• Clinical Research •

Dry eye disease in systemic lupus erythematosus: a cross sectional study

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Received: 2023-10-09 Accepted: 2024-04-11

Abstract

● **AIM:** To explore ocular surface manifestations of dry eye disease (DED) and its influencing factors in systemic lupus erythematosus (SLE) patients.

● **METHODS:** Ophthalmological examinations were conducted in SLE patients (*n*=43) and controls (*n*=41), including Ocular Surface Disease Index (OSDI), objective scatter index (OSI), tear meniscus height (TMH), lipid layer thickness (LLT), non-invasive Keratograph tear breakup time (NIKBUT), corneal fluorescein score (CFS), Schirmer I test. DED was diagnosed according to the Tear Film and Ocular Surface Society Dry Eye Workshop II Criteria. SLE patients were further divided into DED group and non-DED group, the disease activity, clinical manifestations and laboratory investigations were compared between the two groups. The disease activity was evaluated by Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K). Receiver operative characteristic (ROC) curve and multiple-factor binary logistic regression were performed.

● **RESULTS:** SLE patients showed higher OSDI [9.1 (2.8-15.9) *vs* 6.3 (2.2-7.5), *P*=0.035], higher OSI [1.67 (1.09-2.60) *vs* 0.96 (0.87-1.60), *P*=0.001], higher CFS [1 (0-2) *vs* 0 (0-1), *P*=0.001], lower LLT [65 (42-100) *vs* 100 (79.5-100), *P*=0.010], and lower NIKBUT [8.03 (4.02-9.73) *vs* 9.67 (5.26-12.71), *P*=0.030] than controls. The 32.6% of SLE patients had DED, which was higher than 12.2% of healthy controls. DED group showed higher SLEDAI-2K score [9.7±6.1 *vs* 5.4±3.4, *P*=0.025], higher anti-cardiolipin antibody (ACL) [8.7 (3.5-13.2) *vs* 3.6 (2.0-6.9), *P*=0.035], and higher proportion of patients with cutaneous eruption [42.9% *vs* 6.9%, *P*=0.015] than non-DED group. According to multiple-factor binary logistic regression analysis, the SLEDAI-2K score (OR=1.194, *P*=0.041) and cutaneous eruption (OR=7.094, *P*=0.045) could be consider as risk factors for DED in SLE patients. The ROC curve of the combined factors including age, disease duration, SLEDAI-2K score, ACL, and cutaneous eruption was analyzed, with a sensitivity of 0.786, a specificity of 0.793, and an area under curve of 0.820.

● **CONCLUSION:** Ocular surface affection is frequent in SLE patients, and patients with high disease activity and cutaneous eruption show increased risk of DED.

● **KEYWORDS:** autoimmune disease; systemic lupus erythematosus; dry eye disease

DOI:10.18240/ijo.2024.07.09

Citation: Kang SF, Wang YX, Zhang QC, Wang ZL, Chen GL. Dry eye disease in systemic lupus erythematosus: a cross sectional study. *Int J Ophthalmol* 2024;17(7):1255-1261

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complicated systemic autoimmune disease, which has the propensity to invade multiple organs and systems of the body. Thus there are various clinical manifestations among different patients[1]. The prevalence of SLE in the world vary from 3.2 to 159 per 100 000 persons per year[2]. The prevalence also vary by populations and sex. Specifically, studies indicated that SLE among African, Asian are more common than European, the prevalence are significantly higher among females compared with males[3]. SLE significantly affects the quality of life and imposes great economic burden in SLE patients[4-5]. There are various clinical manifestations among different patients, around one third of SLE patients may have ocular involvement, dry eye disease (DED) is thought to be the most frequent manifestation of ocular involvement[6].

DED is one of the most common ocular surface diseases in clinical practice, which significantly affects quality of life. DED was previously referred to as dry eye, dry eye syndrome, keratoconjunctivitis sicca, *etc*. The Tear Film and

Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) defined that DED is a multifactorial disease of the ocular surface[7]. TFOS DEWS II Epidemiology Report indicated increasing risk for DED in patients with autoimmune disease[8]. A recent Meta-analysis reported that the overall prevalence of DED was 16%, and SLE patients were four times more likely to get DED than healthy controls[9]. Since the high incidence in SLE, assessment for DED in SLE patients has received growing attention. There are few studies about the ocular surface characteristics as well as influencing factors of DED in SLE patients[10-11]. Therefore, further studies should be performed to provide more information for clinicians.

The present study intended to identify the ocular surface manifestations, and explore influencing factors of DED in SLE patients.

SUBJECTS AND METHODS

Ethical Approval This study adhered to the tenets of the Declaration of Helsinki, and were approved by the Research Ethics Committee of the Second Hospital of Shandong University (No.KYLL-2023LW028). Written Informed consent was obtained from all participants. The study was registered before patients' recruitment at Chinese Clinical Trial Registry (https://www.chictr.org.cn/), the trial registration number is ChiCTR2300071965.

Subjects The current cross sectional study was performed at the Second Hospital of Shandong University between June 2023 and August 2023. The study included 43 SLE patients and 41 age and gender matched controls. SLE patients were further divided into two subgroups including DED group and non-DED group according to the TFOS DEWS II diagnostic criteria: symptoms [Ocular Surface Disease Index (OSDI) ≥13] and non-invasive tear breakup time (NIBUT) <10s[12]. Participants were recruited from the Department of Rheumatology and the Center for Health Examination of the Second Hospital of Shandong University.

Inclusion criteria: SLE patients met the European League Against Rheumatism and the American College of Rheumatology classification criteria for SLE[1]. Healthy volunteers were recruited as controls; age between 18-60y.

Exclusion criteria: 1) History of eye surgical procedures; 2) History of diseases affecting ocular surface conditions; 3) Current and past contact lens wearers; 4) The time of using visual display terminal was equal to or more than 8h each day. Participants who meet any one of the exclusion criteria were excluded from the study. To eliminate the influence of secondary Sjögren's syndrome, SLE patients who meet the classification criteria for Sjögren's syndrome proposed by the American-European Consensus Group was ruled out[13].

Sample Size The sample size was analyzed using PASS 21.0 software. According to our preliminary experiment, non-invasive Keratograph tear breakup time (NIKBUT) was selected as the main outcome, the mean±standard deviation (SD) of NIKBUT was 7.6±4.0 in SLE group, and 10.5±4.0 in control group. The two-sample *t*-tests assuming equal variance was selected, with alpha=0.05, and power=0.8. The minimum sample size in our study was 31. Considering a possible 20% wastage rate, a total of 38 participants were needed.

Rheumatology Assessment Demographic data, clinical manifestations and laboratory investigations of SLE patients were identified by reviewing hospital records. Complete blood count, complete urine, serum creatinine, erythrocyte sedimentation rate were assessed. Immunological tests included the assessment of anti-double-strand DNA antibody, complement 3 and complement 4, serum levels of immunoglobulin G/A/M, anti-Smith antibody. Anti-phospholipids including anti-cardiolipin antibody (ACL) and anti-β2 glycoprotein I antibody were examined. The disease activity was evaluated by Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)[14].

Ophthalmology Assessment Ophthalmic examinations were performed to all participants. Basic ophthalmic examinations including visual acuity, tonometry, slit-lamp examination. Ocular surface examinations were performed in the sequence as follows. An interval of 10min was allowed between each two examinations. The right eye of each participant was measured and analyzed. All examinations were performed by the same two ophthalmologists in the ophthalmology outpatient clinic.

Ocular Surface Disease Index The OSDI questionnaire was adopted to describe ocular surface symptoms for all participants. It is a 12-item questionnaire which assessed the frequency of symptoms, functional limitation and environmental factors. The overall score of the questionnaire range from 0 to 100, where higher score represent more severe symptoms[15].

Tear meniscus height The tear meniscus height (TMH) was measured by ocular surface analyzer Keratograph 5M (Oculus, Wetzlar, Germany). Adjusting Keratograph 5M to fit subject's position, tear meniscus was focused and then the ruler was pulled to measure TMH. The mean value of three measurements was collected and analyzed. The reference value of TMH for normal subjects is greater than or equal to 0.20 mm.

Non-invasive Keratograph tear breakup time The NIKBUT was measured by the ocular surface analyzer Keratograph 5M (Oculus, Wetzlar, Germany). First, Keratograph 5M was adjusted to focus on the center of the pupil. After blinking twice, subject was instructed to keep their eyes open until the measurement finished. Then the analyzer will calculate the NIKBUT automatically. The mean value of three measurements was collected and analyzed. The measurement unit of NIKBUT was second.

Table 1 Demographic data and ocular surface characteristics of SLE patients and controls median (IQR)

Characteristics	SLE patients (*n*=43)	Controls (*n*=41)	χ^2/Z	*P*
Age (y)	35 (24, 47)	37 (25.5, 47.5)	-0.434	0.664
Gender (female/male)	40/3	38/3	0.000	1.000
DED/non-DED	14/29	5/36	4.972	0.026
OSDI	9.1 (2.80, 15.90)	6.3 (2.20, 7.50)	-2.110	0.035
OSI	1.67 (1.09, 2.60)	0.96 (0.87, 1.60)	-3.369	0.001
TMH (mm)	0.12 (0.11, 0.15)	0.13 (0.12, 0.15)	-1.847	0.065
LLT (ICU)	65 (42, 100)	100 (79.50, 100)	-2.592	0.010
NIKBUT (s)	8.03 (4.02, 9.73)	9.67 (5.26, 12.71)	-2.170	0.030
CFS	1 (0, 2)	0 (0, 1)	-3.314	0.001
SIT (mm)	8 (5, 17)	11 (6.50, 15)	-0.556	0.578

SLE: Systemic lupus erythematosus; IQR: Interquartile range; DED: Dry eye disease; OSDI: Ocular Surface Disease Index; OSI: Objective scatter index; TMH: Tear meniscus height; LLT: Lipid layer thickness; ICU: Interferometry color units; NIKBUT: Non-invasive Keratograph tear breakup time; CFS: Corneal fluorescein score; SIT: Schirmer I test.

Objective scatter index The double-pass Optical Quality Analysis System (Visiometrics S.L., Tarrasa, Spain) was adopted to measure objective scatter index (OSI). Refraction errors were corrected by the instrument. After naturally blink twice, subjects were instructed to keep their eyes open, the consecutive OSI of 20s were measured in an interval of 0.5s, with the subject instructed to avoid blinking. The mean OSI of 20s consecutive measurements was recorded and analyzed.

Lipid layer thickness LipiView interferometer (TearScience Inc., Morrisville, North Carolina, USA) was adopted to measure average lipid layer thickness (LLT). Subject was instructed to gaze at the camera, then interferometry image of the lipid layer was recorded and LLT was calculated automatically. The measurement unit of LLT was interferometry color units (ICU), 1 ICU was equal to 1 nm. The LipiView interferometer ouputs a maximum of 100 ICU even though the LLT was larger.

Corneal fluorescein score The standard fluorescein strip (Tianjin Jingming New Technological Development Co, Ltd., China) was soaked with saline. The lower palpebral conjunctiva was stained with impregnated strip. Subjects were instructed to blink naturally three times and then keep their eyes open. Corneal fluorescein staining was then observed by slit lamp microscope using cobalt blue light. The staining score was counted as follows: 0, 0 dot; 1, 1-5 dots; 2, 6-30 dots; 3, ≥30 dots. Confluent patches, staining within pupil or filaments were counted as one extra points, respectively. The maximum score of each patient was 6[16].

Schirmer I test The Schirmer I test (SIT) was conducted using standard Schirmer paper strip (Tianjin Jingming New Technological Development Co, Ltd.) without anesthesia. The strip was folded at the notch and the shorter folded end was hanged at the temporal one-third of the lower eyelid margin. Subjects were instructed to keep their eyes closed. The length of wetting from the notch during 5min was measured.

Statistical Analysis All statistical analyses were performed by IBM SPSS, version 25.0. The normality test of the data was conducted using Shapiro-Wilk's test. Equality of Variance was conducted by the Levene's test. Continuous numeric variables were presented as mean±SD and two independent sample *t*-test was adoptd to assess group differences in case of normal distribution data, variables were presented as median and interquartile range (IQR) and Mann-Whitney *U* test was used to assess group differences in case of deviating from a normal distribution data. Categorical variables were presented as number (%) and the Chi-square test was used to assess group differences. Receiver operative characteristic (ROC) and multiple-factor binary logistic regression analysis were used to analyze influencing factors of DED and the efficiency of differentiating DED from non-DED in SLE patients. The statistical significance was regard as $P<0.05$ (bilateral).

RESULTS

Demographics and Ocular Surface Characteristics of SLE Patients and Controls No statistical differences were found in age and sex between SLE patients and controls. The percentage of DED was higher in SLE patients than controls. Compared with controls, OSDI, OSI, corneal fluorescein score (CFS) were higher, NIKBUT and LLT were lower in SLE patients, the differences between the two groups were significant (all $P<0.05$). While there were no significant differences of TMH and SIT between SLE patients and controls (all $P>0.05$; Table 1).

Clinical and Laboratory Features in DED Group and Non-DED Group Compared to non-DED group, SLEDAI-2K scores were higher and cutaneous eruption was more common in DED group (all $P<0.05$; Table 2). ACL of DED group was higher than that of non-DED group ($P<0.05$; Table 3).

Evaluation of Influencing Factors of DED in SLE Patients Age, disease duration, SLEDAI-2K score, ACL, cutaneous

Table 2 Demographic data and clinical manifestations of DED group and non-DED group *n* (%)

Parameters	SLE patients (*n*=43)		$\chi^2/Z/t$	*P*
	DED group (*n*=14)	Non-DED group (*n*=29)		
Age (y)	35 (31, 42)	32 (21, 50)	-0.804	0.421
Sex (female/male)	13/1	27/2	0.000	1.000
Disease duration (y)	0.7 (0.1, 4.0)	2.0 (0.2, 6.5)	-0.651	0.515
SLEDAI-2K, mean±SD	9.7±6.1	5.4±3.4	-2.451	0.025
Joint involvement	4 (28.6)	6 (20.7)	0.035	0.851
Alopecia	4 (28.6)	2 (6.9)	2.110	0.146
Lupus nephritis	6 (42.9)	5 (17.2)	2.048	0.152
Cutaneous eruption	6 (42.9)	2 (6.9)	5.863	0.015
Pericardial effusion	4 (28.6)	2 (6.9)	2.110	0.146
Fever	1 (7.1)	3 (10.3)	0.000	1.000

DED: Dry eye disease; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000 score; SLE: Systemic lupus erythematosus.

Table 3 Laboratory investigations of DED group and non-DED group

Parameters	SLE patients (*n*=43)		$\chi^2/Z/t$	*P*
	DED group (*n*=14)	Non-DED group (*n*=29)		
Anti-dsDNA (IU/mL)	220.1±267.4	195.1±204.7	-0.339	0.737
ACL (RU/mL)	8.7 (3.5, 13.2)	3.6 (2.0, 6.9)	-2.109	0.035
Anti-β2-GPI (RU/mL)	15.8 (6.7, 20.4)	16.6 (11.2, 30.8)	-0.752	0.452
SCr (μmol/L)	54.5 (45.5, 59.0)	53.0 (46.0, 62.0)	-0.130	0.897
ESR (mm/h)	11.0 (2.8, 24.0)	11.0 (4.0, 23.5)	-0.169	0.866
C3 (g/L)	0.79±0.38	0.87±0.30	0.785	0.437
C4 (g/L)	0.18 (0.07, 0.24)	0.15 (0.10, 0.19)	-0.259	0.795
IgG (g/L)	15.1 (10.6, 19.0)	16.1 (11.1, 19.4)	-0.648	0.517
IgA (g/L)	2.2±0.9	2.7±1.2	1.230	0.226
IgM (g/L)	0.8±0.5	0.9±0.5	0.998	0.324
Anti-Sm	4 (28.6)	12 (41.4)	0.663	0.416
Leukopenia	4 (28.6)	5 (17.2)	0.208	0.649
Thrombocytopenia	1 (7.1)	3 (10.3)	0.000	1.000
Lymphopenia	5 (35.7)	10 (34.5)	0.000	1.000
Proteinuria	6 (42.9)	8 (27.6)	0.428	0.513
Hematuria	4 (28.6)	3 (10.3)	1.158	0.282

Data is presented as median (IQR), mean±SD, or positive number of subjects (% of positive subjects). SLE: Systemic lupus erythematosus; DED: Dry eye disease; Anti-dsDNA: Anti-double-strand DNA antibody; ACL: Anti-cardiolipin antibody; Anti-β2-GPI: Anti-β2 glycoprotein I antibody; SCr: Serum creatinine; ESR: Erythrocyte sedimentation rate; C3/C4: Complement 3/4; IgG/IgA/IgM: Immunoglobulin A/G/M; Anti-Sm: Anti-Smith antibody; Leukopenia: White blood cell count <3000/mm^3; Thrombocytopenia: Platelet count <100 000/mm^3; Lymphopenia: Lymphocyte count <1100/mm^3; Proteinuria: >0.5 g/24h; Hematuria: >5 red blood cells/high power field.

eruption were taken into model for multiple-factor binary logistic regression. The results indicated that SLEDAI-2K score and cutaneous eruption significantly affected the onset of DED (all $P<0.05$). Odds ratio (OR) value of SLEDAI-2K score and cutaneous eruption were 1.194 and 7.094 (Table 4). The combined efficiency of age, disease duration, SLEDAI-2K score, ACL, cutaneous eruption was analyzed by ROC curve, showed a sensitivity of 0.786, a specificity of 0.793, and an area under curve (AUC) of 0.820 (Figure 1).

DISCUSSION

Autoimmune rheumatic diseases are a group of diseases related to abnormality of immune system. The symptoms and signs of Immune-related DED were significantly more severe than simple DED[17-18]. SLE is a specific kind of autoimmune rheumatic diseases. DED is also one of the ocular involvement in SLE[19]. Several studies reported that factors such as age, disease activity may be associated with the risk of DED in patients with SLE[20]. The interest has arisen in identifying more factors influencing DED in patients with SLE. The present study was aimed to observe ocular surface manifestations in SLE patients, and explore influencing factors of DED in SLE patients.

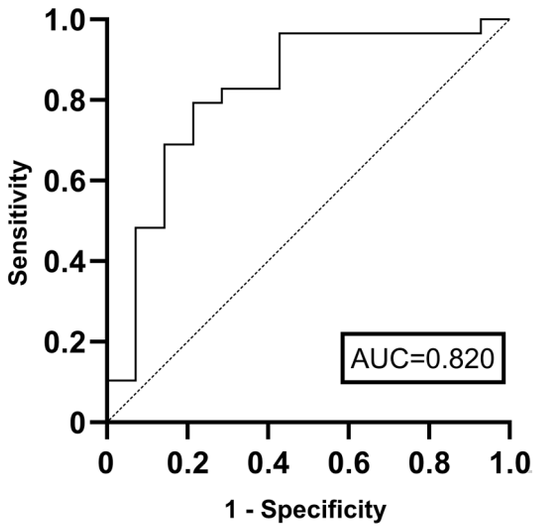

Figure 1 The ROC curve was adopted to analyze the efficiency of combined factors including age, disease duration, SLEDAI-2K score, ACL, cutaneous eruption ROC: Receiver operative characteristic; AUC: Area under curve; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; ACL: Anti-cardiolipin antibody.

Table 4 Multiple-factor binary logistic regression analysis for DED incidence in SLE patients

Parameters	*B*	SE	OR	95%CI	*P*
Age	0.028	0.034	1.028	0.962-1.099	0.415
Disease duration	-0.001	0.071	0.999	0.869-1.148	0.986
SLEDAI-2K	0.177	0.087	1.194	1.007-1.416	0.041
ACL	0.033	0.036	1.033	0.964-1.108	0.357
Cutaneous eruption	1.959	0.976	7.094	1.047-48.092	0.045

DED: Dry eye disease; SLE: Systemic lupus erythematosus; *B*: Regression coefficient; SE: Standard error; OR: Odds ratio; CI: Confidence interval; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000 score; ACL: Anti-cardiolipin antibody.

TFOS DEWS II reported that ocular symptoms including discomfort and visual disturbance remain fundamental component of DED[7]. The OSDI questionnaire was used to quantify and standardize symptoms of DED. In the current study, OSDI scores were higher in SLE patients than controls. Previous study reported that the increased risk of dry eye syndrome was observed in SLE patients[21]. Symptoms were generally consistent with DED, intermittent symptoms might suggest a pre-clinical state of DED. What's more, many patients complained of dry eye symptoms before they were diagnosed with autoimmune rheumatic diseases. Therefore, attention should be paid to the surveillance of DED as well as diagnosis of autoimmune rheumatic diseases among patients with dry eye symptoms.

A stable preocular tear film has long been viewed as manifestation of healthy ocular surface conditions[22]. The measurement of the tear breakup time (TBUT) is the most frequently employed test of tear film stability. Traditional TBUT was measured in an invasive manner by using fluorescein, which could contact the ocular surface tissue, and it is difficult to control the instilled volumes and concentrations of the fluorescein. What's more, measurement of traditional TBUT could be affected by subjectivity of the observer[12]. In recent years, the newly developed non-invasive technique Keratograph 5M was widely used to measure TBUT. The NIKBUT recorded with Keratograph allows evaluation of ocular surface non-invasively without interfering homeostasis of the tear film, with a sensitivity of 84.1% and a specificity of 75.6%[23]. This study showed that NIKBUT was statistically shorter in SLE patients than controls, suggesting poorer tear film stability in SLE patients. The result is in agreement with the result reported by Gu *et al*[20]. Precorneal tear film behaves as a single dynamic functional unit, the decrease of tear film stability may attribute to abnormalities of the lacrimal gland, conjunctiva, and meibomian gland in SLE patients[19]. In current study, normal subjects also showed variability in NIKBUT, which might attribute to their excessive exposure to air pollution, weather, unhealthy lifestyle, *etc*.

The preocular tear film provided the first refractive surface for light entering the eye, and the stability of the tear film could affect the optical quality of the eye[22]. The optical quality is related to each isolated refractive component of the whole eye, such as tear film, cornea, lens, vitreous body, *etc*. However, during a short period of 20s, the change of optical quality is mainly from tear film alternations. Real dynamic assessment of OSI has been developed to evaluate tear film optical quality[24]. OSI is a measurement of light scattering, the higher OSI indicate the greater scattering of light and the lower optical quality[25]. In this study, the mean tear film OSI in 20 successive seconds is significantly higher in SLE patients than controls, suggesting greater scattering of light and lower optical quality in SLE patients. Any factor that affects the stability of the tear film can cause increased light scattering, the difference might attributed to the unstable tear film in SLE patients. Tear film optical quality measurement could be a useful tool for monitoring and early prevention of DED in SLE patients[24]. To our knowledge, this is the first study conducted to evaluate tear film optical quality in SLE patients until now. There probably were limitations in detecting tools of optical quality in the past, resulting in an inadequate assessment and overlooking of the optical quality in SLE patients.

The tear film is composed of three layers including a mucin layer, an aqueous layer, and a lipid layer[22]. Meibomian glands secrete lipids onto the ocular surface and form the lipid layer of tear film, which could prevent the evaporation of the tear film[26]. Therefore, the LLT could be used as a representative indicator of meibomian gland function[22]. In this study, the mean LLT was thinner in SLE patients than

controls, which was consistent with lipid layer grades assessed in previous study using Keratograph 5M[20]. The results of current study suggested that lipid deficiency was presented in SLE patients. The thickness of tear film lipid layer was correlated with meibomian gland[27]. Previous studies reported meibomian gland alternations in SLE patients[28-29]. In the light of our findings and previous studies, we speculate that lipid deficiency might be attributed to meibomian gland abnormalities in SLE patients. Further researches are needed to delve into alternations of the meibomian gland structure and function in SLE patients. What's more, lipid-containing eye drops and physical treatments such as warm compress should be taken into consideration in clinical practice[30].

A population-based cohort study reported increased risk of DED and cornea damage in SLE patients[31]. Sodium fluorescein was widely used to evaluate corneal epithelial integrity, the occurrence of corneal fluorescein staining reflects the disruption of corneal epithelial integrity[32]. In current study, SLE patients exhibited higher CFS than controls, the result was consistent with the results reported by previous study[10], suggesting disruption of corneal epithelial integrity in SLE patients. The disruption of tear film lipid layer could accelerate the rate of tear evaporation, and thus leads to tear hyperosmolarity, which eventually contribute to the onset of DED[33]. Duru *et al*[34] reported that tear film hyperosmolarity was associated with SLE. Hyperosmolarity of tear film may disturb the homeostasis of ocular surface and thus result in damage of ocular surface epithelial integrity[33]. What's more, in current study, there was no significant difference between SLE patients and controls in TMH and SIT, the results was consistent with the results reported by Li *et al*[28], suggesting that SLE patients may not have a severe aqueous deficiency.

The SLEDAI-2K was employed as a clinical index for the measurement of disease activity, which consisted of variables including clinical manifestations and laboratory investigations in SLE patients[14]. High disease activity in SLE patients is associated with an increased risk of organ damage[35]. SLE patients recruited in this study were divided into DED group and non-DED group according to TFOS DEWS II diagnostic criteria. Disease activity, clinical manifestations and laboratory investigations were compared, and there were significant differences in terms of SLEDAI-2K score, proportion of cutaneous eruption, serum concentration of ACL between the two groups, indicating that these factors might be associated with occurrence of DED in SLE patients. Further regression analysis was conducted to explore the impact of these factors on the development of DED. Age, disease duration, SLEDAI-2K score, ACL, and cutaneous eruption were taken into model for multiple-factor binary logistic regression analysis. The efficiency of combined factors to discriminate DED and non-DED in SLE patient was evaluated by ROC curves. The results showed that SLEDAI-2K score and cutaneous eruption were risk factors of DED in SLE patients, the results was consistent with the results reported by previous study[11]. Previous investigations of the correlation between DED and SLE disease activity in SLE patients are rare. Chen *et al*[10] reported that the severity of dry eye syndrome is correlated with anti-double-strand DNA antibody and complement 3. Gu *et al*[20] reported that SLEDAI score was higher in SLE patients with DED than without DED. Both abnormalities of clinical manifestations and laboratory investigation reflect ongoing disease activity. In the light of our findings and previous studies, we speculate that SLE disease activity might contribute to development of DED in SLE patients. Therefore, high disease activity should alert the ophthalmologists and rheumatologists to the likely presence of DED in SLE patients in clinical practice. The ROC curve showed that AUC of the combined factors was between 0.7 and 0.9, indicating that the efficiency of these factors for discriminating DED was moderate. These factors may have further practical clinical applications.

There were still certain limitations of the current study: 1) This was a cross-sectional study, which limits the generalization of the results. 2) The participants were only recruited from the Second Hospital of Shandong University, thus there may be bias generated from territorial restrictions.

In conclusion, DED was more commonly observed in SLE patients, the symptoms and signs of DED were more severe in SLE patients. The combined factors of age, disease duration, SLEDAI-2K score, ACL, cutaneous eruption showed a moderate efficiency for the discrimination of DED in SLE patients. Special attention should be paid to SLEDAI-2K score and cutaneous eruption, which were significantly associated with DED in SLE patients. The findings of current study suggest the necessity for regular ophthalmology visit and follow-up of patients with SLE. The early diagnosis is the key to a better management and successful treatment for DED, these findings might aid in prevention and diagnosis of DED for clinicians.

ACKNOWLEDGEMENTS

Conflicts of Interest: Kang SF, None; **Wang YX,** None; **Zhang QC,** None; **Wang ZL,** None; **Chen GL,** None.

REFERENCES

1 Aringer M, Costenbader K, Daikh D, *et al*. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis* 2019;78(9):1151-1159.

2 Fatoye F, Gebrye T, Mbada C. Global and regional prevalence and incidence of systemic lupus erythematosus in low-and-middle income countries: a systematic review and meta-analysis. *Rheumatol Int* 2022;42(12):2097-2107.

3 Tian JR, Zhang DY, Yao X, Huang YQ, Lu QJ. Global epidemiology of systemic lupus erythematosus: a comprehensive systematic analysis and modelling study. *Ann Rheum Dis* 2023;82(3):351-356.

4 Román Ivorra JA, Fernández-Llanio-Comella N, San-Martín-Álvarez A, *et al*. Health-related quality of life in patients with systemic lupus erythematosus: a Spanish study based on patient reports. *Clin Rheumatol* 2019;38(7):1857-1864.

5 Kariburyo F, Xie L, Sah J, Li N, Lofland JH. Real-world medication use and economic outcomes in incident systemic lupus erythematosus patients in the United States. *J Med Econ* 2020;23(1):1-9.

6 Dias-Santos A, Tavares Ferreira J, Pinheiro S, Cunha JP, Alves M, Papoila AL, Moraes-Fontes MF, Proença R. Ocular involvement in systemic lupus erythematosus patients: a paradigm shift based on the experience of a tertiary referral center. *Lupus* 2020;29(3):283-289.

7 Craig JP, Nichols KK, Akpek EK, *et al*. TFOS DEWS II definition and classification report. *Ocul Surf* 2017;15(3):276-283.

8 Stapleton F, Alves M, Bunya VY, *et al*. TFOS DEWS II epidemiology report. *Ocul Surf* 2017;15(3):334-365.

9 Wang LX, Xie Y, Deng YP. Prevalence of dry eye in patients with systemic lupus erythematosus: a meta-analysis. *BMJ Open* 2021;11(9): e047081.

10 Chen A, Chen HT, Hwang YH, Chen YT, Hsiao CH, Chen HC. Severity of dry eye syndrome is related to anti-dsDNA autoantibody in systemic lupus erythematosus patients without secondary Sjogren syndrome: a cross-sectional analysis. *Medicine (Baltimore)* 2016;95(28):e4218.

11 Wang A, Gu ZY, Liao RF, Shuai ZW. Dry eye indexes estimated by keratograph 5M of systemic lupus erythematosus patients without secondary sjögren's syndrome correlate with lupus activity. *J Ophthalmol* 2019;2019:8509089.

12 Wolffsohn JS, Arita R, Chalmers R, *et al*. TFOS DEWS II diagnostic methodology report. *Ocul Surf* 2017;15(3):539-574.

13 Vitali C, Bombardieri S, Jonsson R, *et al*. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;61(6):554-558.

14 Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002;29(2):288-291.

15 Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the ocular surface disease index. *Arch Ophthalmol* 2000;118(5):615-621.

16 Whitcher JP, Shiboski CH, Shiboski SC, *et al*. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's Syndrome International Registry. *Am J Ophthalmol* 2010;149(3):405-415.

17 Wang H, Wang PB, Chen T, Zou J, Li YJ, Ran XF, Li QX. Analysis of clinical characteristics of immune-related dry eye. *J Ophthalmol* 2017;2017:8532397.

18 Shan HM, Liu WH, Li YY, Pang KP. The autoimmune rheumatic disease related dry eye and its association with retinopathy. *Biomolecules* 2023;13(5):724.

19 Musa M, Chukwuyem E, Ojo OM, Topah EK, Spadea L, Salati C, Gagliano C, Zeppieri M. Unveiling ocular manifestations in systemic lupus erythematosus. *J Clin Med* 2024;13(4):1047.

20 Gu ZY, Lu QY, Zhang A, Shuai ZW, Liao RF. Analysis of ocular surface characteristics and incidence of dry eye disease in systemic lupus erythematosus patients without secondary Sjögren's syndrome. *Front Med* 2022;9:833995.

21 Hsu CS, Hsu CW, Lu MC, Koo M. Risks of ophthalmic disorders in patients with systemic lupus erythematosus -a secondary cohort analysis of population-based claims data. *BMC Ophthalmol* 2020;20(1):96.

22 Willcox MDP, Argüeso P, Georgiev GA, *et al*. TFOS DEWS II tear film report. *Ocul Surf* 2017;15(3):366-403.

23 Hong JX, Sun XH, Wei AJ, Cui XH, Li YM, Qian TT, Wang WT, Xu JJ. Assessment of tear film stability in dry eye with a newly developed keratograph. *Cornea* 2013;32(5):716-721.

24 Wu MF, Gao H, Zhao LJ, Chen H, Huang YK. Real dynamic assessment of tear film optical quality for monitoring and early prevention of dry eye. *Medicine (Baltimore)* 2020;99(31):e21494.

25 Pan AP, Ma YJ, Hu RL, Cao XJ, Wu YF, Zhou KJ, Tu RX, Shao X, Chen SH, Yu AY. Simultaneous real-time analysis of tear film optical quality dynamics and functional visual acuity in dry eye disease. *Eye Vis(Lond)* 2023;10(1):16.

26 Xu XJ, Li GL, Zuo YY. Effect of model tear film lipid layer on water evaporation. *Invest Ophthalmol Vis Sci* 2023;64(1):13.

27 Bai YQ, Ngo W, Khanal S, Nichols KK, Nichols JJ. Human precorneal tear film and lipid layer dynamics in meibomian gland dysfunction. *Ocul Surf* 2021;21:250-256.

28 Li YX, Ou SK, Lin SJ, Qian HY, Zhao ZY, Zhang MQ, Li SY, Liu Y, Shi GX. Meibomian gland alteration in patients with systemic lupus erythematosus. *Lupus* 2022;31(4):407-414.

29 Yılmaz Tuğan B, Sönmez HE, Şahin N, Yüksel N. Analysis of meibomian glands in juvenile systemic lupus erythematosus patients without dry eye symptoms and signs. *Jpn J Ophthalmol* 2023;67(1):32-37.

30 Jones L, Downie LE, Korb D, *et al*. TFOS DEWS II management and therapy report. *Ocul Surf* 2017;15(3):575-628.

31 Tseng CH, Tai YH, Hong CT, Dai YX, Chen TJ, Cherng YG, Lai SC. Systemic lupus erythematosus and risk of dry eye disease and corneal surface damage: a population-based cohort study. *Int J Environ Res Public Health* 2023;20(5):3776.

32 Komai S, Yokoi N, Kato H, Komuro A, Sonomura Y, Kinoshita S, Sotozono C. Clinical implication of patchy pattern corneal staining in dry eye disease. *Diagnostics* 2021;11(2):232.

33 Zemanová M. Dry eye disease. A review. *Cesk Slov Oftalmol* 2021;77(3):107-119.

34 Duru N, Altinkaynak H, Uysal BS, Duru Z, Can ME, Erten S, Yuksel N, Kalkan Akcay E. Increased tear film osmolarity in systemic lupus erythematosus. *Semin Ophthalmol* 2017;32(5):582-587.

35 Hill DD, Eudy AM, Egger PJ, Fu QG, Petri MA. Impact of systemic lupus erythematosus disease activity, hydroxychloroquine and NSAID on the risk of subsequent organ system damage and death: analysis in a single US medical centre. *Lupus Sci Med* 2021;8(1):e000446.