Multistep Grading System for Evaluation of Chronic Ocular Sequelae in Patients With Stevens-Johnson Syndrome

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• PURPOSE: To propose a new scoring system for grading of chronic ocular sequelae in Stevens-Johnson syndrome (SJS).

• DESIGN: Reliability and validity analysis.

• METHODS: Participants: Four hundred eyes of 200 patients with chronic ocular SJS/toxic epidermal necrolysis (TEN) were included in the study. Settings: Single-center, tertiary eye care referral center. Procedure: All patients with SJS/TEN with chronic (more than 1 year) ocular sequelae were recruited for the study. Corneal, eyelid, and conjunctival signs were evaluated and given scores ranging from 0 to 5 depending on the increasing severity. Twelve signs (6 corneal, 3 conjunctival, and 3 eyelid) were evaluated to obtain the total severity score for each eye. Based on the corrected distance visual acuity (CDVA) and total score, each eye was graded using receiver operating characteristic (ROC) analysis. Main Outcome Measures: Correlation of CDVA with the severity score determined on the basis of 12 corneal, eyelid, and conjunctival signs.

• RESULTS: Mean age was 24.09 ± 10.9 years. The most common inciting agent for SJS was oral medications (85%). The scores of 12 ocular surface parameters correlated significantly with CDVA ($P < .001$). ROC analysis revealed 4 grades of total severity score of 0-11 (stage 0), 12-16 (stage 1), 17-22 (stage 2), and 23-53 (stage 3). The total severity score correlated significantly with logMAR visual acuity grades with an agreement of 60.7% using Cohen's kappa analysis (kappa coefficient = 0.420 ± 0.03). The most common stage of total severity score was stage 3 in 49% of eyes (196/400), followed by stage 0 (107/400, 26.7%).

• CONCLUSIONS: The multistep scoring system of chronic ocular features in SJS/TEN sequelae is a useful tool to grade all levels of severity. This may help to evaluate the efficacy of the surgical intervention by comparing preoperative with postoperative ocular grades. (Am J Ophthalmol 2019;203:69–77. © 2019 Elsevier Inc. All rights reserved.)

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STEVENS-JOHNSON SYNDROME (SJS)/TOXIC EPIDERMAL necrolysis (TEN) is a rare, life-threatening, immune complex–mediated hypersensitivity disorder characterized by mucocutaneous blister formation that may be incited by a number of drugs or infections.[1,2] It is a delayed hypersensitivity reaction that usually occurs after a dormancy of 4-28 days following the triggering event.[3–5] The condition can be classified as SJS, overlapping SJS-TEN, or TEN when skin surface involvement is less than 10%, 10%-30%, or more than 30%, respectively.[6] The incidence of SJS/TEN is 1.2 to 12.35 cases for every million population.[7–11] The medications associated with the SJS and TEN include sulfonamide antibiotics, carbamazepine, acetazolamide, phenobarbitol, allopurinol, nonsteroidal anti-inflammatory drugs, and others.[12] Rarely, infections with *Mycoplasma pneumonia* or herpes simplex virus may also trigger SJS and TEN.[13,14]

Ocular involvement occurs in 50%-100% of cases in the acute phase of SJS/TEN. Among them, approximately 35%-90% of cases have chronic ophthalmic sequelae. In the acute phase, ocular involvement may vary from a simple conjunctival hyperemia to extensive ocular involvement. Loss of goblet cells, lacrimal functioning unit disruption, and limbal stem cell injury can occur during the acute insult, which can lead to chronic ocular sequelae.[15–20]

Chronic ocular sequelae of SJS/TEN include conjunctivalization of the cornea, corneal keratinization, deep corneal vascularization, and symblepharon formation. The management and prognosis in such cases depends on the severity of the ocular changes. Thus, it is essential to have an objective method of scoring the ocular features in chronic SJS/TEN that will help in planning the treatment strategy and evaluating the efficacy of the management protocol. In 2007, Sotozono and associates gave a

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grading system for chronic ocular manifestations in SJS patients by evaluating 138 eyes with chronic SJS sequelae.[21] However, the presentation of the cases differs significantly in developing countries such as India. The cases that we see often present with greater severity than has been described in literature. Therefore, we believe a multistep grading system that takes into account more severe cases is required to include cases from this part of the world.

The aim of the study is to propose an objective method for the evaluation of chronic ocular manifestation in SJS/TEN sequelae to include all grades of severity. To the best of our knowledge, this is the largest study with the highest number of cases used to grade the ocular severity in SJS reported to date.

METHODS

THE STUDY INCLUDED ALL PATIENTS WITH CLINICALLY DIAGnosed chronic ocular SJS/TEN sequelae referred to the outpatient department of the Dr Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India from May 2011 to July 2017. Ethical approval was obtained from the Ethics Committee/Institutional Review Board of All India Institute of Medical Sciences, New Delhi, India. Cases with at least 1 year after onset of the disease and chronic ocular sequelae were recruited. Patients with history of any prior ocular surgery, systemically unstable patients, and patients who expressed their inability to follow up were excluded. A detailed history including demographic details, the inciting agents, and the initial treatment received were recorded in all the cases. All patients underwent a detailed ophthalmic examination including uncorrected distance visual acuity, spectacle-corrected distance visual acuity (CDVA), detailed slit-lamp examination with and without fluorescein staining, intraocular pressure measurement (using Tonopen; Reichert Technologies, New York, USA), Schirmer test, tear film break-up time (whenever possible), posterior segment B-scan ultrasonography (whenever required), and anterior segment clinical photography. The guidelines of the Declaration of Helsinki in Biomedical Research Involving Human Subjects were followed, and written informed consent was obtained from all patients.

Four hundred eyes of 200 patients were included in the study. The chronic ocular features of these eyes were divided into 3 main components: corneal, conjunctival, and eyelid features. Corneal features included conjunctivalization, loss of palisades of Vogt (POV), neovascularization, keratinization, epithelial defect, and opacification. Conjunctival features included hyperemia, keratinization, and symblepharon formation. Eyelid features included mucocutaneous junction involvement, meibomian gland involvement, and punctal involvement. The grading system by Sotozono and associates was modified to concentrate on all grades of severity of SJS/TEN sequelae reported, by giving a score from 0 to a maximum of 5 to each feature of the 3 main components.[21] Hence, each eye obtained total score from 0 to 53. The classification system used for ocular features of chronic of SJS/TEN patients is described in Table 1 (Figure 1 and 2). Apart from these features, the presence of other eye complications such as cataract, glaucoma, or posterior segment anomaly that may have an effect on the visual acuity were also evaluated.

Each eye was evaluated by 3 trained dedicated cornea specialists for different features as mentioned above, and a score was given to each feature. At the end, a sum of total score was obtained for each eye, which was in the range of 0-53, where 53 was defined as the most severe form of ocular involvement in SJS/TEN sequelae.

On the basis of CDVA on the day of presentation, all eyes were categorized into 4 grades: grade 1, CDVA up to 6/18 (up to logMAR 0.47) (n = 63 eyes); grade 2, less than 6/18 to 6/60 (logMAR 0.48 to 0.99) (n = 78 eyes); grade 3, less than 6/60 to 1/60 (1 meter finger counting) (log MAR 1 to 1.59) (n = 68 eyes); and grade 4, less than 1/60 (log MAR 1.6) (n = 191 eyes).

• **STATISTICAL ANALYSIS:** STATA ver. 9.0 software (StataCorp, USA) was used for all statistical analyses. Spearman correlation coefficient was used to evaluate all 12 parameters of ocular surface with logMAR CDVA. Further stepwise multivariate linear regression analysis was used to predict logMAR outcomes based on 12 parameters. Analysis of variance test was applied for comparison of various ocular features of SJS with CDVA based on various grades. Receiver operating characteristic (ROC) analysis was used for determining the cutoff score for total severity scores to categorize the eyes as mild, moderate, severe, and very severe. Cohen's kappa statistics were performed for analysis of agreement between total score categories and CDVA groups. All statistical analysis was done at 5% level of significance and 95% confidence interval.

RESULTS

THE BASELINE CHARACTERISTICS ARE SUMMARIZED IN Table 2. A total of 101 patients were male (50.5%) and 99 were female (49.5%), with age ranging from 6 to 60 years (mean ± standard deviation, 24.09 ± 10.9 years). Out of 200 patients, 31 patients (15.5%) were in the age group of 0-14 years. The mean time to the initial presentation after an acute episode of SJS/TEN was 7.2 ± 6.7 years. Out of 200 patients, 171 patients (85.5%) gave a confirmed history of SJS/TEN following oral medications while the remaining 29 patients (14.5%) gave a history of febrile illness preceding the acute SJS/TEN. Among the drugs known to be involved, nonsteroidal anti-inflammatory drugs (n = 78), antibiotics (n = 35), and antiepileptics

TABLE 1. Ocular Features for Grading of Chronic Ocular Changes in Stevens-Johnson Syndrome

Specific Structure Affected	Chronic Change	Score					
		0	1	2	3	4	5[a]
Corneal features	Conjunctivalization	Nil	Up to 90 degrees clock hours of limbus	Up to 180 degrees clock hours	Up to 270 degrees clock hours	Up to 360 degrees clock hours	End-stage disease
	Loss of palisades of Vogt	Nil	Up to 90 degrees clock hours of Limbus	Up to 180 degrees clock hours	Up to 270 degrees clock hours	Up to 360 degrees clock hours	End-stage disease
	Corneal neovascularization	Nil	Up to 90 degrees clock hours of Limbus	Up to 180 degrees clock hours	Up to 270 degrees clock hours	Up to 360 degrees clock hours	End-stage disease
	Corneal keratinization	Nil	One quarter of corneal surface	One quarter to half of corneal surface	Half to three quarters of corneal surface	More than three quarters to complete corneal surface	End-stage disease
	Corneal epithelial defect	No stain	Punctate epithelial staining	Any size of epithelial defect	Cannot comment because of conjunctivalization, keratinization, or total symblepharon	-	-
	Corneal opacification	Nil	Very mild haze, pupil and iris details clear	Mild haze, pupil detail clear while iris detail hazy	Haze, both iris and pupil details hazy	Severe haze, pupil and iris not visible	End-stage disease
Eyelid features	Mucocutaneous junction involvement	No irregularity	Mild involvement	Moderate	Severe involvement	Total symblepharon, not able to evert the lid	End-stage disease
	Meibomian gland involvement	Clear oily fluid secretion	Yellowish white fluid	Thick cheesy fluid	Not able to express the fluid	-	-
	Punctal involvement	both puncta are patent	1 punctum is occluded	Both puncta are occluded	-	-	-

Continued on next page

TABLE 1. Ocular Features for Grading of Chronic Ocular Changes in Stevens-Johnson Syndrome (*Continued*)

Specific Structure Affected	Chronic Change	Score					
		0	1	2	3	4	5[a]
Conjunctival features	Hyperemia	Nil	hyperemia in one quarter of bulbar conjunctival surface	More than one quarter to up to half conjunctival surface	More than half to three quarters	More than three quarters to near-total conjunctival surface	End-stage disease
	Keratinization	Nil	Up to one quarter of bulbar conjunctival surface	More than one quarter to up to half conjunctival surface	More than half to three quarters	More than three quarters to near-total conjunctival surface	End-stage disease
	Symblepharon	Nil	Not involving corneal surface	Up to a third of the corneal surface	A third to two thirds of corneal surface involvement	Two thirds to total corneal surface	End-stage disease

[a]During end-stage disease, ankyloblepharon is seen and it is not possible to assess the underlying parameters.

(n = 18) were the most commonly identified medications responsible for SJS/TEN. In 40 patients, the medication could not be traced because of simultaneous use of multiple oral medications.

• **CORRELATION OF SCORES OF 12 OCULAR SURFACE COMPONENTS WITH CORRECTED DISTANCE VISUAL ACUITY:** The mean age of the study group did not correlate with logMAR CDVA. Corneal, conjunctival, and eyelid parameters correlated significantly with CDVA ($P = .001$). Among the 12 ocular parameters, conjunctivalization of the cornea, loss of POV, and opacification were strongly correlated with poor visual acuity (correlation coefficient of 0.78, 0.77, and 0.76, respectively) (Table 3). The multivariate regression analysis revealed that corneal conjunctivalization (coefficient = 0.2841), opacification (coefficient = 0.2012), symblepheron formation (coefficient = 0.1047), punctal involvement (coefficient = 0.0994), and meibomian gland involvement (coefficient = -0.0741) had a statistically significant effect on logMAR visual acuity outcomes (Table 4).

• **CORRELATION OF GRADES OF CORRECTED DISTANCE VISUAL ACUITY WITH 12 OCULAR SURFACE COMPONENTS:** Clinical parameters were also correlated with different grades of CDVA using the analysis of variance test (Table 5). The age of the patient did not correlate significantly with the grades of CDVA, affirming that ocular sequelae in SJS are not dependent on age in our study. The corneal, conjunctival, and eyelid parameters correlated significantly with CDVA ($P < .05$). The mean score of each parameter increased with decrease in CDVA. Among the corneal features, the mean scores of conjunctivalization, loss of POV, and vascularization were higher in grade 3 as compared to grade 2, and this was statistically significant ($P = .01$, $P = .01$). Among the eyelid features, the mean score of punctal involvement was significantly higher in grade 3 than in grade 2 ($P = .01$). Among the conjunctival features, conjunctival hyperemia and keratinization were significantly higher in grade 3 than in grade 2 ($P = .01$).

Eyes in each grade (based on presenting CDVA) had total scores in the range of 0-11 in stage 0, 12-16 in stage 1, 17-22 in stage 2, and 23-53 in stage 3. Based on the visual acuity grade, ROC analysis was done for determining of the cutoff for total severity score categories. Accordingly, 4 stages were made with ranges of 0-11, 12-16, 17-22, and 23-53, representing mild, moderate, severe, and very severe ocular SJS, respectively. The mean severity score in each stage was 6.9 ± 6.3 (stage 0, 107 eyes), 11.24 ± 7.9 (stage 1, 48 eyes), 20.05 ± 5.9 (stage 2, 49 eyes), and 27.0 ± 8.9 (stage 3, 196 eyes). The sensitivity and specificity of each stage along with the positive predictive values and negative predictive values are presented in Table 6.

A total of 52 of 63 (82.5%) eyes in grade 0 of CDVA were categorized with stage 0 of total severity score, 15 of

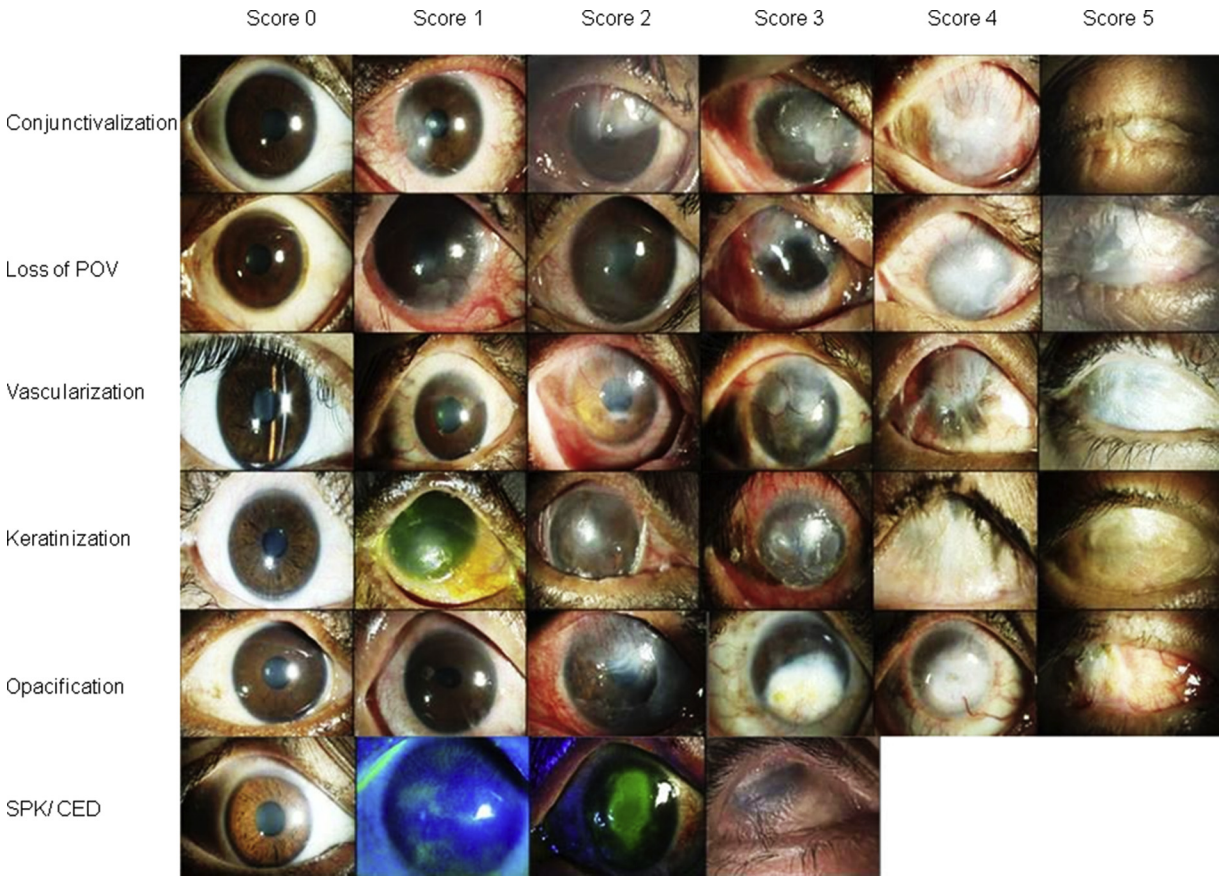

FIGURE 1. Representative images showing the multistep grading system for clinical scoring of corneal complications in chronic ocular sequelae in Stevens-Johnson syndrome eyes showing corneal parameters. POV = palisades of Vogt; SPK/CED = superficial punctate keratitis/corneal epithelial defect.

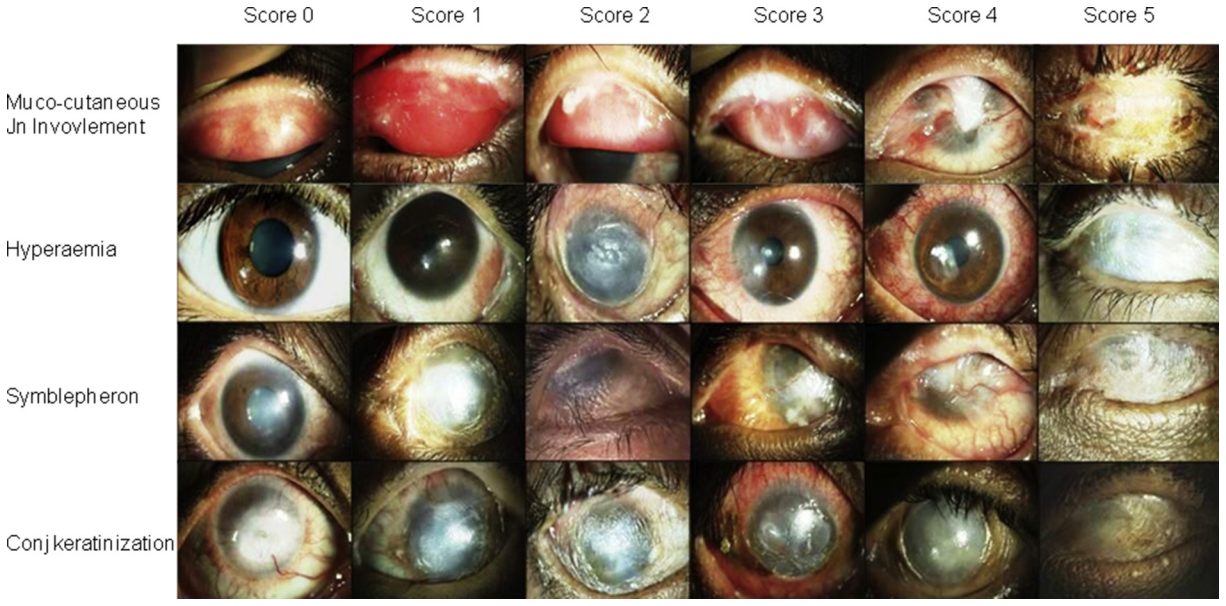

FIGURE 2. Representative images showing the multistep grading system for clinical scoring for mucocutaneous junction involvement and conjunctival complications in chronic ocular sequelae in Stevens-Johnson syndrome eyes.

TABLE 2. Baseline Patient Characteristics

Baseline Parameters	Result
No. of eyes (patients)	400 (200 patients)
Age (years)	
Mean	24.09 ± 10.9
Median	22
Range	6-60
Sex, n (%)	
Male	101 (50.5%)
Female	99 (49.5%)
Causative agent, n (%)	
Drugs	171/200 (85.5%)
NSAIDs	78/171 (45.6%)
Antibiotics	35/171 (20.4%)
Antiepileptics	18/171 (10.5%)
Unknown drug	40/171 (23.3%)
Febrile illness	29/200 (14.6%)
Antimalarial	17/29 (58.6%)
Antiviral	12/29 (41.3%)
Time to onset of SJS to initial presentation (in years)	
Mean	7.2 ± 6.7
Median	6
Range	1-30

NSAID = nonsteroidal anti-inflammatory drug; SJS = Stevens-Johnson syndrome.

TABLE 3. Correlation of Clinical Parameters With LogMAR Corrected Distance Visual Acuity

Variables	Correlation Coefficient	*P* Value
Age (years)	0.0942	.059
Conjunctivalization	0.7873	.0001*
Loss of POV	0.7779	.0001*
Vascularization	0.5667	.0001*
Keratinization	0.4365	.0001*
SPK/CED	0.6911	.0001*
Opacification	0.7647	.0001*
Mucocutaneous junction involvement	0.4747	.0001*
Meibomian gland involvement	0.3536	.0001*
Punctal involvement	0.5890	.0001*
Conjunctival hyperemia	0.2505	.0001*
Conjunctival keratinization	0.4079	.0001*
Symblepharon	0.4125	.0001

CED = corneal epithelial defect; POV = palisades of Vogt; SPK = superficial punctate keratitis.
Asterisk (*) indicates statistical significance.

78 eyes (19.2%) in grade 1 CDVA with stage 1 of total severity score, 18 of 68 eyes (26.5%) in grade 2 CDVA with stage 2 of total severity score, and 158 of 191 eyes (82.7%) in grade 3 CDVA with stage 3 of total severity score (Table 7). Cohen's kappa statistics were done to determine the measure of agreement between these 2. The kappa coefficient was found to be 0.420 ± 0.3 with a moderate agreement of 60.75% ($P = .001$).

TABLE 4. Multivariate Regression Analysis

Variables	Coefficient	95% Confidence Intervals	*P* Value
Conjunctivalization	0.2841	0.2130 to 0.3553	<.001
Opacification	0.2012	0.1295 to 0.2728	<.001
Symblepheron formation	0.1048	0.0424 to 0.1671	.001
Meibomian gland involvement	-0.0741	-0.1423 to -0.0059	.033
Punctal involvement	0.0994	0.0165 to 0.1822	.019

DISCUSSION

THE TREATMENT MODALITIES IN CASES OF SJS WITH ocular involvement have improved over the years, with an increasing number of ophthalmologists being trained in ocular surface reconstruction procedures. Techniques like amniotic membrane graft, cultivated limbal epithelial transplantation, cultivated oral mucosal epithelial transplantation, and minor salivary gland transplantation and advances in keratoprosthesis have opened up new avenues. Decision making regarding the appropriate modality of treatment and prognostication of the case requires a meticulous grading system. The currently available grading systems for SJS have helped clinicians all over the world to predict visual acuity outcomes. However, the disease severity of the cases of ocular SJS at the time of presentation and the subsequent outcomes thereof may not be uniform worldwide, as there are ethnic and genetic differences.

There are several differences in the patient profile between our study and those reported earlier. The mean age was of 24.09 ± 10.9 years, which was younger than that of the previously reported study, which was 47.9 ± 18.9 years.[21] The mean time from onset of SJS to the first presentation was 7.17 ± 6.8 years, which is also earlier than that reported by Sotozono and associates, which was 18.8 ± 15.5 years.[21] Overall 35.2% (141/400) of the eyes had CDVA greater than 6/60 and 64.7% of eyes (259/400) had CDVA less than 6/60 in our study, whereas Sotozono and associates reported 46% of eyes with CDVA >6/60 and 53.5% of eyes with CDVA <6/60.[21]

Thus, our study included a younger age cohort with an earlier age of presentation with chronic sequelae and severity level higher than that of Sotozono and associates.[21] The difference from other studies could be due to ethnic and genetic variations, improper management of the acute stage, delay in seeking medical care, and the

TABLE 5. Comparison of Ocular Surface Parameters of Stevens-Johnson Syndrome Eyes With Different Categories of Corrected Distance Visual Acuity

Variables	CDVA Grade 0 N = 63	CDVA Grade 1 N = 78	CDVA Grade 2 N = 68	CDVA Grade 3 N = 191	Overall *P* Value
Age (years)	21.8 ± 9.2	23.4 ± 11.2	21.2 ± 7.7	25.2 ± 11.3	.059
Schirmer test (mm)	9.9 ± 13.2	7.2 ± 11.4	6.3 ± 10.8	4.6 ± 9.8[c]	.003*
Conjunctivalization	0.4 ± 0.7	1.1 ± 1.3[a]	3 ± 1.0[b,d]	3.5 ± 1.0[c,e]	.0001*
Loss of POV	0.5 ± 0.8	1.2 ± 1.3[a]	2.9 ± 0.9[b,d]	3.5 ± 1.0[c,e]	.0001*
Vascularization	0.9 ± 1.4	1.6 ± 1.6[a]	2.6 ± 1.3[b,d]	3.2 ± 1.3[c,e]	.0001*
Keratinization	0.1 ± 0.6	0.2 ± 0.7	0.1 ± 0.3	1.5 ± 1.9[c,e,f]	.0001*
SPK/CED	0.9 ± 0.5	1.4 ± 0.9[a]	2.2 ± 0.9[b,d]	2.6 ± 0.7[c,e]	.0001*
Opacification	0.4 ± 0.7	1.1 ± 1.1[a]	2.5 ± 1.3[b,d]	3.3 ± 1.1[c,e,f]	.0001*
Mucocutaneous junction involvement	0.8 ± 1.0	0.9 ± 0.8	1.5 ± 0.8	2.0 ± 1.2[c,e]	.0001*
Meibomitis involvement	0.9 ± 0.9	1.0 ± 0.9	1.4 ± 0.9	1.7 ± 0.9[c,e]	.0001*
Punctal involvement	0.2 ± 0.5	0.4 ± 0.8	0.9 ± 1.0[b,d]	1.5 ± 0.8[c,e,f]	.0001*
Conjunctival hyperemia	1.3 ± 1.5	1.9 ± 1.6	2.6 ± 1.5[b]	2.5 ± 1.5[c,e]	.0001*
Conjunctival keratinization	0.2 ± 0.6	0.2 ± 0.6	0 ± 0	1.2 ± 1.6[c,e,f]	.0001*
Symblepharon	0.1 ± 0.3	0.1 ± 0.3	0.2 ± 0.4	0.9 ± 1.3[c,e,f]	.0001*
Corneal complications	3.4 ± 3.9	6.7 ± 5.6[a]	13.5 ± 4.5[b,d]	17.7 ± 5.5[c,e,f]	<.0001*
Eyelid complications	1.9 ± 1.8	2.3 ± 2.0	3.8 ± 2.5[b,d]	5.2 ± 2.4[c,e,f]	<.0001*
Conjunctival complications	1.6 ± 1.6	2.2 ± 1.7	2.8 ± 1.5	4.6 ± 3.1[c,e,f]	<.0001*
Total severity score	6.9 ± 6.2	11.2 ± 7.8	20.1 ± 5.9	27.5 ± 9.0[c,e,f]	<.0001*

CDVA = corrected distance visual acuity; CED = corneal epithelial defect; POV = palisades of Vogt; SPK = superficial punctate keratitis.
Values are expressed as n (number of eyes), mean ± SD.
Asterisk (*) indicates statistical significance.
$P < .05$ for the following grades: [a]grade 1 vs 0, [b]grade 2 vs 0, [c]grade 3 vs 0, [d]grade 2 vs 1, [e]grade 3 vs 1, [f]grade 3 vs 2.

TABLE 6. Sensitivity, Specificity, and Positive and Negative Predictive Values of Visual Acuity Grade With Reference to Total Severity Score Grade

Total Severity Score Categories	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
0-11	83.8% (79.3, 87.5)	82.5% (70.9, 90.1)	96.2% (93.7, 97.3)	48.6% (41.9, 55.3)
12-16	19.2% (12.0, 29.0)	89.7% (85.6, 92.3)	82.1% (80.3, 83.7)	76.0% (71.5, 80.1)
17-22	26.4% (16.5, 38.7)	90.6% (87, 93.5)	36.7% (2.9, 9.6)	85.7% (83.8, 87.5)
23-53	2.4% (77.1, 86.9)	83.8% (77.3, 88.7)	88.3% (83.4, 91.9)	76.3% (79.1, 87.7)

use of over-the-counter drugs, which are available without prescription from ophthalmologists in developing countries.[14,22,23] Owing to differences in presentation and onset, we are justified in modifying the current grading system. This is also demonstrable in the representative illustration of the severity of the disease (Figure 1 and 2).

In this study, 2 new severity scores (4 and 5) were added to include advanced grades of chronic changes in ocular SJS. Similar modifications have been done in the past for other diseases of the eye, such as modification of the Roper-Hall grading system for acute chemical injury by Dua and associates to include all grades of severity.[24] The purpose was to differentiate the more severe cases from the less severe ones, which would have otherwise been put in score 3, if graded according to the previous grading system.[21] This would not have done justice to the severe cases, as the type of surgery planned and surgical outcomes thereof vary in scores 3, 4, and 5. The number represented in each of scores 3, 4, and 5 justifies the categorization in our study. This also helps to stratify the treatment modality that will be used in such cases. An eye with a score of 3 may benefit from a surface procedure with or without keratoplasty, while for a score of 5 an end-stage procedure such as keratoprosthesis may be required.

All 12 parameters used for grading and total severity scores correlated significantly with CDVA of patients, indicating a direct correlation of visual acuity to ocular surface complications in SJS/TEN. The increase in scores of each of the 12 parameters is directly proportional to lowering of visual acuity. These especially included corneal

TABLE 7. Cohen's Kappa Analysis Between Categories of Total Severity Score and Corrected Distance Visual Acuity Grades in Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis Eyes

		Categories of LogMAR BCVA				
Total severity		0	1	2	3	Total
score stages	0	52	8	2	1	63
	1	46	15	9	8	78
	2	9	12	18	29	68
	3	0	13	20	158	191
	Total	107	48	49	196	400

BCVA = best-corrected visual acuity.

components of ocular surface complications like conjunctivalization, vascularization, opacification, and keratinization. Upon multivariate analysis, an inverse correlation was found between meibomian gland involvement and visual acuity. This paradoxical correlation, although difficult to explain, may be due to the fact that the surface changes in SJS largely define the visual acuity, with minimal impact of meibomian gland status in advanced cases. It may be possible that the meibomian gland has an impact on CDVA only in early stages of SJS, but after chronic sequelae start factors such as conjunctivalization and keratinization largely influence the CDVA.

On further analysis it was found that changes in mean scores of conjunctivalization, loss of POV, and vascularization were significant between all the grades of CDVA except between grades 2 and 3 (Table 5). Upon subgroup analysis, there was no significant change in the above parameters between grade 2 and grade 3, even though the visual acuity changed. This led us to interpret that the above changes may not be that important in determining final visual acuity as the disease progresses.

The change in keratinization of the cornea was significant only between grade 1 and grade 3 but not between other CDVA groups. This suggests that the presence of keratinization of the cornea is usually indicative of poor CDVA and advanced stage of the disease.

The total severity scores of SJS eyes were subjected to ROC analysis, which revealed cutoffs for categorizing total severity score so as to correlate to the findings of CDVA grades obtained. The final categories obtained, with their sensitivity and specificity, are depicted in Table 6. The correlation between categories of severity score and the CDVA grades on Cohen's kappa statistic analysis was found to be significant between total severity score categories and logMAR visual acuity grades and yielded an agreement of 60.75% with a kappa coefficient of 0.420 ± 0.03. As per the guidelines quoted by Landis and Koch, the kappa coefficient for inter-rater reliability shows moderate agreement.[25]

To conclude, the multistep grading system of SJS includes all stages of severity of chronic changes in the eye. With this grading system, every case of SJS could be categorized into a particular group of severity that correlates with visual acuity. Although we could not evaluate the application of this scoring system in our patients, as our study was a 1-point study, we propose it could be helpful in several other situations. We believe this will help in explaining the disease severity to the patients. It could help to monitor the response of topical anti-inflammatory therapy; for example, if a patient put on anti-inflammatory therapy continuously progresses to an advanced grade, then it suggests stepping up the therapy. Also, this grading system could help in prognosticating various surgical procedures in cases of chronic ocular sequelae of SJS. Additionally, this method provides a quantitative tool to compare outcomes in SJS, which may help in documenting patient follow-up and progress in an efficient way. However, all of its applicability has to be tested in further studies.

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