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Ocular manifestations in Stevens–Johnson syndrome/toxic epidermal necrolysis in cancer patients

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ABSTRACT

Purpose: To evaluate the characteristics, risk factors, and outcomes of ocular involvement in cancer patients with Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), focusing on the role of immune checkpoint inhibitors (ICIs).

Methods: This retrospective case–control study was conducted at Chang Gung Memorial Hospital, Linkou, Taiwan, between 2004 and 2024. A total of 112 patients with confirmed SJS/TEN and concurrent malignancies were included. The primary outcomes were the prevalence and severity of acute and chronic ocular involvement, assessed using Sotozono's classification. Risk factors for ocular involvement were investigated through univariate and multivariate logistic regression.

Results: Of 112 patients, 46 (41.1 %) developed ocular complications. TEN (adjusted OR, 3.11; 95 % CI, 1.24–7.78; P = 0.02), systemic mucosal involvement (adjusted OR, 4.89; 95 % CI, 1.52–15.80; P = 0.01), and polypharmacy (adjusted OR, 3.52; 95 % CI, 1.36–9.11; P = 0.01) were significant risk factors for ocular involvement. ICI-related SJS/TEN exhibited longer latency (31.0 vs. 13.4 days; P < 0.001) and delayed healing (72.3 vs. 45.8 days; P = 0.002). Chronic ocular complications were more severe in surviving ICI-related patients, as indicated by significantly higher chronic Sotozono scores (7.5 vs. 3.7; P = 0.001), worse dry eye (Schirmer's test 1.8 vs. 3.4 mm; P = 0.01), and poorer visual recovery (0.11 vs. 0.43 logMAR; P = 0.001).

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Conclusions: SJS/TEN in cancer patients, particularly those receiving ICIs, is associated with substantial ocular morbidity. The increasing prevalence of ICI-related SJS/TEN emphasizes the need for vigilant ophthalmologic intervention and long-term monitoring.

1. Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening mucocutaneous disorders that are triggered primarily by medications or infections, characterized by extensive epidermal necrosis and severe complications, particularly involving the ocular surface [1]. Ocular involvement occurs in up to 80 % of patients with SJS/TEN, and often results in long-term sequelae, including dry eye, ocular surface keratinization, corneal neovascularization, cicatricial entropion, trichiasis, symblepharon, and even blindness, all of which profoundly impact patients' quality of life [2,3].

The pathophysiology of SJS/TEN is complex and multifactorial, but an immune-mediated process leading to widespread keratinocyte apoptosis is thought to be central [4]. Concurrent malignancy in patients with SJS/TEN introduces additional challenges, as cancer therapies may exacerbate the severity of the disease or affect ocular manifestations [5,6]. Cancer patients are at markedly greater risk of developing SJS/TEN, with an estimated incidence of up to sixty times higher than that of the general population, likely due to immune dysregulation, the malignancy itself, and frequent exposure to diverse pharmacologic agents, including oncologic therapies as well as non-oncological drugs such as antibiotics, anticonvulsants and nonsteroidal anti-inflammatory drugs (NSAIDs). [7–9]. The increasing use of immune checkpoint inhibitors (ICIs) in cancer therapy has been associated with a rise in a broad spectrum of immune-related adverse events (irAEs), including severe cutaneous reactions such as SJS/TEN [10,11]. ICIs, targeting programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), enhance immune activation but also increase the risk of autoimmune complications, including ocular damage [12–14].

While comprehensive reviews on SJS/TEN in cancer patients exist, there is a notable paucity of research specifically addressing ocular manifestations in this population, particularly those treated with ICIs [9,15]. Furthermore, the distinct mechanisms of ICI-associated SJS/TEN raise questions about whether its ocular manifestations differ in severity compared with those of SJS/TEN triggered by other drugs. Although animal models of ICI-induced irAEs exist [16–18], the underlying pathomechanisms responsible for ocular damage remain poorly understood. This study aimed to investigate the characteristics and clinical outcomes of ocular involvement in cancer patients with new-onset SJS/TEN, with a focus on ICI-associated cases.

2. Methods

2.1. Study design and patient population

This retrospective case–control study was conducted at Chang Gung Memorial Hospital, Linkou, and included patients diagnosed with SJS/TEN and concurrent malignancies from January 2004 to December 2024. The inclusion criteria were as follows: (1) aged ≥18 years; (2) a confirmed diagnosis of malignancy; (3) a confirmed diagnosis of SJS, SJS/TEN overlap, or TEN by dermatologists after the onset of cancer on the basis of established clinical criteria proposed by the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) [19]. The exclusion criteria were patients with incomplete medical records or an uncertain diagnosis of SJS/TEN or malignancy. All patients were diagnosed and followed up by dermatologists and ophthalmologists at our hospital. Each malignancy was diagnosed and staged according to the Clinical Practice Guidelines in Oncology from the National Comprehensive Cancer Network (NCCN). A total of 116 patients with SJS/TEN and concurrent malignancies were enrolled in this study. Four patients were excluded from further analysis because of incomplete medical records or incompatible pathological diagnoses. The study was approved by the Institutional Review Board (IRB) of Chang Gung Memorial Hospital, Taoyuan, Taiwan (IRB No. 202500055B0) and followed the Declaration of Helsinki. The patient consent was waived given the retrospective nature of the study.

2.2. Data collection and definitions

Demographic data (age, sex, comorbidities, and malignancy-related information) were collected. Data on SJS/TEN characteristics, including systemic involvement, the severity-of-illness score for toxic epidermal necrolysis (SCORTEN) scale, culprit medications, treatments, and duration of follow-up, were extracted. The severity of SJS/TEN was evaluated using the SCORTEN scale, which incorporates factors such as age, heart rate, blood urea nitrogen, presence of malignancy, extent of body surface area affected, and serum glucose and bicarbonate levels [5]. The SCORTEN scores were calculated on the day of SJS/TEN diagnosis. To assess the likelihood of drug causality and exclude potential interference from confounding comedications, the Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN), which is specific to SJS and TEN, was applied to each patient [20]. Only drugs with a "probable" ALDEN score (≥4) were considered causative to reduce the risk of misattribution. Polypharmacy was defined as the concurrent use of more than one probable culprit medication (ALDEN score ≥4), and these cases were carefully adjudicated.

2.3. Ocular clinical assessment and management

Ocular involvement was assessed and graded using the Sotozono classification system, which provides standardized criteria for both acute and chronic ocular severity [21,22]. Acute ocular involvement (within the first 2 months of disease onset) was categorized into four grades: grade 0, no ocular involvement; grade 1, conjunctival hyperemia; grade 2, pseudomembrane formation or ocular surface epithelial defects; grade 3, both pseudomembrane formation and ocular surface epithelial defects. Chronic ocular complications (evaluated at least 6 months after onset) were assessed using Schirmer's test without anesthesia for dry eye, along with 13 ocular surface and adnexal components graded on a scale of 0–3: (1) corneal complications including superficial punctate keratopathy, epithelial defects, loss of the palisades of Vogt (POV), conjunctivalization, neovascularization, opacification, and keratinization; (2) conjunctival complications including hyperemia and symblepharon formation; and (3) eyelid complications, including trichiasis, mucocutaneous (MC) junction involvement, meibomian gland involvement, and punctal damage.

Visual acuity (VA) was assessed using Snellen charts and converted to the logarithm of the minimum angle of resolution (logMAR) for analysis. VA was recorded at the time of acute diagnosis and again at 6-month follow-up after standard ophthalmic treatment.

Since 2015, systemic treatment has included steroid pulse therapy (methylprednisolone 1–1.5 mg/kg/day intravenously until the skin lesions are healed) and subcutaneous etanercept (25–50 mg twice weekly until the skin lesions are healed) for patients with progressive blistering or erythema despite steroid treatment or in cases where steroid therapy is contraindicated [23]. As previously described, ophthalmic treatment during the acute stage was adjusted on the basis of severity [15]. The conjunctival pseudomembrane was removed every 2–4 days until total conjunctival re-epithelialization was achieved. Amniotic membrane

(AM) dressing with or without suturing was applied within one week of onset to protect the ocular surface in cases of corneal and/or conjunctival epithelial defects [23,24]. After discharge, regular follow-up examinations were conducted.

2.4. Statistical analysis

Continuous variables are presented as the mean ± standard deviation (SD), whereas categorical variables are reported as counts and percentages. Group comparisons were conducted using the independent *t*-test for normally distributed continuous variables and the Wilcoxon rank-sum test for continuous variables with small sample sizes or skewed distributions. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Changes in VA were assessed using the Wilcoxon signed-rank test to evaluate functional outcomes.

To identify independent risk factors for ocular involvement, univariate logistic regression analyses were performed, followed by multivariate logistic regression to adjust for potential confounders. To account for clinical heterogeneity, additional covariates, including type of malignancy, cancer stage, prior lines of oncologic therapy, comorbidities, and polypharmacy, were incorporated into the regression model.

Statistical significance was defined as a P value less than 0.05. All the statistical analyses were performed using SPSS software (version 29.0, IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patient demographics and clinical characteristics

Among the 112 patients included in this study, 46 (41 %) presented with ocular involvement (Sotozono's acute grade ≥1) (Table 1). The mean age was comparable between patients with and without ocular involvement (61.2 ± 14.1 years with ocular involvement vs. 64.0 ± 11.9 years without ocular involvement; P = 0.26). Male patients showed a slight predominance of ocular involvement (59 % vs. 41 %), although the difference did not reach statistical significance (P = 0.08). Patients with ocular involvement had a significantly greater percentage of TEN than did those without ocular involvement (28 % vs. 12 %; P = 0.04), whereas the SCORTEN scores were similar between the two groups (3.0 ± 1.5 vs. 2.9 ± 1.2, P = 0.59).

Solid tumors were present in most patients, both with and without ocular involvement. Lung cancer was the most common malignancy in both groups (28 % and 27 %, respectively), followed by hepatocellular carcinoma (HCC) (15 % and 17 %, respectively). Advanced cancer (stage IV or metastases) was more common in patients with ocular involvement (59 % vs. 39 %), although this difference was only marginally significant (P = 0.05).

At 6 months of follow-up, 82 patients (73 %) remained alive, and 30 (27 %) had died. Compared with survivors, non-survivors were older, more frequently diagnosed with TEN, had higher SCORTEN scores, lower serum albumin, higher CRP, and more frequent mucosal involvement (all P < 0.01). Detailed data are presented in Supplemental Table S1.

3.2. Risk factors for ocular involvement

In multivariate analysis, TEN (adjusted OR [aOR], 3.11; 95 % CI, 1.24–7.78; P = 0.02), mucosal involvement (oral/genital ulcers; aOR, 4.89; 95 % CI, 1.52–15.80; P = 0.01), and polypharmacy (aOR, 3.52; 95 % CI, 1.36–9.11; P = 0.01) were independently associated with ocular involvement (Table 2). Male sex (OR, 2.05; 95 % CI, 0.96–4.41; P = 0.07), fever at onset (OR, 2.22; 95 % CI, 0.99–4.95; P = 0.05), and anticonvulsant use (OR, 2.56; 95 % CI, 0.95–6.88; P = 0.06) showed trends toward association in univariate analysis, but did not reach statistical significance in multivariate analysis. By analyzing the impact of other cancer-related variables, including cancer type, disease stage, and prior lines of oncologic therapy, no statistically significant difference was found.

Table 1
Demographics of cancer patients with Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) with or without ocular involvement.

	No. (%)		P value
Characteristics	With ocular involvement (n = 46)	Without ocular involvement (n = 66)	
Age, mean (SD), y	61.2 (14.1)	64.0 (11.9)	0.26
Sex			
Male	27 (59 %)	27 (41 %)	0.08
Female	19 (41 %)	39 (59 %)	
Disease type			
SJS	28 (61 %)	48 (73 %)	0.22
SJS/TEN overlap	5 (11 %)	10 (15 %)	0.58
TEN	13 (28 %)	8 (12 %)	0.04
SCORTEN score, mean (SD)	3.0 (1.5)	2.9 (1.2)	0.59
Culprit medications			
Anticonvulsants	8 (17.4 %)	9 (13.6 %)	0.60
Antibiotics	12 (26.1 %)	18 (27.3 %)	0.99
NSAIDs	5 (10.9 %)	8 (12.1 %)	0.99
Chemotherapy	4 (8.7 %)	9 (13.6 %)	0.55
Targeted therapy drugs	10 (21.7 %)	10 (15.2 %)	0.45
ICIs	13 (28.3 %)	19 (28.8 %)	0.99
Proton pump inhibitors	4 (8.7 %)	3 (4.5 %)	0.44
Allopurinol	0	2 (3.0 %)	0.51
Cold medicine	0	1 (1.5 %)	0.99
Infections	1 (2.2 %)	1 (1.5 %)	0.99
Miscellaneous drugs[a]	4 (8.7 %)	5 (7.6 %)	0.99
Type of malignancy			
Solid tumors	44 (96 %)	63 (96 %)	0.99
Lung cancer	13 (28 %)	18 (27 %)	0.99
Hepatocellular carcinoma	7 (15 %)	11 (17 %)	0.99
Head and neck cancer (including oral, NPC, ear)	7 (15 %)	4 (6 %)	0.19
Breast cancer	2 (4 %)	8 (12 %)	0.19
Colorectal cancer	3 (7 %)	3 (5 %)	0.69
Other gastrointestinal cancer	4 (9 %)	6 (9 %)	0.99
Genitourinary cancer	4 (9 %)	7 (11 %)	0.99
Gynecologic cancer	3 (7 %)	5 (8 %)	0.99
Other solid neoplasms[b]	1 (2 %)	2 (3 %)	0.99
Hematological tumors	2 (4 %)	3 (5 %)	0.99
Multiple myeloma	2 (4 %)	0	0.17
Lymphoma	0	2 (3 %)	0.51
Leukemia	0	1 (1.5 %)	0.99
Multiple neoplasia[c]	0	2 (3 %)	0.51
Advanced cancer, stage 4	28 (61 %)	28 (39 %)	0.05
Treatment for malignancy			
Chemotherapy	23 (50 %)	42 (64 %)	0.16
Hormone therapy	3 (7 %)	3 (5 %)	0.69
Radiation therapy	18 (39 %)	21 (32 %)	0.43
Targeted therapy	22 (48 %)	29 (44 %)	0.70
Combined therapy	11 (23.9 %)	20 (30.3 %)	0.52
Acute mortality specific to SJS/TEN[d]	12 (26.1 %)	18 (27.3 %)	0.99

Abbreviations: SJS, Steven–Johnson syndrome; TEN, toxic epidermal necrolysis; SCORTEN, severity-of-illness score for toxic epidermal necrolysis; ICI, immune checkpoint inhibitor; NPC, nasopharyngeal carcinoma.

[a] Miscellaneous drugs include Denosumab, Entecavir, Lamivudine, Remdesivir, Febuxostat, Furosemide, Fentanyl, Palonosetron, Sulindac, and Ultracet.

[b] Other solid neoplasms include melanoma, thyroid cancer, malignancies of the central nervous system.

[c] Multiple neoplasia: hepatocellular carcinoma and prostate cancer, hepatocellular carcinoma and esophageal squamous cell carcinoma.

[d] Acute mortality specific to SJS/TEN is defined as death occurring within 6 months after disease onset.

Table 2
Risk factors for ocular involvement in cancer patients with Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).

	Univariate analysis		Multivariate analysis[a]	
Variables	Crude OR (95 % CI)	P value	Adjusted OR (95 % CI)	P value
Sex (male)	2.05 (0.96–4.41)	0.07	2.49 (0.80–7.80)	0.12
Age (years)	0.98 (0.95–1.01)	0.26		
TEN	2.86 (1.07–7.60)	**0.04**	3.11 (1.24–7.78)	**0.02**
SCORTEN score ≥5	1.77 (0.60–5.30)	0.30		
Mucosal involvement[b]	4.33 (1.61–11.66)	**0.004**	4.89 (1.52–15.80)	**0.01**
Fever at onset	2.22 (0.99–4.95)	0.05	1.42 (0.53–3.77)	0.49
Comorbidities[c]	1.26 (0.57–2.78)	0.57		
Hematologic neoplasm	0.96 (0.15–5.95)	0.96		
Solid neoplasm	1.05 (0.17–6.53)	0.96		
Lung cancer	1.05 (0.45–2.43)	0.91		
Hepatocellular carcinoma	0.90 (0.32–2.52)	0.84		
Head and neck cancer (including oral, NPC, ear)	2.78 (0.76–10.13)	0.12		
Advanced cancer stage	1.26 (0.58–2.72)	0.56		
Prior lines of cancer therapy	1.38 (0.63–3.03)	0.43		
Culprit medications				
Antibiotics	1.10 (0.46–2.62)	0.83		
Anticonvulsants	2.56 (0.95–6.88)	0.06	2.82 (0.94–8.44)	0.06
ICIs	1.05 (0.45–2.43)	0.91		
Polypharmacy[d]	2.63 (1.17–5.89)	**0.02**	3.52 (1.36–9.11)	**0.01**

Abbreviations: TEN, toxic epidermal necrolysis; SCORTEN, severity-of-illness score for toxic epidermal necrolysis; ICI, immune checkpoint inhibitor.
[a] Variables which P ≤ 0.10 were included in the multivariable regression.
[b] Mucosal involvement includes oral ulcer and/or genital ulcer.
[c] Comorbidities are defined as the presence of one or more chronic conditions, including hypertension, diabetes mellitus, chronic kidney disease or dialysis, cirrhosis, chronic obstructive pulmonary disease, asthma, coronary artery disease, heart failure, cerebrovascular accident, or autoimmune diseases.
[d] Polypharmacy is defined as the concurrent use of ≥2 probable culprit drugs (ALDEN score ≥4).

3.3. Culprit medications for SJS/TEN

Antineoplastic medications were the most common culprit agents (n = 65, 44.5 %) in patients with malignancies, followed by antibiotics (n = 30, 20.5 %) and anticonvulsants (n = 17, 11.6 %) (Table 3). ICIs accounted for the majority of this category (n = 32). The incidence of ICI-related SJS/TEN increased significantly from 2014 to 2024 compared with that from 2004 to 2013 (0 % vs. 25.4 %; P = 0.01). Over the study period from 2004 to 2024, the use of anticonvulsants as causative medications for SJS/TEN significantly decreased (35 % vs. 7.9 %; P = 0.03). A detailed distribution list is provided in the Supplemental Table S2.

3.4. Ocular involvement in ICI-associated SJS/TEN

Among patients with ICI-related SJS/TEN, 41 % exhibited ocular involvement, a rate comparable to that of non-ICI patients (41 %, P = 0.88) (Table 4). Within the ICI subgroup, anti-PD-1 agents accounted for 26 cases (10 with ocular involvement), anti-PD-L1 for 6 cases (3 with ocular involvement), and anti-CTLA-4 for 3 cases, none of which involved the ocular surface (Supplemental Table S3). Notably, the latency to disease onset was significantly longer in the ICI group (31.0 ± 24.9 days vs. 13.4 ± 12.1 days; P < 0.001). The mean time to heal was also significantly extended in ICI-related patients (72.3 ± 34.6 days vs. 45.8 ± 28.2 days; P = 0.002), highlighting the prolonged disease course associated with ICIs. Nevertheless, acute ocular severity and the mortality rate attributable to SJS/TEN did not differ significantly between the ICI- and non-ICI-related groups.

Chronic ocular outcomes were more severe in the surviving ICI-related SJS/TEN patients, with a higher mean chronic Sotozono score (7.5 ± 3.8 vs. 3.7 ± 4.0; P = 0.001) and more pronounced dry eye (Schirmer's test: 1.8 ± 1.2 mm vs. 3.4 ± 2.8 mm; P = 0.01) (Table 5). ICI-related cases demonstrated a higher prevalence of severe chronic corneal complications, such as superficial punctate keratitis (2.2 ± 0.9

Table 3
Distribution of culprit medications of Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) between 2004 and 2024.

No. (%)	2004–2024	2004–2013	2014–2024	P value
Anticonvulsants	17 (11.6 %)	7 (35 %)	10 (7.9 %)	0.003
Antibiotics	30 (20.5 %)	7 (35 %)	23 (18.3 %)	0.13
Chemotherapy	13 (8.9 %)	0	13 (10.3 %)	0.22
Targeted therapy	20 (13.7 %)	1 (5 %)	19 (15.1 %)	0.31
ICIs	32 (21.9 %)	0	32 (25.4 %)	0.01
NSAIDs	13 (8.9 %)	2 (10 %)	11 (8.7 %)	0.69
Proton pump inhibitors	7 (4.8 %)	0	7 (5.6 %)	0.59
Cold medicine	1 (0.7 %)	1 (5 %)	0	0.14
Infections	2 (1.4 %)	0	2 (1.6 %)	0.99
Allopurinol	2 (1.4 %)	1 (5 %)	1 (0.8 %)	0.19
Miscellaneous drugs[a]	9 (6.2 %)	1 (5 %)	8 (6.3 %)	0.99

Abbreviations: ICI, immune checkpoint inhibitor; NSAID, nonsteroidal anti-inflammatory drug.
[a] Miscellaneous drugs include Denosumab, Entecavir, Lamivudine, Remdesivir, Febuxostat, Furosemide, Palonosetron, Sulindac, and Ultracet.

Table 4
Acute ocular severity and mortality in cancer patients with immune checkpoint inhibitor-associated Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).

	No. (%)		P value
	ICI related SJS/TEN (n = 32)	Non-ICI related SJS/TEN (n = 80)	
Spectrum			
SJS	23 (72 %)	53 (66 %)	0.66
SJS/TEN overlap	5 (16 %)	10 (13 %)	0.76
TEN	4 (13 %)	17 (21 %)	0.42
Latency period, mean (SD), day	31.0 (24.9)	13.4 (12.1)	<0.001
Acute ocular involvement (Sotozono grading)	No. of eyes = 64	No. of eye = 160	
Grade 0	38 (59 %)	94 (59 %)	0.99
Grade 1	12 (19 %)	30 (19 %)	0.99
Grade 2	8 (13 %)	18 (11 %)	0.82
Grade 3	6 (9 %)	18 (11 %)	0.81
Baseline VA, mean (SD), logMAR	0.49 (0.33)	0.60 (0.47)	0.20
Treatment for SJS/TEN			
Steroid alone	18 (56 %)	43 (54 %)	0.84
Biologic agents alone	1 (3 %)	4 (5 %)	0.99
Combined steroid + biologic agents[a]	13 (41 %)	28 (35 %)	0.67
Others (cyclosporine, IVIG)	0	5 (6.3 %)	0.32
Time to heal, mean (SD), days	40.2 (37.9)	25.5 (11.6)	0.02
Mortality specific to SJS/TEN	8 (25 %)	22 (26 %)	0.97

Abbreviations: ICI, immune checkpoint inhibitor; VA, visual acuity; IVIG, intravenous immunoglobulin.
[a] Biologic agents include etanercept, adalimumab, and tofacitinib.

Table 5
Chronic ocular complications of immune checkpoint inhibitor-associated Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) in cancer patients.

	No. (%)		
Chronic Sotozono score	ICI related SJS/TEN No. of eyes = 20	Non-ICI-related SJS/TEN No. of eyes = 48	P value
0–5	6 (30 %)	34 (71 %)	0.003
6–10	6 (30 %)	8 (17 %)	0.19
11–15	5 (25 %)	2 (4 %)	0.02
≥ 16	3 (15 %)	4 (8 %)[a]	0.41
Mean ± SD	7.5 ± 3.8	3.7 ± 4.0	0.001
Follow-up VA, mean (SD), logMAR	0.51 (0.38)	0.28 (0.30)	0.03
Change in VA, mean (SD), logMAR	0.43 (0.52)	0.11 (0.38)	0.001
Dry eye (Schirmer's test), mean (SD), mm	1.8 (1.2)	3.4 (2.8)	0.01
Chronic grading parameters, mean ± SD			
Conjunctival complications			
Conjunctival hyperemia	1.5 ± 0.7	1.0 ± 0.9	0.03
Symblepharon	0.1 ± 0.2	0	0.34
Corneal complications			
Superficial punctate keratitis	2.2 ± 0.9	0.9 ± 1.1	<0.001
Epithelial defect	0.2 ± 0.4	0.1 ± 0.5	0.91
Loss of Palisades of Vogt	0.1 ± 0.2	0	0.14
Conjunctivalization	0.3 ± 0.4	0	<0.001
Neovascularization	0.1 ± 0.3	0.1 ± 0.2	0.58
Keratinization	0.1 ± 0.3	0	0.03
Opacification	0.2 ± 0.4	0.1 ± 0.2	0.05
Eyelid complications			
Trichiasis	1.0 ± 0.6	0.1 ± 0.4	<0.001
Mucocutaneous junction	0.4 ± 0.5	0.4 ± 0.8	0.96
MGD	1.7 ± 0.8	0.7 ± 0.8	<0.001
Punctal involvement	0.1 ± 0.2	0	0.34

Abbreviations: ICI, immune checkpoint inhibitor; VA, visual acuity; MGD, meibomian gland dysfunction.
[a] Culprit medications include phenytoin and valproic acid.

vs. 0.9 ± 1.1; P < 0.001) and conjunctivalization (0.3 ± 0.4 vs. 0; P < 0.001). Eyelid complications, including trichiasis and meibomian gland dysfunction, were also significantly more common in the ICI group (P < 0.001 for both). Representative clinical images are presented in Figs. 1 and 2, illustrating severe ocular involvement and management in non-ICI-related (Fig. 1) and ICI-related (Fig. 2) SJS/TEN cases.

3.5. Changes in VA after treatment for SJS/TEN

VA outcomes were assessed in patients with ocular involvement following ophthalmic treatment for SJS/TEN (Fig. 3). Overall, the mean VA significantly improved from the initial presentation to 6 months after treatment (logMAR 0.56 ± 0.43 to 0.34 ± 0.33; P = 0.01) (Supplemental Table S4). Subgroup analysis revealed a significant improvement in the non-ICI group (logMAR 0.60 ± 0.47 to 0.28 ± 0.30; P = 0.002), whereas the ICI group exhibited no significant change (logMAR 0.49 ± 0.33 to 0.51 ± 0.38; P = 0.23). When comparing changes in VA between the groups, the non-ICI group demonstrated an average improvement of 0.43 ± 0.52 logMAR, while the ICI group experienced a minimal change of 0.11 ± 0.38 logMAR (P = 0.001) (Table 5).

4. Discussion

This study highlights the significant ocular morbidity associated with SJS/TEN in cancer patients, particularly those treated with ICIs. Compared with patients receiving other culprit medications, cancer patients receiving ICIs experienced more severe chronic ocular complications, as evidenced by higher chronic Sotozono scores, more pronounced chronic ocular surface sequelae, and poorer visual recovery. In contrast, non-ICI patients experienced significant improvement in visual acuity at 6-month follow-up. Notably, TEN, polypharmacy and systemic mucosal involvement were identified as independent risk factors for ocular complications, underscoring the need for early identification and targeted intervention in these high-risk patients.

In general populations, ocular involvement occurs in 60–80 % of cases and often leads to sequelae such as symblepharon, trichiasis and corneal scarring [25]. Acute-phase ocular involvement, including conjunctival inflammation and epithelial defects, has been identified as a strong predictor of long-term complications [15,26]. In cancer patients, the prevalence and severity of SJS/TEN are increased, with an increased incidence reported in those with hematologic malignancies or undergoing chemotherapy [27]. Moreover, we observed that patients with more extensive disease, particularly TEN, tripled the risk of ocular complications [27], and systemic mucosal involvement increased the risk nearly fivefold, which likely reflects widespread epithelial damage and exacerbated inflammatory responses predisposing patients to severe ocular involvement.

Growing evidence has recognized ICIs as an emerging cause of SJS/TEN, characterized by the delayed onset of adverse events and the potential for severe systemic manifestations [28–31]. However, detailed analyses of ocular manifestations in ICI-associated SJS/TEN patients, particularly in cancer patients, remain limited. Our data illustrate a rising trend of ICI-associated SJS/TEN accompanied by a decline in anticonvulsant-related cases, reflecting changes in pharmacological practice and a shifting etiology of SJS/TEN. The apparent rise in ICI-related cases likely reflects the successful pharmacogenetic prevention of anticonvulsant-induced SJS/TEN (e.g., HLA-B*15:02 screening) and the later introduction of ICIs, rather than a genuine increase in relative risk [32,33]. Dermatologic adverse events affect up to 45 % of ICI-treated patients [34], whereas ophthalmic complications occur in approximately 1–5 % of cases, most commonly manifesting as dry eye, conjunctivitis, blepharitis, anterior uveitis, and keratitis [35,36]. In our cohort, pembrolizumab and nivolumab were the most frequent culprit medications, which is consistent with prior reports [30,31]. Although the overall incidence of ocular involvement was comparable between ICI- and non-ICI-related cases, chronic ocular complications were more severe in the ICI group, suggesting prolonged and debilitating immune-mediated damage.

The pathophysiology underlying severe chronic ocular complications associated with ICIs likely involves increased T-cell activation and autoreactivity, promoting an aberrant immune response against the cornea and conjunctiva [37,38]. Classical SJS/TEN involves cytotoxic T cells and natural killer cells mediating keratinocyte apoptosis via granulysin, Fas-Fas ligand interactions, and the perforin/granzyme B pathway [39–41]. In the context of ICI-induced SJS/TEN, disrupted T-lymphocyte homeostasis likely triggers self-directed cytotoxic and inflammatory reactions, contributing to severe and chronic ocular damage [42]. Evidence indicates that $CD8^+$ T-cell infiltration of the corneal surface and lacrimal glands exacerbates dry eye and sicca syndrome [37].

An intriguing finding in patients with ICI-induced SJS/TEN is the trend toward prolonged latency and healing time. This aligns with previous research, including analyses of clinical trials and the FDA pharmacovigilance database, which reported that SJS/TEN typically developed several weeks to months after initiating ICI therapy [28,29,43]. Unlike conventional drug-induced SJS/TEN, which results from an immediate immune reaction to medications, ICIs gradually increase immune activity and may require additional triggers to initiate the pathological response. This progressive immune dysregulation ultimately culminates in severe dermatologic reactions and chronic ocular complications [44,45]. Delayed wound healing in ICI-treated SJS/TEN may further reflect direct drug toxicity, prolonged inflammation and impaired tissue repair processes, similar to chronic wounds and inflammatory skin conditions [46]. Additional factors likely contribute to this protracted course, including the long half-lives of ICIs, progressive

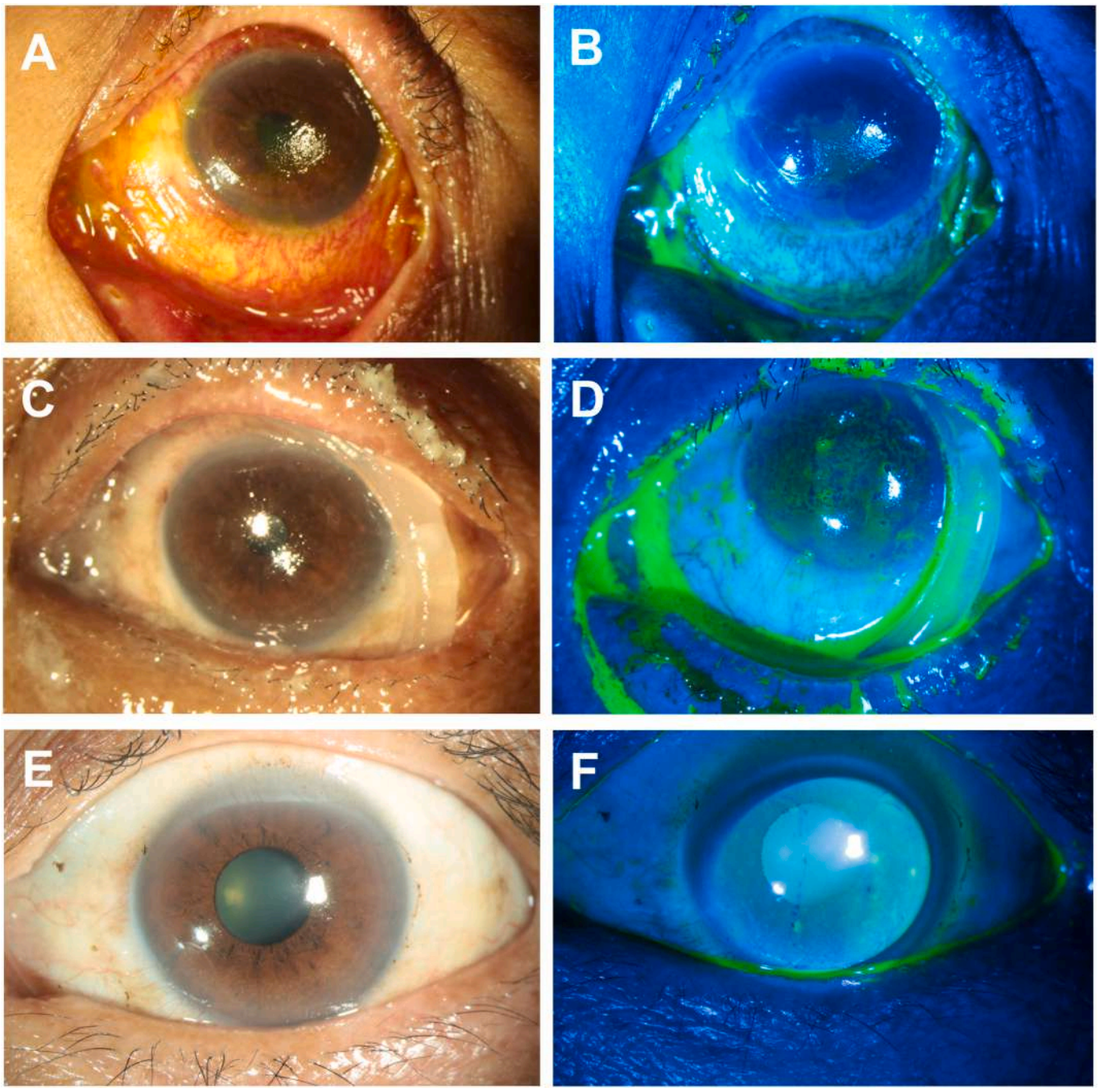


Fig. 1. Representative ocular surface images in patients with Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). A 55-year-old man with stage IV lower third esophageal cancer, gastric inlet obstruction, and pericardial metastases, who was undergoing palliative radiotherapy and chemotherapy, was admitted for suspected pneumonia and received antibiotics including teicoplanin. SJS developed 10 days after the initiation of antibiotics, primarily affecting both eyes with large corneal and conjunctival epithelial defects and pseudomembrane formation (A, B). A sutureless amniotic membrane (AM) dressing was performed in which the fornix was maintained by an infusion tube ring, and the edge of AM was fixated to the lids by cyanoacrylate glue to protect the entire ocular surface. Photographs taken 2 weeks after the operation showed that the AM had essentially dissolved, but no further corneal and conjunctival epithelial defect was observed (C, D). Three months after the onset, the corneal surface became smooth without any punctate lesions (E, F). The patient passed away 7 months after the onset of SJS.

loss of peripheral tolerance, and the therapeutic dilemma of ICI discontinuation in cancer patients [29].

Agent-level differences across ICI classes have been reported in the literature. For instance, nivolumab has been linked to a longer latency to SJS/TEN onset than pembrolizumab [29], while corneal adverse events appear more frequent with anti-PD-(L)1 than with anti-CTLA-4 therapy [47]. Although our cohort was dominated by PD-1 inhibitors, the small sizes of individual ICI subgroups limited reliable drug-specific comparisons of ocular outcomes. Nevertheless, distinct pharmacologic mechanisms among ICI classes likely explain differences in latency and clinical spectrum. PD-1 inhibitors primarily restore exhausted T cells activity, leading to delayed but sustained irAEs [37]. PD-L1 inhibitors act more directly on tumor and antigen-presenting cells, producing earlier but often less persistent irAEs [37]. CTLA-4 inhibitors trigger broad immune activation at the priming stage, resulting in early, severe, and systemic inflammatory events [37]. These mechanistic distinctions likely contribute to the variability in ocular irAE onset and severity across ICI classes.

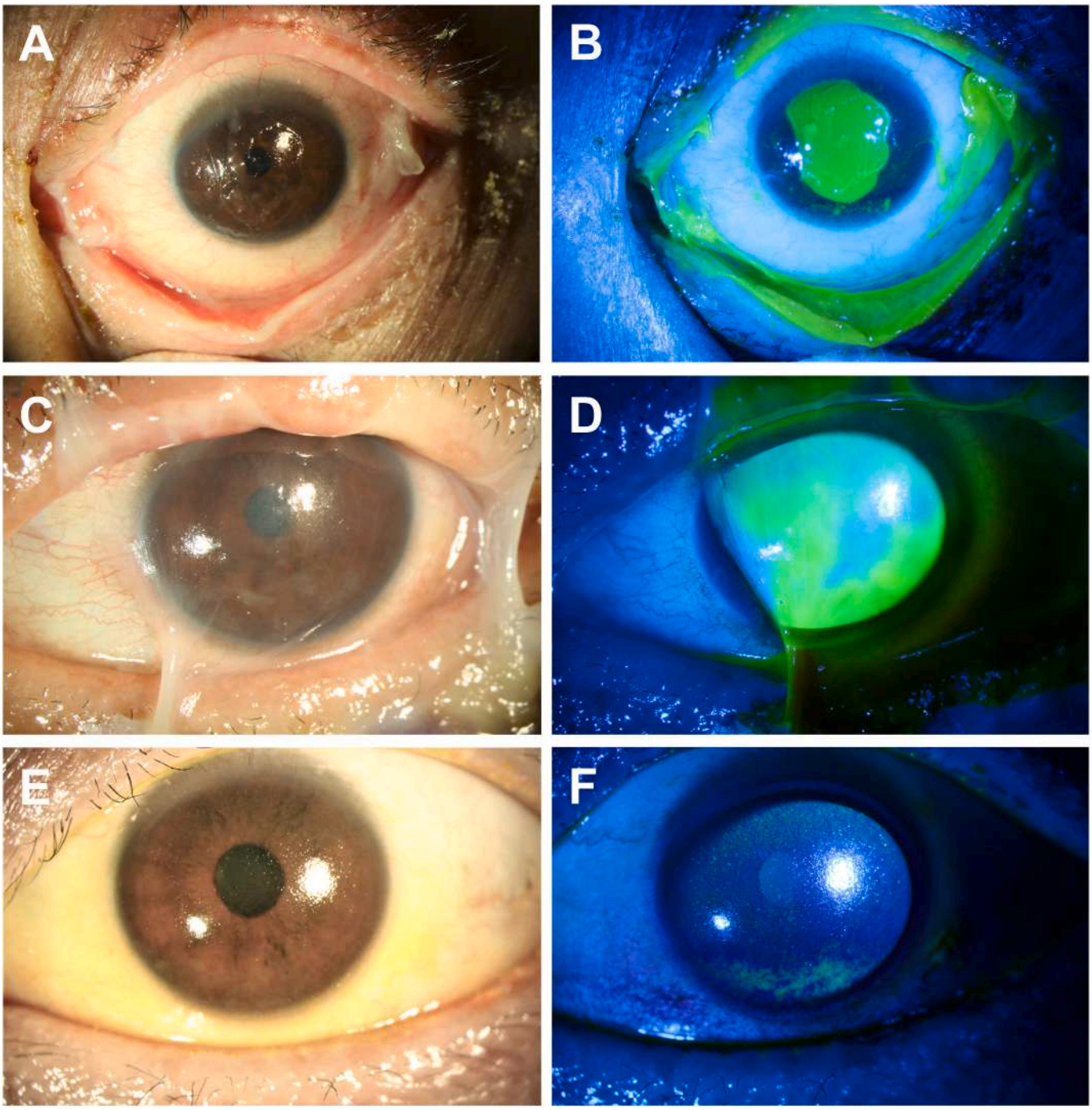


Fig. 2. Representative ocular surface images in patients with Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). A 42-year-old man with stage IVb squamous carcinoma of the tongue had undergone total glossectomy, bilateral modified radical neck dissection, radiotherapy, and chemotherapy. However, the tumor recurred and spread to the right axilla and left upper lung. He started immunotherapy with Pembrolizumab, and two weeks later, SJS developed, with skin necrosis extending to the neck, as well as ocular and oral mucosal involvement. In the acute stage, large corneal and conjunctival epithelial defects with pseudomembranes were observed (A, B). Cyanoacrylate glue-fixed sutureless amniotic membrane (AM) dressing was performed to protect the entire ocular surface. Due to delayed re-epithelialization and dissolution of the AM (C, D), a repeated AM dressing was applied to the left eye. The cornea was completely healed one month later, with residual inferior corneal epitheliopathy (E, F). The patient passed away two months after the onset of SJS.

With respect to the mortality rates of ICI-related SJS/TEN, our findings demonstrated similar outcomes between the two groups (25 % vs. 26 %; P = 0.97), which is consistent with previously reported rates of 24.5 %–30.8 % [43,48]. However, some reports suggest higher mortality in ICI-associated SJS/TEN. Bray et al. observed increased mortality in patients with ICI-associated epidermal necrosis than in non-ICI-related patients, likely because of an aggressive disease course [48]. Similarly, Quiruz et al. reported that ophthalmic irAEs associated with ICIs may indicate more severe disease progression and poorer survival outcomes [35]. In our cohort, the 6-month mortality was 27 %, and, as expected, non-survivors had higher baseline severity and systemic inflammation than survivors [5,49].

In addition to ICIs, antibiotics and anticonvulsants remain the leading causative medications for SJS/TEN in cancer patients. Phenytoin and carbamazepine were the primary anticonvulsant culprits, which is consistent with previous studies that reported these agents as

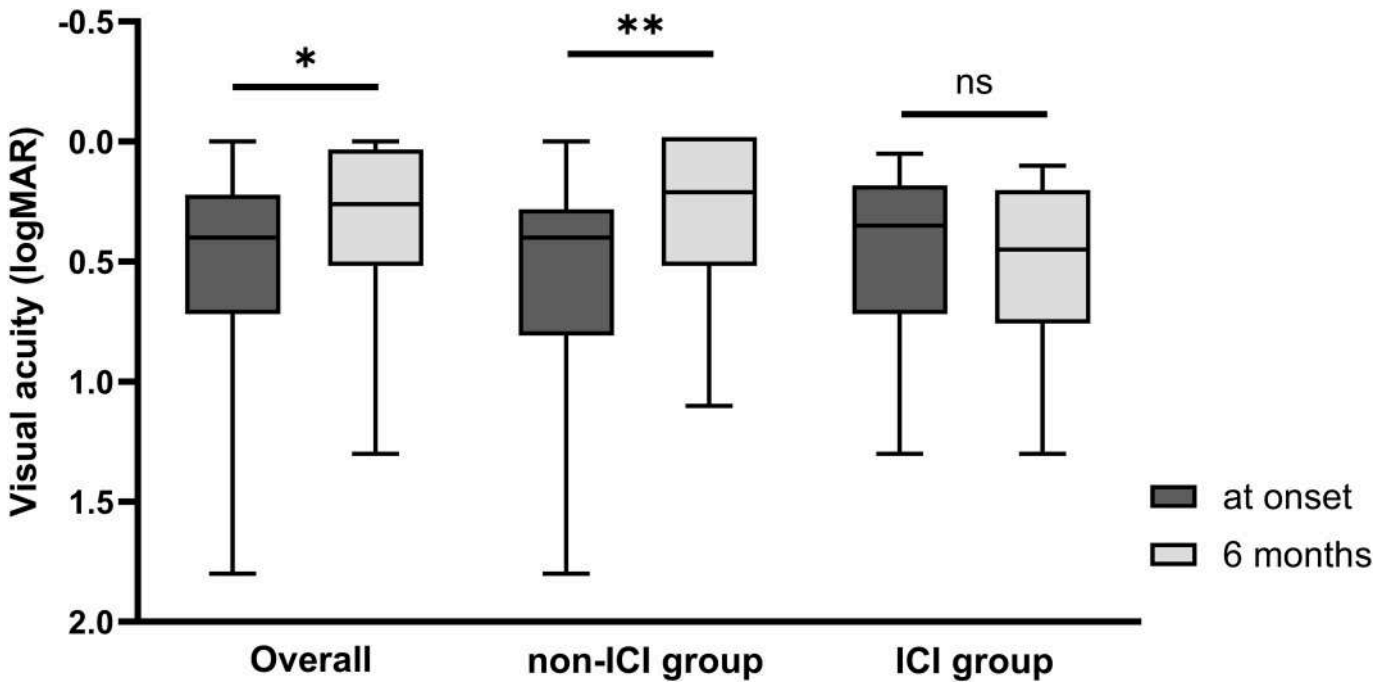


Fig. 3. Visual acuity at disease onset and 6-month follow-up in patients with Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Visual acuity was assessed at the time of diagnosis ("at onset") and at 6-month follow-up ("6 months"), and is presented in logMAR units. P values were determined using the Wilcoxon signed-rank test. Asterisks denote statistical significance: $P < 0.05$ (*), $P < 0.01$ (**); ns = not significant. ICI, immune checkpoint inhibitor.

high-risk drugs for SJS/TEN [50]. Our multivariate analysis suggested that anticonvulsant use, fever at onset and male sex were potentially associated with ocular involvement, although these did not remain statistically significant after adjustment. Further investigations are warranted to validate their roles in ocular complications. Importantly, concomitant use of multiple causative medications was frequent in our cohort. Cancer patients often receive a wide array of medications. This extensive polypharmacy complicates the determination of actual causation and may exert a cumulative effect on mucocutaneous and ocular immune responses [7,9]. While prior studies have primarily focused on single culprit drugs, our findings highlight polypharmacy as an independent risk factor for ocular complications (aOR, 3.52; $P = 0.01$). These results emphasize the importance of maintaining vigilance for early signs of SJS/TEN in patients receiving complex drug combinations.

This study has several strengths. To the best of our knowledge, this study is one of the first to comprehensively analyze ocular outcomes of SJS/TEN in cancer patients, focusing on ICIs as emerging culprit medications. Our robust dataset and use of validated grading systems, such as Sotozono's scores, enhance the statistical reliability of our findings. By identifying independent risk factors for ocular involvement, our work provides actionable insights for early risk identification and intervention in high-risk patients.

However, our study is not without limitations. First, its retrospective design may introduce selection bias, and the reliance on medical records could lead to incomplete data collection. Second, the relatively small sample size, particularly in subgroups such as ICI-related SJS/TEN, limits the generalizability of our findings. Third, the heterogeneity of cancer types and treatments in our cohort may have confounded some of the results. To address these limitations, we used multivariate analyses to control for potential confounders and focused on well-defined outcomes. Future prospective studies with larger cohorts and standardized treatment protocols are warranted to validate our results and explore the underlying mechanisms to better predict patients at highest risk for developing SJS/TEN and its complications.

5. Conclusion

This study underscores the importance of ocular morbidity associated with SJS/TEN in cancer patients, particularly those treated with ICIs. Polypharmacy, TEN and the presence of systemic mucosal involvement are strong predictors of ocular complications. ICI-related SJS/TEN is associated with more severe chronic ocular manifestations and worse visual outcomes. Given the high prevalence of chronic ocular complications in this population, it is crucial to adopt a multidisciplinary approach that involves dermatologists, ophthalmologists, and oncologists. Early identification of patients at risk for ocular involvement is essential for timely intervention and may help mitigate long-term ocular complications in this vulnerable population.

CRediT authorship contribution statement

Jin-Jhe Wang: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Chun-Bing Chen:** Writing – review & editing, Resources, Project administration, Investigation, Data curation, Conceptualization. **Eugene Yu-Chuan Kang:** Writing – review & editing, Visualization, Validation, Methodology, Conceptualization. **Wen-Hung Chung:** Writing – review & editing, Validation, Resources, Data curation. **John Wen-Cheng Chang:** Writing – review & editing, Validation, Resources, Data curation. **Kevin Sheng-Kai Ma:** Resources, Investigation, Data curation, Conceptualization. **Yueh-Ju Tsai:** Validation, Resources, Investigation, Data curation. **Ming-Tse Kuo:** Validation, Resources, Data curation. **Chi-Chin Sun:** Validation, Resources, Methodology, Data curation. **Hung-Chi Chen:** Validation, Software, Resources, Data curation. **Shin-Yi Chen:** Validation, Resources, Data curation. **Kuo-Hsuan Hung:** Validation, Resources, Data curation. **Hsin-Yuan Tan:** Validation, Resources, Data curation. **Pier Luigi Surico:** Visualization, Validation. **David Hui-Kang Ma:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

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Declarations of interest

No conflicting relationship exists for any author. The authors of this manuscript have no financial conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtos.2025.10.010.

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