artificial tears	1016 (82.7)	-0.162	<.001	-0.173	<.001

SD = standard deviation.

$\beta > 0$ means increased symptom rank score when compared with signs rank score, and vice versa.

key roles in age-related DED.^{14,17} This phenomenon can possibly be explained by the corneal mechanical threshold, which increases with age in patients with DED, leading to a significant reduction in corneal sensitivity.¹⁸ Our study supported the conclusion that corneal sensitivity decreases with age.¹⁹ In addition, younger patients with DED undergo an acute inflammatory process with severe symptoms and keratopathy, whereas older patients may be in the chronic inflammatory phase with prominent lacrimal damage and low tear function,¹⁷ possibly explaining why the symptoms and signs of DED in less consistent in older adults.

In this study, 79.3% of the patients with DED were women. We observed a sex difference in the discordance between symptoms and signs of DED. Specifically, female patients were more likely to report symptoms than male patients, even when the severity levels of signs were similar.^{17,20} Any of several underlying mechanisms may explain this phenomenon. First, sex differences in ocular surface sensitivity and pain perception may be involved.^{20,21} Women generally have lower pain thresholds and therefore experience more pain related to stimuli than do men.²² Second, numerous hormonal states and variations are associated with ocular surface changes.²¹ Sex hormones affect the regulation of ocular surface and adnexal tissues, such as the meibomian and lacrimal glands.^{23–25} In addition, androgens tend to enhance the function of ocular adnexal tissues,

whereas estrogens may antagonize this action and stimulate an inflammatory response.²⁵ Third, female patients are more likely to have DED-related comorbidities, such as allergies, depression, and autoimmune diseases like Sjögren disease.^{20,24,26} These underlying conditions may contribute to differences in symptomatology between the sexes.²⁰ Fourth, the sociocultural role of gender may be influential. Specifically, men generally underreport symptoms, and women are more willing to report pain than are men.^{20,21} However, this study found no evidence of significant sex differences in initial presenting symptoms, which led us to conclude that no statistically significant differences exist in primary complaints between the sexes at the onset of DED.

Symptoms related to DED—such as foreign body sensation, dryness, and ocular redness—often develop after cataract surgery.^{27,28} Cataract surgery may induce or exacerbate DED.^{28–31} Surgical manipulations of the ocular surface destroy the organization of the corneal innervation. Furthermore, the administration of topical anesthetics (which contain preservatives), intraoperative exposure to light from the microscope, and vigorous irrigation of the cornea all contribute to reduced goblet cell density and impaired corneal sensitivity, tear production, and tear film stability.^{27–30,32} Moreover, inflammatory mediators such as oxygen free radicals, proteolytic enzymes, and cyclooxygenase released after corneal incision during cataract surgery

may affect the corneal nerves and lead to tear film instability.^{30,31,33} A local inflammatory reaction triggers abnormal impulse activity in damaged corneal nociceptor fibers, causing sensitization of the ocular surface and sustained sensations of discomfort and pain in patients after phacoemulsification.^{30,34}

In our study, the patients who had undergone cataract surgery were prone to greater symptom severity scores than sign severity scores. Notably, ophthalmologists should pay particular attention to older adults who have undergone cataract surgery, among whom pre-existing DED is believed to be more prevalent.²⁹ Advanced age was associated with a lower symptom severity score than sign severity score; however, cataract surgery could reverse this correlation, leading to more DED symptoms and postoperative ocular complaints. Cataract surgery improves visual acuity, and the restoration of tear film integrity can reduce postoperative refractive error.³⁵ Early recognition and appropriate management of patients with DED and cataracts are essential to optimize surgical outcomes.³⁶ Consequently, the enhancement of postoperative dry eye care can further promote patient satisfaction and quality of life, especially among older adults.

In addition to cataract surgery, our analysis revealed that pterygium excision and correction of conjunctivochalasis were also associated with higher symptom severity scores compared with sign severity scores. Pterygium contributes to an uneven ocular surface and an unstable tear film. However, research has shown that tear film abnormalities can improve after pterygium excision surgery.³⁷ Patients with conjunctivochalasis exhibit redundant conjunctival folds and ocular surface inflammation, which are correlated with certain dry eye symptoms and signs.³⁸ Previous studies have demonstrated significant improvements in both dry eye symptoms and signs after addressing conjunctivochalasis-related issues.³⁹

In our investigation, the use of artificial tears emerged as a noteworthy predictor associated with a lower occurrence of DED symptoms compared with clinical signs. Artificial tears refer to topical ocular formulations designed to alleviate dry eyes by enhancing moisture retention on the external eye surface. Traditionally used across all stages of DED treatment, they constitute a primary approach for symptom improvement.⁴⁰ Apart from their mucous membrane safeguarding and lubricating role, artificial tears serve to replenish deficient tear film components, enhancing wetting and spread.⁴⁰ Moreover, they contribute to lowering the ocular surface osmolarity by diluting inflammatory cytokines, consequently reducing susceptibility to inflammation.⁴¹

Patients with DM are more susceptible to ocular surface diseases than are those without DM.^{42,43} In our study, DM was associated with lower symptom severity scores than sign severity scores in the univariate analysis. DeMill and associates⁴² observed that clinical signs but not symptoms of DED increased with the severity of diabetic peripheral neuropathy, which is a risk factor for DED among patients

with DM.⁴⁴ In addition, reductions in tear film stability, subbasal nerve density, and corneal sensitivity in patients with DM may lead to corneal hypoesthesia and thus may prevent patients from being severely symptomatic despite the presence of advanced clinical DED signs.^{42,45} Furthermore, chronic hyperglycemia may have a profound influence on tear film composition by increasing the inflammatory process on the ocular surface, causing microvascular changes in the lacrimal gland and decreasing goblet cell density in patients with DM.⁴⁶ Therefore, the discordance between the signs and symptoms of DED, where signs are present without a corresponding degree of the presence of symptoms, is likely to be greater among patients with DM.

In 1 study, dry eye ocular surface findings were shown to dissociate with subjective symptoms in patients with Sjögren disease.⁴⁷ This finding was consistent with that of Vehof and associates,¹⁰ who found that Sjögren disease was associated with the presence of fewer DED symptoms than signs. However, such discordance was not evident in the present study. In addition, the present study found no association between DED and rheumatoid arthritis or systemic lupus erythematosus. Patients with Sjögren disease, rheumatoid arthritis, or systemic lupus erythematosus made up relatively small proportions of our study population (15.9%, 6.3%, and 2.3%, respectively), whereas patients with Sjögren disease, rheumatoid arthritis, or systemic lupus erythematosus made up 44.4%, 19.1%, and 5.1% of the study population of Vehof and associates,¹⁰ respectively. Ethnic differences might also play a role. Further research should address these issues to explore discordance in patients with autoimmune diseases.

A strength of this study was the large size of the cohort and the use of multivariate analysis, which rendered our results more applicable to real-world conditions. Furthermore, the assessment of DED signs, including the Schirmer test and the measurement of TBUT, was conducted by a single ophthalmologist who used standardized protocols, leading to relatively consistent and reliable results.

Notably, our study had several limitations. First, this study was cross-sectional and retrospective; therefore, the outcome and exposure results were obtained simultaneously. Thus, although the researcher may decide whether an exposure is associated with an outcome, no evidence is available to determine that the exposure led to the outcome.⁴⁸ Therefore, our findings must be validated by longitudinal follow-up research. Second, we used the OSDI for the evaluation of DED symptoms, and the self-reported questionnaire was prone to recall bias. Third, we collected patient data from the first outpatient visit; however, some of the patients may have received previous treatment at other institutions. Fortunately, those patients accounted for only a small proportion of our sample (<1%) and therefore will not have substantially affected the results. Fourth, several key predictors reported by Vehof and associates,¹⁰ such as chronic pain syndrome and self-perceived health, were not

considered in our study because of difficulty collecting related data with a retrospective study approach. Fifth, data regarding the duration and severity of DM were not collected, therefore the subsequent analysis may not account for these factors. In addition, our study did not encompass significant factors affecting dry eye, such as occupation and an individual's working hours. We contacted 120 patients (9.8%) by phone to collect data on their occupation and average working hours. Unfortunately, there was no significant correlation between these factors and the discordance between symptoms and signs. Future research should prioritize the inclusion of these aspects for a more comprehensive examination.

To summarize, this study identified several strong predictors of incongruity between DED symptoms and signs, including older age, female gender, surgical history involving

cataract, pterygium, or conjunctivochalasis, as well as the application of artificial tears. In the realm of clinical practice, ophthalmologists should allocate greater attention to symptoms rather than relying solely on clinical signs when dealing with female patients, those with ocular allergies, and individuals who have undergone surgical interventions for cataract, pterygium, or conjunctivochalasis. Conversely, it is essential not to dismiss the potential presence of DED solely based on the absence of subjective symptoms, especially among older adults, those with pre-existing cataracts or DM, and those using artificial tears. Furthermore, it is recommended that further research be undertaken to delve into the disconnection between DED symptoms and signs. This exploration holds the potential to enhance the reliability of the predictive factors identified within the scope of this study.

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