DOI: 10.14744/eer.2021.39974
Eur Eye Res 2021;1(2):69–74

EUROPEAN EYE RESEARCH

ORIGINAL ARTICLE

Ocular surface changes and meibomian gland dysfunction evaluation in patients with Stevens–Johnson syndrome

Irmak Karaca, Ozlem Barut Selver, Melis Palamar, Sait Egrilmez, Ayşe Yağcı

Department of Ophthalmology, Ege University Faculty of Medicine, Izmir, Turkey

Abstract

Purpose: The purpose of the study was to assess the ocular surface changes and Meibomian gland (MG) dysfunction with meibography in patients with chronic ocular involvement due to Stevens–Johnson syndrome (SJS).

Methods: Twelve eyes of 6 patients with SJS who had chronic ocular involvement (Group 1) and 64 eyes of 32 healthy individuals (Group 2) were enrolled. Comprehensive eye examination including Schirmer 1 test, tear film break-up time (t-BUT), fluorescein staining of ocular surface and Oxford scoring, ocular surface disease index (OSDI) questionnaire, and assessment of lower and upper eyelid MG (from grade 0 [no loss of MG] to grade 3 [>2/3 gland loss of the total MG]) with an infrared filter of slit-lamp biomicroscope was performed.

Results: The mean ages of Group 1 and Group 2 were 42.2±9.9 (range, 31–58) and 45.4±11.7 (range, 33–59), respectively (p=0.667). In Group 1, mean best-corrected visual acuity, Schirmer 1 test, and t-BUT were lower, while Oxford scale and OSDI scores were higher significantly in comparison to Group 2 (p<0.05). The lower, upper and total (upper+lower) meiboscores were 2.7±0.4 (range, 2–3), 2.8±0.3 (range, 2–3), and 5.6±0.5 (range, 5–6) respectively, and significantly higher than Group 2 (p<0.001, for all variables).

Conclusion: SJS seems to be associated with severe MG dysfunction that can objectively be demonstrated with meibography, in addition to other ocular surface problems. Future studies are needed to validate these findings.

Keywords: Dry eye; meibography; meibomian gland dysfunction; ocular surface; Stevens–Johnson syndrome.

Stevens–Johnson syndrome (SJS) is a rare, but severe, immune-mediated, mucocutaneous disorder with high morbidity and mortality rates.[1] SJS is mostly triggered by certain medications and infections in a genetically susceptible individual.[2] When the disease is initiated, it is represented by extensive, rapid apoptosis of keratinocytes with epidermal necrosis, significant inflammation, and loss of surface epithelium.[1,3,4] Besides skin and mucous membranes, ocular surface is one of the main sites being involved during the disease pathogenesis.[4,5] Although SJS is a self-limited disease and systemic findings usually subside within 2 months after the onset, ocular surface inflammation may persist and cicatrization of the ocular surface may progress, leading to ocular discomfort and even

Cite this article as: Karaca I, Barut Selver O, Palamar M, Egrilmez S, Yağcı A. Ocular surface changes and meibomian gland dysfunction evaluation in patients with Stevens–Johnson syndrome. Eur Eye Res 2021;1:69-74.

Correspondence: Irmak Karaca, M.D. Department of Ophthalmology, Ege University Faculty of Medicine, Izmir, Turkey
Phone: +90 232 388 14 69 **E-mail:** irmakkaracamd@gmail.com
Submitted Date: 08.03.2021 **Accepted Date:** 08.04.2021

visual loss.[6,7] Ocular surface involvement with chronic inflammation, desiccation, and scarring is assumed to be the most dreadful and important sequelae of SJS, as it concerns 20–79% of the survivors and may potentially end up with blindness.[4]

Dry eye syndrome (DES) is known to be the major ocular sequela in the long-term follow-up of SJS.[7,8] In addition to decreased wettability due to corneal surface alterations through squamous metaplasia/keratinization, it has been shown that both "aqueous deficient" and "evaporative" type DES are involved in the ocular sequelae of SJS at the chronic stage.[7] While severe aqueous deficient DES was detected in 55.2% of the cases,[9] severe Meibomian gland (MG) involvement was indicated as the second most common ocular complication at the chronic stage of SJS following the loss of Vogt palisades (73.9% and 82.6%, respectively).[10] However, MG health and functions were frequently assessed with clinical observation or digital pressure on slit lamp biomicroscope in those previous reports.[9–11] Furthermore, as evaporative DES is primarily linked to MG dysfunction and tear lipid layer abnormalities,[12] objective evaluation of MG changes in patients with SJS carries special importance.

Meibography is a non-invasive and objective tool in terms of assessing the morphological changes and the dropout in MG.[13] Among various technologies, infrared meibography is the current choice of use in clinical practice for the investigation of MG dysfunction in several disorders.[14,15] To date, there are few studies demonstrating MG loss with meibography in patients with SJS.[7,16–18] However, there is no prospective, controlled study on this topic yet, and there was only limited information about other DES tests, particularly the subjective dry eye symptoms. Therefore, this study aimed to thoroughly assess ocular surface changes and MG dysfunction with meibography in patients with SJS who had chronic ocular involvement.

Materials and Methods

This prospective, cross-sectional observational study enrolled 12 eyes of 6 patients (4 female, 2 male) with SJS who had chronic ocular involvement for more than 5 years (Group 1), and 64 eyes of 32 age- and sex-matched healthy subjects (22 female and 10 male) (Group 2). All patients in Group 1 had already been diagnosed as SJS previously and were followed for their chronic ocular involvement. Subjects with a history of smoking, contact lens wear, topical anti-glaucoma medication use, ocular surgery or trauma, and any other systemic or ocular surface diseases were excluded. Institutional Review Board of our university approved the study. Each participant stated a written informed consent before the examination, and the tenets of Helsinki Declaration were followed.

Detailed eye examination was performed to all participants sequentially as follows: Slit-lamp anterior segment and fundus examination including assessment of eyelid margin abnormalities, Oxford scoring following 2% fluorescein staining of the ocular surface, tear film break-up time (t-BUT), and Schirmer 1 test.[14,19] Subjective dry eye symptoms were evaluated with the ocular surface disease index (OSDI) questionnaire.

Eyelid margin abnormalities were identified as 0 or 1 for either absence or presence of the following changes, respectively: plugging in the MG orifices, vascular engorgement, irregular eyelid margin, and anterior/posterior displacement of the mucocutaneous junction.[20]

Noncontact infrared meibography set on a slit lamp biomicroscope (SL-D701 with DC-4 digital camera and BG-5 background illuminator, TOPCON, Tokyo, Japan) was used to assess partial/complete dropout of the MG following eversion of the eyelids in all subjects. Grading of the gland loss was noted as grade 0 (no loss of MG), grade 1 (gland loss <1/3 of the total MG), grade 2 (gland loss 1/3–2/3 of the total MG), and grade 3 (gland loss >2/3 of the total MG) for each eyelid by the masked researcher.[14] The meiboscores of the lower, upper, and total (upper and lower) eyelids were summed for each eye.

The long-term ocular sequela other than MG loss, including limbal stem cell deficiency (LSCD), punctal occlusion, and symblepharon formation, were also evaluated as either absent or present on examination by slit lamp biomicroscope. The LSCD was diagnosed according to clinical findings of the conjunctivalization such as corneal epithelial haze, loss of limbal Vogt palisades, neovascularization, and opacification of cornea.[21]

Statistical analysis was conducted with SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Data of the right eyes were used in the statistical analysis. Mann–Whitney U test and Fisher's exact test were used to compare continuous and categorical variables between the groups, respectively. $P<0.05$ was considered to be statistically significant.

Results

The mean age of Group 1 and Group 2 were 42.2±9.9 (range, 31–58) and 45.4±11.7 years (range, 33–59), respectively ($p=0.667$). Best-corrected visual acuity of Group 1 was significantly lower than Group 2 (0.9±0.9 [range, 0–3] vs. 0.0±0.0 [range, 0–0]) ($p<0.001$).

Table 1. The clinical characteristics of the SJS patients and healthy controls

	SJS patients (Group 1) (Mean±SD, range)	Healthy controls (Group 2) (Mean±SD, range)	p-value
Male-to-female ratio (M:F)	2:4	10:22	0.543
Mean age (years)	42.2±9.9 (31–58)	45.4±11.7 (33–59)	0.667
BCVA (LogMAR)	0.9±0.9 (0–3)	0.0±0.0 (0–0)	<0.001
Triggering agents –			
Medications	6 (100%)		
NSAIDs	3 (50%)		
Carbamazepine	1 (13.3%)		
Valproic acid	1 (13.3%)		
Lamotrigine	1 (13.3%)		

BCVA: Best-corrected visual acuity; NSAID: Non-steroidal anti-inflammatory drugs; SJS: Stevens–Johnson syndrome.

The age for SJS onset ranges from 14 to 48 years. The triggering agents were medications in all patients with SJS. The clinical characteristics of Group 1 were given in Table 1. In Group 1 patients, Schirmer 1 test and t-BUT values were significantly lower, while Oxford and OSDI scores were significantly higher as compared to Group 2 (Table 2). Besides, OSDI scores had a significant negative correlation with Schirmer 1 test and t-BUT values, whereas positive correlation with upper, lower, and total meiboscores ($p<0.001$, Spearman correlation analysis). The mean lower, upper, and total eyelid meiboscores in Group 1 were 2.7±0.4 (range, 2–3), 2.8±0.3 (range, 2–3), and 5.6±0.5 (range, 5–6), respectively (Figs. 1 and 2). Nine eyes (75%) had grade 3 MG loss, and among them, 6 eyes (50%) had total MG dropout. The difference between meiboscores of the groups for both lower upper and total eyelids was statistically significant ($p<0.001$, for all variables) (Table 2).

Evaluation of eyelid margin abnormalities revealed that none of the patients had plugged MG orifices, 10 (83.3%) eyes had vascular engorgement, 6 (50%) eyes had irregular eyelid margin, and 9 (75%) eyes had displaced mucocutaneous junction in Group 1 (Table 2).

Regarding other long-term sequelae, total punctual occlusion was observed in 1 eye (8.3%), whereas none of the pa-

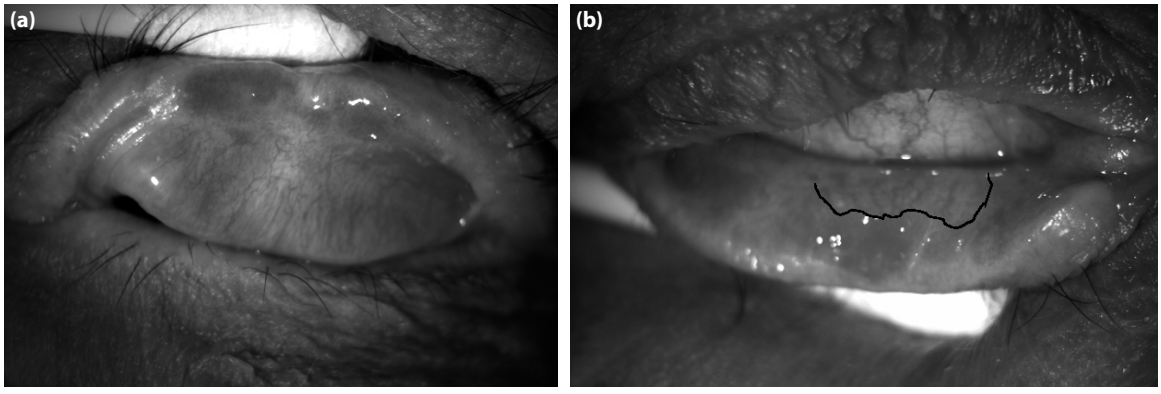

Fig. 1. **(a)** The upper and **(b)** lower meibography appearances of a patient with SJS. The only viable Meibomian gland area was pointed with black line.

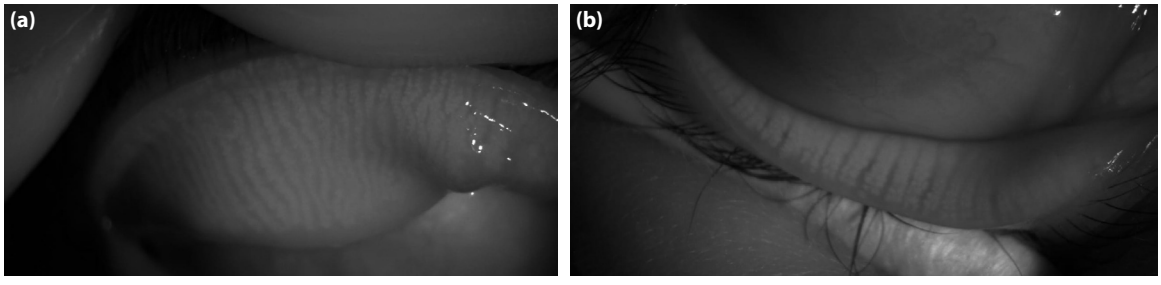

Fig. 2. **(a)** The upper and **(b)** lower meibography appearances of a healthy subject. No meibomian gland loss was observed.

Table 2. The dry eye tests and meiboscores of SJS patients and healthy controls

	SJS patients (Group 1) (Mean±SD, range)	Healthy controls (Group 2) (Mean±SD, range)	p-value
Schirmer 1 (mm)	1.5±1.2 (0–5)	25.2±4.9 (14–30)	<0.001
t-BUT (sec)	1.3±2.6 (0–8)	14.6±3.8 (10–23)	<0.001
Oxford score	3.7±1.6 (2–5)	0.1±0.1 (0–1)	<0.001
OSDI score	87.6±12.9 (62.5–93.8)	10.7±4.8 (2.1–22.7)	<0.001
Total eyelid abnormality score	2.1±0.8 (2–3)	0.4±0.1 (0–1)	<0.001
Upper meiboscore	2.8±0.3 (2–3)	0.7±0.3 (0–1)	<0.001
Lower meiboscore	2.7±0.4 (2–3)	0.3±0.2 (0–1)	<0.001
Total meiboscore	5.6±0.5 (5–6)	1.3±0.4 (0–2)	<0.001

SD: Standard deviation; t-BUT: Tear break-up time; OSDI: Ocular surface disease index. SJS: Stevens–Johnson syndrome.

tients had either punctual plug or surgical punctual ablation. Mild-to-moderate LSCD and symblepharon formation were present in all patients.

Discussion

This cross-sectional observational study assessed the alterations in the ocular surface along with MG dysfunction in patients with SJS who had chronic ocular involvement for more than 5 years. The results indicated significant MG loss in SJS as compared to healthy controls which are objectively demonstrated with infrared meibography.

SJS is a life-threatening but self-limited disease with a gradual decrease in systemic signs in a few months after the onset.[7] However, ocular inflammation may prolong, and extensive increase in pro-inflammatory markers in addition to epithelial loss may adversely affect the ocular surface health.[3,7] While acute involvement of the ocular structures was detected in 50–88% of the cases, chronic ocular sequela composes one of the most important long-term complications in these patients, with the rate of 35%.[11,22] Besides, in spite of no association between acute ocular involvement and SJS disease severity,[11] ocular sequela was directly related to the severity of the ocular involvement at the acute stage.[7,8,11] Sotozono et al.[7,8] reported that the DES prevalence at the chronic stage rises with the increase of acute ocular severity. In addition, Sotozono et al.[10] proposed a grading system for the severity of chronic ocular manifestations which indicated MG dysfunction as a second most common long-term ocular complication. All these findings signify the objective assessment of MG dysfunction in these patients, particularly at the chronic stage. Recently, Shrestha et al.[18] retrospectively evaluated 16 SJS cases with Keratograph in terms of MG loss and demonstrated MG dysfunction in 87.5% of the patients with the mean total meiboscore of 3.6±1.9. They established a significant correlation between the severity of MG parameters (meiboscores, meibum expressibility score, and meibum quality score) and acute ocular involvement score, acute systemic involvement score, and chronic ocular manifestation score. They suggested the presence of acute ocular complications as a risk factor for severe MG dysfunction in SJS. Lekhanont et al.[17] also reported mild-to-severe MG dysfunction in all of 32 Thai patients with SJS who had the disease for at least 1 year. There was severe MG loss in the vast majority (81.3%), while total MG loss was seen in 62.5% (n=20) of the study population. The present study demonstrated that 83.3% of SJS patients had grade 3 MG loss and the mean total meiboscore value was 5.7±0.6, all of which are consistent with the literature. Besides, despite the absence of acute stage findings, all patients with SJS in this study had the disease for more than 5 years, which seems quite longer than the other study reports.[17,18] Therefore, it may be thought that MG dysfunction may become more profound as the disease duration increases, as well as the more prominent decrease in Schirmer 1 test and t-BUT values.

There are several causes leading to DES in patients with SJS.[4,7,11] Aside from aqueous DES mainly caused by injury to lacrimal gland and associated ducts, significant inflammation along with necrosis of the conjunctiva in the acute stage induces destruction of goblet cells and a decrease in mucin production. Corneal epithelial injury precipitated by LSCD interferes with tear adhesion. All these changes lead to tear film instability, lipid layer deficiency, and evaporative DES at the end.[11] Eyelid complications and conjunctival retraction also incite a mechanical effect that increases the evaporation of the tear film. In addition, tarsal conjunctival scarring may be related to duct obliteration and atrophy in MG, as well as eyelid abnormalities including trichiasis and distichiasis which are also linked to metaplastic changes in MG.[4] In the present study, 5 of 6 SJS patients (83.3%) had displaced mucocutaneous junction, and all patients (100%) showed some degree of tarsal conjunctival scarring. These

findings also supported the presence of severe MG dysfunction in the study group. On the other hand, Shrestha et al.[18] excluded SJS patients who had eyelid abnormalities. In addition to the lack of data regarding SJS disease duration, this exclusion might have ended up with mild MG involvement in their study.

DES is a symptomatic disease, and moderate-to-severe DES is linked to significant ocular discomfort, restriction in daily activities, limited life motivation, and possibly depression.[23] In this regard, OSDI questionnaire assesses the frequency of DES-related symptoms, effects of the environment, and vision-related life quality.[24] Unlike the other studies,[16–18] the present study evaluated patients with SJS in terms of subjective DES symptoms as well and demonstrated significantly higher OSDI scores as compared to healthy controls. In addition, OSDI scores were significantly correlated with meiboscores, Schirmer 1 test, and t-BUT values in this study. Previously, Kaido et al.[25] also reported significantly reduced National Eye Institute Visual Function Questionnaire-25 scores in SJS patients. These results give an objective insight on the severity of ocular discomfort in patients with SJS, as well as the degree of suffering from DES in their daily life.

This study has some limitations, including small sample size, cross-sectional methodology, and lack of acute-phase data of the patients. On the other hand, this is the first controlled study assessing SJS patients regarding MG dysfunction with meibography objectively. For sure, race, age, sex, and especially genetic susceptibility of the study participants might have affected the results of the present study. However, despite the low number of patients, we thought that this severe MG involvement is significant enough to document and broaden the literature for the ocular surface health of patients with SJS. Future prospective cohort studies with a larger sample size assessing the course of the disease in terms of acute stage findings, MG dysfunction, and other DES parameters would give more idea about the disease pathogenesis and the outcomes for each disease severity stage. Besides, this is the first study that interpreted meibography and other objective DES tests with subjective symptoms at the same time in these patients. The significant correlation between objective DES tests, meiboscores, and OSDI scores also indicated the importance of how severely the patients with SJS are suffering from that ocular surface problem in their daily life.

Conclusion

SJS seems to be associated with DES and particularly severe MG dysfunction at the chronic stage. In addition to severe meibography and DES test results, the patients with SJS are highly symptomatic due to these ocular surface alterations. Therefore, not only systemic interventions for this rare disease but also intensive ocular treatment should be provided to these patients starting from the acute stage of the disease to prevent possible catastrophic complications and relieve their symptoms.

Ethics Committee Approval: This study was approved by Ege University Faculty of Medicine Ethics Committee (date: 29.05.2019; number: 19-5.2T/47).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: I.K., O.B.S., M.P., A.Y.; Design: O.K., O.B.S., M.P., A.Y.; Supervision: M.P., A.Y., S.E.; Resource: M.P., S.E.; Materials: M.P., S.E., A.Y.; Data Collection and/or Processing: I.K., O.B.S., M.P.; Analysis and/or Interpretation: I.K., O.B.S., M.P.; Literature Search: I.K., O.B.S., M.P.; Writing: I.K., O.B.S., M.P.; Critical Reviews: M.P.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Kohanim S, Palioura S, Saeed HN, et al. Stevens-Johnson syndrome/toxic epidermal necrolysis--a comprehensive review and guide to therapy. I. systemic disease. Ocul Surf 2016;14:2–19. [CrossRef]
2. Sassolas B, Haddad C, Mockenhaupt M, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: Comparison with case-control analysis. Clin Pharmacol Ther 2010;88:60–8. [CrossRef]
3. Chung WH, Hung SI, Yang JY, et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. Nat Med 2008;14:1343–50. [CrossRef]
4. Kohanim S, Palioura S, Saeed HN, et al. Acute and chronic ophthalmic involvement in stevens-johnson syndrome/toxic epidermal necrolysis a comprehensive review and guide to therapy. II. Ophthalmic disease. Ocul Surf 2016;14:168–88.
5. Saeed HN, Chodosh J. Ocular manifestations of Stevens-Johnson syndrome and their management. Curr Opin Ophthalmol 2016;27:522–9. [CrossRef]
6. Power WJ, Ghoraishi M, Merayo-Lloves J, Neves RA, Foster CS. Analysis of the acute ophthalmic manifestations of the erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis disease spectrum. Ophthalmology 1995;102:1669–76. [CrossRef]
7. Sotozono C, Ueta M, Yokoi N. Severe dry eye with combined mechanisms is involved in the ocular sequelae of SJS/TEN at the chronic stage. Invest Ophthalmol Vis Sci 2018;59:DES80–6.
8. Sotozono C, Ueta M, Nakatani E, et al. Predictive factors associated with acute ocular involvement in Stevens-Johnson syndrome and toxic epidermal Necrolysis. Am J Ophthalmol

2015;160:228–3700. [CrossRef]
9. Di Pascuale MA, Espana EM, Liu DT, et al. Correlation of corneal complications with eyelid cicatricial pathologies in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis syndrome. Ophthalmology 2005;112:904–12. [CrossRef]
10. Sotozono C, Ang LP, Koizumi N, et al. New grading system for the evaluation of chronic ocular manifestations in patients with Stevens-Johnson syndrome. Ophthalmology 2007;114:1294–302. [CrossRef]
11. López-García JS, Rivas Jara L, García-Lozano CI, Conesa E, de Juan IE, Murube del Castillo J. Ocular features and histopathologic changes during follow-up of toxic epidermal necrolysis. Ophthalmology 2011;118:265–71. [CrossRef]
12. Shimazaki J, Sakata M, Tsubota K. Ocular surface changes and discomfort in patients with meibomian gland dysfunction. Arch Ophthalmol 1995;113:1266–70. [CrossRef]
13. Tomlinson A, Bron AJ, Korb DR, et al. The international workshop on meibomian gland dysfunction: Report of the diagnosis subcommittee. Invest Ophthalmol Vis Sci 2011;52:2006–49.
14. Arita R, Itoh K, Inoue K, Amano S. Noncontact infrared meibography to document age-related changes of the meibomian glands in a normal population. Ophthalmology 2008;115:911–5. [CrossRef]
15. Pult H, Riede-Pult BH. Non-contact meibography: Keep it simple but effective. Cont Lens Anterior Eye 2012;35:77–80. [CrossRef]
16. Alsuhaibani AH, Carter KD, Abràmoff MD, Nerad JA. Utility of meibography in the evaluation of meibomian glands morphology in normal and diseased eyelids. Saudi J Ophthalmol 2011;25:61–6. [CrossRef]
17. Lekhanont K, Jongkhajornpong P, Sontichai V, Anothaisintawee T, Nijvipakul S. Evaluating dry eye and meibomian gland dysfunction with meibography in patients with Stevens-Johnson syndrome. Cornea 2019;38:1489–94. [CrossRef]
18. Shrestha T, Moon HS, Choi W, et al. Characteristics of meibomian gland dysfunction in patients with Stevens-Johnson syndrome. Medicine (Baltimore) 2019;98:e16155. [CrossRef]
19. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea 2003;22:640–50. [CrossRef]
20. Arita R, Itoh K, Maeda S, et al. Proposed diagnostic criteria for obstructive meibomian gland dysfunction. Ophthalmology 2009;116:2058–630. [CrossRef]
21. Le Q, Xu J, Deng SX. The diagnosis of limbal stem cell deficiency. Ocul Surf 2018;16:58–69. [CrossRef]
22. Chang YS, Huang FC, Tseng SH, Hsu CK, Ho CL, Sheu HM. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis: acute ocular manifestations, causes, and management. Cornea 2007;26:123–9. [CrossRef]
23. Craig JP, Nelson JD, Azar DT, et al. TFOS DEWS II report executive summary. Ocul Surf 2017;15:802–12. [CrossRef]
24. Wolffsohn JS, Arita R, Chalmers R, et al. TFOS DEWS II diagnostic methodology report. Ocul Surf 2017;15:539–74. [CrossRef]
25. Kaido M, Yamada M, Sotozono C, et al. The relation between visual performance and clinical ocular manifestations in Stevens-Johnson syndrome. Am J Ophthalmol 2012;154:499–5110. [CrossRef]