• Clinical Research •

Influencing factors of ocular pain in dry eye disease patients at high altitude

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Abstract

● **AIM:** To quantify the severity and frequency of ocular pain in Tibetan plateau patients with dry eye, and to evaluate the related factors affecting ocular pain.

● **METHODS:** A retrospective study included 160 cases of dry eye disease (DED) patients who were treated from July 2022 to June 2023. Age, gender, occupation, illness course, anxiety, plateau duration, plateau protection, ocular surface disease index scale (OSDI), break-up time (BUT), Schirmer I test (SIT), conjunctivitis, history of ophthalmic medication, autoimmune disease, the workload of daily near vision range, smoking and overnight stay were obtained *via* comprehensive ophthalmic assessment, and their duration was followed up. Logistic regression analysis was used to determine the related factors affecting ocular pain.

● **RESULTS:** Totally 77.5% (124/160) of DED patients had ocular pain, of which the severity of ocular pain was mild, moderate, and severe in 30.0%, 36.3%, and 11.3% of patients, respectively. Frequency of ocular pain was reported occasional, half the time, frequent, and persistent pain in 19.4%, 36.9%, 16.9%, and 4.4%. OSDI score was 19.67±5.70 (13 to 36), and the level of pain was lowly correlated with OSDI (r_s=0.316, P<0.001). Logistic regression showed that in plateau DED patients, increased anxiety led to increased severity and frequency of ocular pain [odds ratio (OR)=3.662, 5.613, 2.387, and 4.870; all P<0.05], professional eye protection and improvement of daily sleep quantity decreased pain (OR=0.307, 0.572, 0.418, and 0.789; all P<0.05), while smoking and general protection of plateau did not affect the severity and frequency of ocular pain (all P>0.05).

● **CONCLUSION:** Ocular pain is a common complaint in high-altitude DED patients during the pandemic. Anxiety, eye protection, and adequate sleep during the epidemic period are significantly associated with the severity and frequency of ocular pain in patients with plateau DED, while symptoms of DED have relatively little influence on them.

● **KEYWORDS:** dry eye disease; ocular pain; high plateau
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INTRODUCTION

In recent years, with the continued prevalence of the novel coronavirus, corona virus disease 2019 (COVID-19), the Tibetan plateau has not been exempted. In plateau, it is more common in women (male to female ratio of 0.73:1), and most of them are ordinary type (96.8%, 120/124), severe type (3.2%, 4/124), and no patient was critical due to COVID[1]. During the epidemic, people's environment and lifestyle changes such as frequent indoor sterilization, increased use of video terminals nearby, long-term mask wearing and anxiety stress can trigger or exacerbate dry eye disease (DED)[2-3]. DED is a multifactorial disease characterized by decreased tear film stability and ocular surface tissue lesions[4-5]. Clinically, it may cause ocular pain, irritation, inflammation, and other disorders of the ocular microenvironment, and may even impair vision. For plateau dwellers, such as Tibetans, mountaineers, and garrison officers, exposed to special conditions such as low humidity, strong ultraviolet rays, cold and dry weather, and low pressure and hypoxia, the eyes are the first to suffer, and are very vulnerable to damage, with DED being the

most common[6]. The medical plateau refers to areas above 2500 m where the human body's functions are significantly affected, and the prevalence of plateau DED is 26.1%, which is significantly higher than that (11.9%) of the plain[7]. Meanwhile, DED at high-altitude presents the characteristics of youthfulness, severe symptoms, long treatment period, and recurrence[8].

Ocular pain is one of the important symptoms of DED, but its incidence in patients with DED is unknown. The physical sensation of ocular pain varies with each individual and can be complained of as burning, discomfort, gritty sensation or stinging pain[9], which is difficult to characterize accurately. However, the degree and frequency of ocular pain can significantly affect patients' quality of life and reduce treatment compliance[10]. Therefore, it is crucial to understand the ocular pain among DED patients and its influencing factors, which will facilitate the adoption of individualized therapy strategies. This study was designed to investigate and analyze ocular pain and factors affecting it among DED patients in the highlands during the epidemic outbreak.

PARTICIPANTS AND METHODS

Ethical Approval This study received approval from the Ethics Committee of General Hospital of Central Theater Command (No.2023028-01) and adhered to the principles outlined in the Declaration of Helsinki. All subjects were duly informed and consented to participate in the research.

Participants Totally 160 cases of patients with DED (320 eyes) who were admitted to the Medical team of the General Hospital of Central Theater Command from July 2022 to June 2023 were included as the participants. Inclusion criteria: 1) Patients complained of one of the subjective symptoms such as dryness, foreign body sensation, burning, fatigue, malaise, eye redness, and visual fluctuations; 2) Ocular surface disease index (OSDI) ≥13 points; 3) Fluorescein stained tear film break-up time (FBUT) <10s or non-anesthetic tear secretion test (Schirmer I test, SIT) <10 mm/5min; 4) The duration of DED did not exceed the length of stay in the plateau, regardless of gender and age. Exclusion criteria were: 1) those with combined corneal disease, corneal contact lens wear, ocular trauma, history of surgery or other eye diseases causing pain; 2) systemic chronic diseases such as diabetes, hypertension, or chronic bronchitis; 3) mental abnormalities or poor compliance.

Research Methods A retrospective study was conducted among DED patients at high altitudes. Data were obtained by history consultation, on-site questionnaire, and ocular surface specialist examination, including age, gender, occupation (outdoor or indoor), duration (months), daily near vision work (hours), the prevalence of anxiety (extreme, mild or none)[11], time spent on the plateau (months), related protection in the plateau (anti-UV glasses, sunglasses or color-changing glasses for eyes; general protection such as highland sunscreen, brimmed hat or mask; none), daily sleep amount (hours), whether there is a history of smoking, artificial tear medication, conjunctival inflammation, autoimmune diseases such as Sjögren's syndrome, rheumatoid arthritis, or thyroid-related diseases, *etc*. A field questionnaire on the OSDI scale and ocular pain status was also recorded, and a specialist examination of FBUT and SIT was performed. With averages taken for both eyes, the data at enrollment were used as study data and implementations were all done by the same ophthalmologist (Zhang PC). In addition, patients were followed up for 4mo, with every 2wk as a course of treatment, and the individual follow-up time, which was from enrollment to discontinuation of therapy or loss or end of follow-up, was recorded.

Ocular Pain Evaluation Indicators The degree of ocular pain varied according to a nine-point scale level[12-13], from no pain (0') to the most severe pain (9'): 1' to 3' was mild, 4' to 6' was moderate, and 7' to 9' was severe. At the same time, the frequency of ocular pain for the subjects was based on the OSDI and included none (0'), occasional (1'), half-time (2'), frequent (3'), and persistent (4').

Statistical Analysis The statistical analysis was performed using SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA), and GraphPad Prism version 8.0 was utilized to make the graphs. As assessed with Shapiro-Wilk test, a normal distribution was described by mean and standard deviation and data not normally distributed was presented as median and quartile. The categorical data were described by frequency and percentage. Pearson or Spearman test was used to determine the correlations, and logistic regression analyses were utilized to determine the clinical risk factors affecting ocular pain. The test level was α=0.05.

RESULTS

General Information A total of 160 patients (320 eyes) were studied with a male-to-female ratio 129/31 and an age of 31.2±7.8 (range, 19-52)y. The duration of DED was 9.9±8.6 (1-36)mo; Medication was received by 68.8% (110/160), of which 21.9% (35/160), 24.4% (39/160) and 22.5% (36/160) were treated for <1mo, 1 to 3mo and >3mo; the use of artificial tear was in 47.5% (76/160). FBUT (s) and SIT (mm/5min) were 5.8±2.0 (1-10) and 6.1±2.2 (1-10), respectively. The epidemic anxiety rate was 61.9% (99 of 160), with 41.3% mild and 20.6% severe. Residence time in the plateau was 23.9±31.3 (1 to 216)mo, smoking 44.4% (71 of 160), and daily sleep time 6.7±1.6 (2 to 10)h.

Level and Frequency of Ocular Pain The results for the degree level of ocular pain were 22.5% (36/160) without pain and 77.5% (124 of 160) with various levels of pain, of which 30.0% (48 cases) had mild (1' to 3'), 36.3% (58 cases) had

moderate (4' to 6'), and 11.3% (18 cases) had severe (7' to 9'); based on the nine-point system, average ocular pain was 3.3±2.5, as shown in Figure 1. The duration of follow-up was moderately negatively correlated with the level of ocular pain (Spearman test, r_s=-0.434, P<0.001), and the trend of change in the duration of follow-up with the ocular pain level was shown in Figure 2. In addition, the frequency of ocular pain based on the OSDI: 19.4% (31 cases) showed pain occasionally (1'), 36.9% (59 cases) half the time (2'), 16.9% (27 cases) frequently (3'), and 4.4% (7 cases) with constant ocular pain (4').

Relationship Between Ocular Pain and OSDI The OSDI score was 19.67±5.70 (13-36), which was moderately correlated with FBUT and SIT (Pearson test: r=-0.458, -0.384, P<0.001). There was a low correlation between the nine-point level of ocular pain and the OSDI score (Spearman test, r_s=0.316, P<0.001), and correlations with different indicators of OSDI are shown in Table 1.

Factors Affecting the Ocular Pain Univariate analysis of clinical factors and the severity of ocular pain was performed by binary logistic regression, as shown in Table 2; the factors with P<0.1 were included, followed by a multivariate binary logistic regression, and the results were shown in Table 3; finally, the dominant factors with P<0.05 were included again for multivariate analysis in ordinal logistic regression, and it presented in Table 4.

The predictive accuracy of the binary logistic regression model was 85% (>60%), with Hosmer-Lemeshow test (χ^2=8.591, P=0.378), indicating a good model fit. Anxiety under the epidemic was an independent risk factor for ocular pain in highland patients with DED [odds ratio (OR)=2.612, P<0.05], protection, smoking, and adequate sleep were independent protective factors (OR=0.499, 0.301, 0.480, all P<0.05), while FBUT, time spent on the plateau, autoimmune disease, and OSDI were not significant (all P>0.05).

In ordinal logistic regression analysis, the model fits were statistically significant (likelihood ratio test, χ^2=45.334, 23.442; P<0.001), and all parallel line tests passed (χ^2=1.373, 12.225; P=0.968, 0.428). As shown in Figure 3, the aggravation of anxiety could increase the severity and frequency of ocular pain in high-altitude patients with DED (OR=3.662, 5.613, 2.387, 4.870; all P<0.05), and the professional protection for eye at high-altitude and adequate daily sleep could reduce the level and frequency of pain (OR=0.307, 0.572, 0.418, 0.789, all P<0.05), while smoking and general protection in plateau did not affect the ocular pain (all P>0.05).

DISCUSSION

Ocular pain has received relatively little attention in the series of symptoms of DED patients[14], which is associated with its symptom diversity and difficulty in characterization. However, the severity and frequency of pain that are too high can significantly affect the quality of life and treatment compliance,

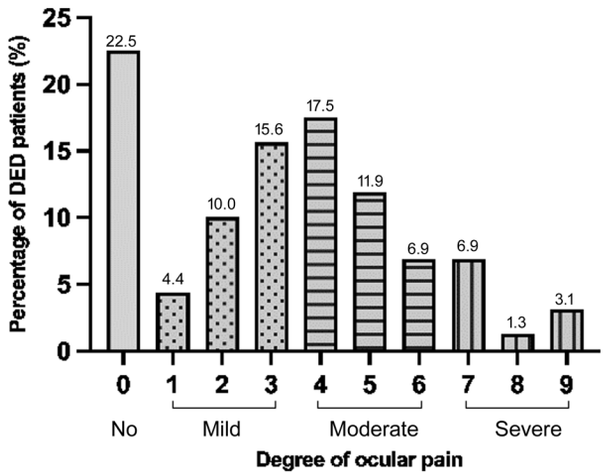

Figure 1 Bar chart of the level of ocular pain DED: Dry eye disease.

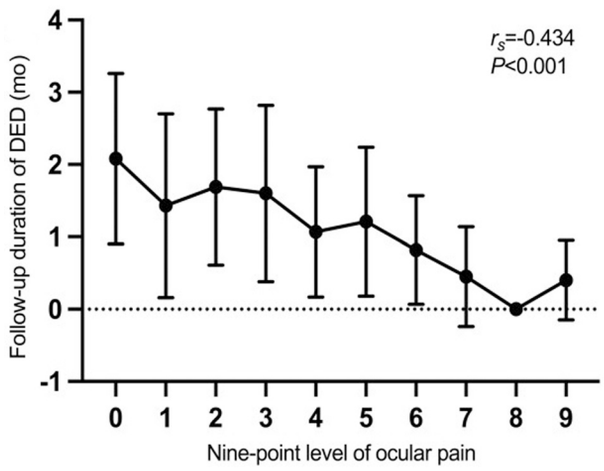

Figure 2 Trend chart of follow-up duration of DED with the level of ocular pain DED: Dry eye disease.

Table 1 Correlations between ocular pain level and OSDI components (160 cases)

Ocular Pain	OSDI score
Ocular symptoms	
Light sensitivity	P=0.009; r_s=0.205
Grittiness	P=0.037; r_s=0.165
Pain frequency	P<0.001; r_s=0.759
Blurred vision	P=0.343
Poor vision	P=0.622
Daily activities	
Reading	P=0.127
Night vision	P=0.691
PC or handset	P=0.599
Television	P=0.389
Environmental triggers	
Wind	P=0.817
Dry	P=0.806
Air condition	P=0.120

OSDI: Ocular surface disease index; PC: Personal computer.

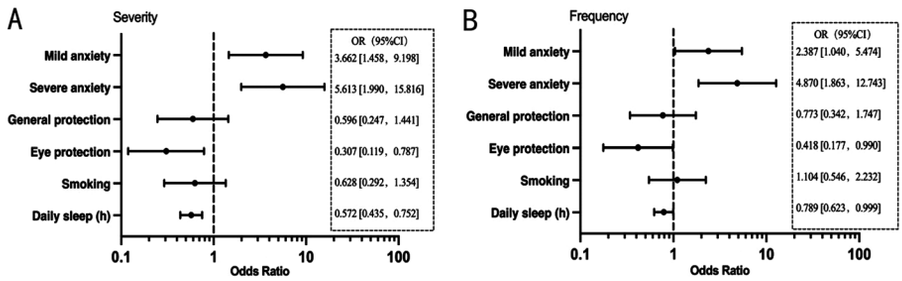

Figure 3 Forest plots of factors influencing the severity and frequency of ocular pain (124 cases).

Table 2 Relationships between ocular pain and clinical factors in patients with DED in the plateau (160 cases)

Parameters	Ocular pain		*P*
	No (*n*=36)	Yes (*n*=124)	
Age	30.78±6.86	31.35±8.05	0.695
Gender (female/male)	28/8	101/23	0.624
Job (outdoor/indoor)	21/15	78/46	0.619
Duration (mo)	9.78±11.21	11.17±12.38	0.545
Conjunctivitis (yes/no)	10/26	27/97	0.453
FBUT (s)	6.69±1.81	5.51±2.01	0.003
SIT (mm/5min)	6.17±2.02	6.02±2.20	0.727
Near vision work (h)	5.78±2.04	5.81±2.13	0.926
Anxiety (severe/mild/no)	1/12/23	32/54/38	0.000
Time in the plateau (mo)	13.33±21.05	26.98±33.13	0.026
Protection (eye/general/no)	21/12/3	40/40/44	0.001
AID (yes/no)	1/35	31/93	0.018
Smoking (yes/no)	25/11	46/78	0.001
Daily sleep (h)	7.83±1.28	6.34±1.50	0.000
Artificial tears	20/16	56/68	0.273
OSDI	17.64±5.34	20.26±5.68	0.019

AID: Autoimmune disease; FBUT: Fluorescein tear film breakup time; SIT: Schirmer I test; OSDI: Ocular surface disease index.

reduce vision and even cause mental disorders[15]. Moreover, ocular pain is not currently involved in the typology of dry eye, so the subcategories of dry eye may be optimized according to the peculiarity of ocular pain[16]. So, it is essential to evaluate ocular pain in DED patients. This retrospective study was conducted to identify the influencing factors associated with ocular pain in DED highlanders, which is conducive to intervention and targeted treatment. The subjects were mainly highlanders, with a balanced distribution of all age groups, and they were in a special epidemic period in recent years. The duration of included DED highlanders (1-36mo) coincided with the COVID-19 epidemic in China, especially when this study stage was also at the peak of the epidemic in Tibet. The data showed that 77.5% of DED had related ocular pain, with moderate-to-severe accounting for 47.5%. A longitudinal study showed that patients with severe ocular pain were more likely to have dynamic long-term DED[17].

Descriptive analysis was performed first, showing that highlands patients with DED were younger (average, 31 years old); the symptoms were evident, with FBUT (s) and SIT (mm/5min) of 5.78 and 6.06, respectively, and the average OSDI score was 19.67; with a long and recurrent duration of treatment (more than 1mo, 22.5% even longer than 3mo), and ocular pain was common (124/160). The respondents had anxiety (61.88%), outdoor work (99/160), and smoking (71/160). Figure 1 shows that except for painless, the distribution of level of ocular pain severity is approximately normal, with moderate being the majority (average, 3.28). The duration of follow-up was moderately negatively correlated with the level of ocular pain (r_s=-0.434, P<0.001; Figure 2), that is, ocular pain can reduce the therapy adherence of DED patients to a certain extent.

This study showed that OSDI was significantly negatively correlated with FBUT and SIT, and the correlation between the level of ocular pain and OSDI score was similar to that of previous studies[18-19], showing a low positive correlation (r_s=0.316, P<0.001). Table 1 shows that there was no correlation between pain level and multiple indicators of OSDI, but only a positive association with photophobia, foreign body sensation and ocular pain frequency, among which there was a high positive correlation with ocular pain frequency (r_s=0.759, P<0.001). Satitpitakul *et al*[19] concluded that there was a good correlation between OSDI and BUT in patients without ocular pain, whereas this correlation gradually weakened with increasing ocular pain. Such a trend is not evident in the present study, which is considered to be due to a greater proportion of neurogenic ocular pain factors for DED in the high-altitude environment. Neurogenicity, refers to neurological factors acting on the ocular surface, that lead to inconsistency in symptoms and signs of ocular pain, which can be one of the important indicators for self-perceived health[20]: stronger symptoms than signs predict the possible presence of systemic chronic pain syndrome, allergies, depression or osteoarthrosis; weaker symptoms than signs predict Sjogren's syndrome, aging or graft-versus-host disease. Predictability is good when a neuronal function is normal; as nerves are damaged, innervation-based symptoms may be less pronounced than those characterized by physical signs, resulting in decreased strength of association or even disappearance[21]; and those with neuropathic pain have more

Table 3 Relationship between ocular pain and influencing factors (160 cases)

Parameters	Ocular pain		*B*	OR (95%CI)	*P*
	No (*n*=36)	Yes (*n*=124)			
FBUT (s)	6.69±1.81	5.51±2.01	-0.006	0.994 (0.740, 1.336)	0.970
Anxiety (severe/mild/no)	1/12/23	32/54/38	0.960	2.612 (1.097, 6.220)	0.030
Time in the plateau (mo)	13.33±21.05	26.98±33.13	0.023	1.023 (0.995, 1.052)	0.109
Protection (eye/general/no)	21/12/3	40/40/44	-0.695	0.499 (0.253, 0.983)	0.045
AID (yes/no)	1/35	31/93	1.832	6.246 (0.629, 62.000)	0.118
Smoking (yes/no)	25/11	46/78	-1.202	0.301 (0.110, 0.818)	0.019
Daily sleep (h)	7.83±1.28	6.34±1.50	-0.733	0.480 (0.316, 0.730)	0.001
OSDI	17.64±5.34	20.26±5.68	0.038	1.038 (0.937, 1.151)	0.472

AID: Autoimmune disease; FBUT: Fluorescein tear film breakup time; OSDI: Ocular surface disease index; *B*: Regression coefficient; OR: Odds ratio; CI: Confidence interval.

Table 4 Relationships between severity and frequency of ocular pain and associated factors (124 cases)

Parameters		The severity of ocular pain			$OR_{0;}P_0$	Frequency of ocular pain				$OR_{1;}P_1$
		Mild, *n*=48	Moderate, *n*=58	Severe, *n*=18		While, *n*=31	Half, *n*=59	Frequent, *n*=27	Constant, *n*=7	
Anxiety	No[a]	23	13	2		15	18	4	1	
	Mild	20	27	7	3.662; 0.006	15	24	13	2	2.387; 0.040
	Severe	5	18	9	5.613; 0.001	1	17	10	4	4.870; 0.001
Protection	No[a]	12	22	10		10	17	14	3	
	General	15	19	6	0.596; 0.251	7	22	10	1	0.773; 0.536
	Eye	21	17	2	0.307; 0.014	14	20	3	3	0.418; 0.048
Smoking	No[a]	26	38	14		20	35	18	5	
	Yes	22	20	4	0.628; 0.235	11	24	9	2	1.104; 0.783
Daily sleep (h)		7.1±1.2	6.1±1.3	5.3±1.9	0.572; 0.000	6.8±1.5	6.3±1.8	6.1±1.4	5.1±2.1	0.789; 0.049

[a]This parameter is set to zero. OR: Odds ratio.

symptoms than physical signs. Therefore, dry eye treatment needs to be considered holistically rather than simply restoring ocular symptoms[22].

Binary logistic regression showed that anxiety was an independent risk factor for ocular pain, personal protection in the plateau, smoking, and adequate sleep were independent protective factors, while FBUT, duration of residence in the plateau, autoimmune disease and OSDI were not. It suggests that systemic factors play an important role in the somatosensory extent of ocular pain rather than clinical ocular factors[23]. In a study assessing the relationship between depression and eye disease in the general population based on a Beijing population screening that included 3468 participants[24], dry eye was the only common eye disease associated with increased depression scores. Neurostimulation or mental stress produces dry eye symptoms without significantly inducing tear film abnormalities[25]. Abnormalities in neural regulation of tear secretion can imbalance ocular surface homeostasis and cause dry eyes, while persistent abnormality in the tear film of dry eyes can damage ocular surface neural repair mechanisms and stimulate chronic inflammation[26]. The repeated vicious circle makes the affected eye sensitive and the ocular pain progressively worse. There are both intrinsic (corneal nerve, systemic diseases, and even mental health) and extrinsic (air pollution, surgical and medical stimuli) factors that contribute to ocular pain in DED individuals, which can inform the suspected etiology and guide management decisions targeting nerve pain[27-28]. Multiple ordinal logistic regression analysis showed that increased anxiety led to an increase in the degree and frequency of ocular pain, which was mitigated by eye protection and daily sleep supplementation, while smoking and general protection were useless. It suggests that timely professional eye protection, adequate sleep, and a healthy mindset are essential for relieving ocular pain in DED patients. Professional eye protection, such as protective glasses and long-brimmed hats, can avoid direct light, wind and sand irritation and has a moisturizing effect. Under psychological factors, the ocular pain threshold decreases, so symptoms of dry eye aggravate with increased anxiety[29]; the origin of pain in DED patients, especially when there is no significant abnormality from the ocular surface, may be neurogenic, that is, neuropathic pain[30]. The central role of neuropathic pain is to monitor, protect and restore ocular surface tear film homeostasis[31]. Therefore, attention to ocular pain is of great value because of its poor response to conventional treatment with tear replenishment, which may be systemically related and needs to be addressed simultaneously. In addition, the association between DED and systemic disorders is not

specific to anxiety and depression; it shows correlations in conditions such as post-traumatic stress, insomnia, or chronic pain[32]. Dry eye-induced hypersensitivity and hyperalgesia are caused by central sensitization in the trigeminal nucleus with upregulation of the α2δ-1 subunit[33]. Smokers can avoid ocular pain to a certain extent, but it cannot be a protective factor. Keall *et al*[34] studied pain relief by opioid in patients with advanced cancer, which was possible in the early stages but tended to be abused frequently and ineffectively in the later stages. Studies[35-37] have shown that DED is closely related to psychological factors such as anxiety, obsessive-compulsive disorder, and even depression, both of which may be causal to each other and change with symptoms, signs, sleep quality[38] and age, but no in-depth exploration has been focused on its ocular pain. Other studies have confirmed that somatosensory dysfunction is likely to underlie DED ocular pain[39]. Vehof *et al*[18] have focused on the inconsistency between symptoms and signs in plain DED, suggesting that chronic pain syndrome, atopic diseases, various drug abuse, allergies, and autoimmune diseases may be predictive factors for it. Kalangara *et al*[40] found that 89% of DED patients complained of ocular pain, which was significantly correlated with dry eye symptoms scores (r=0.57-0.66), but the severity of ocular pain had nothing to do with dry eye symptoms. This study targets specific populations and periods at high altitudes, and the influencing factors of ocular pain vary. Based on sleep disorders, the epidemic anxiety and plateau-specific protection for the eye are different from other studies. Furthermore, this article suggests that the effect of dry eye symptoms on ocular pain is relatively weak.

In contrast to previous studies, this study tentatively analyzes the risk factors of ocular pain in highland DED patients as a point of interest. Evaluation of ocular pain will help to tailor treatment plans based on the tear film and/or neurological status. When the symptoms of dry eye are consistent with the signs, ocular surface factors should be considered mainly, but if they are inconsistent, systemic factors should be taken into account and appropriate treatment is given. A relatively stringent selection of influential factors was made in serial regression analysis, and the results were sought reliably. In addition, the findings remain applicable to non-epidemic periods. Viral pandemics bring together internal and external factors that predispose to dry eye, accentuating the corresponding symptoms and signs, which are still present during a non-epidemic. However, there are still some limitations, such as the absence of plain DED patients as controls, a predominance of males and the scale for assessing pain that, although proven to be reliable and safe[41], is still a primary assessment of pain; and the etiological hypothesis needs to be established for further exploration.

In summary, complaints of ocular pain are relatively common in DED patients on the plateau. Epidemic-induced anxiety, professional protection for the eye, and adequate sleep are significantly associated with the severity and frequency of ocular pain in dry eye patients, while the effect of dry eye symptoms was relatively weak.

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