Evaluation of the Factors Influencing Mortality in Patients with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Multicenter Study of 166 Patients

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ABSTRACT

Introduction: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening acute mucocutaneous disorders usually triggered by drugs. In this study, we aimed to evaluate the factors affecting mortality in patients with SJS-TEN.

Methods: Our study is a retrospective cohort study, analyzing data collected from a total of 12 tertiary care centers between April 2012 and April 2022.

Results: The study included 59 males and 107 females, a total of 166 patients, with an average age of 50.91 ± 21.25 years. Disease classification was TEN in 50% of cases, SJS in 33.1%, and SJS-TEN overlap in 16.9%. The average SCORTEN within the first 24 h was 2.44 ± 1.42. Supportive care was provided to 99.4% of patients. The most commonly used systemic immunomodulatory treatments were systemic steroids (84.3%), IVIG (intravenous immunoglobulin) (49.3%),

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and cyclosporine (38.6%). Plasmapheresis was administered to five patients.

While 66.3% of patients were discharged, 24.1% resulted in exitus. Our comparative analysis of survivors and deceased patients found no effect of systemic steroids, IVIG, and cyclosporine treatments on mortality. Univariate analysis revealed that the SCORTEN scores on days 1 and 3 as well as the rates of detachment at the onset and during follow-up were significantly higher in deceased patients compared to survivors. The rates of fever, positive blood cultures, and systemic antibiotic use were higher in deceased patients compared to survivors. The presence of comorbidities, diabetes, and malignancy were significantly more common in deceased patients. Multivariate regression analysis indicated that over SCORTEN 2, the mortality risk exponentially rose with each SCORTEN increment, culminating in an 84-fold increase in mortality at SCORTEN 5–6 (odds ratio [95% confidence interval]: 13.902–507.537, $p < 0.001$) compared to SCORTEN 0–1. Additionally, the utilization of plasmapheresis was associated with a 22-fold increase in mortality (odds ratio [95% confidence interval]: 1.96–247.2, $p = 0.012$).

Conclusion: Our study found that a high SCORTEN score within the first 24 h and the use of plasmapheresis were related to increased mortality, while systemic steroids, IVIG, and cyclosporine treatments had no impact on mortality. We believe that data gathered from one of the most comprehensive studies which we conducted on SJS-TEN will enrich the literature, although additional research is warranted.

Keywords: Stevens-Johnson syndrome; Toxic epidermal necrolysis; SCORTEN; Plasmapheresis; Mortality; Survival

Key Summary Points

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, life-threatening conditions primarily induced by medications.

We aimed to analyze factors influencing mortality in our multicenter retrospective cohort study involving 166 patients with SJS-TEN. Disease classification was TEN in 50% of cases, SJS in 33.1%, and SJS-TEN overlap in 16.9%.

Systemic corticosteroids were administered to 140 patients (84.3%). Sixty-four patients (38.6%) underwent cyclosporine treatment. IVIG (intravenous immunoglobulin) treatment was administered to 82 patients (49.4%). Plasmapheresis treatment was received by five cases (3%). The total mortality rate observed in our study was 24.1%.

Multivariate regression analysis revealed that beyond SCORTEN 2, the mortality risk exponentially increased with each increment in SCORTEN, leading to a significantly higher mortality rate (84 times) at SCORTEN 5-6 (odds ratio [95% confidence interval]: 13.902-507.537, $p < 0.001$) compared to SCORTEN 0-1.

Moreover, the utilization of plasmapheresis was correlated with a 22-fold escalation in mortality rates (odds ratio [95% confidence interval]: 22 [1.96–247.2], $p = 0.012$). It was found that systemic corticosteroids, IVIG, and cyclosporine treatments did not have an impact on mortality.

The conclusions drawn from our study highlight the imperative for additional research endeavors aimed at formulating enhanced therapeutic approaches for SJS-TEN.

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, life-threatening

conditions that belong to the same disease spectrum. Clinically, they are characterized by widespread erythematous targetoid plaques accompanied by severe mucosal erosions [1]. Cutaneous lesions exhibit Nikolsky's sign positivity and epidermal detachment. Full-thickness epidermal necrosis is observed in pathological evaluations. The distinction between SJS and TEN is made based on the extent of body surface area involvement; SJS involves < 10% of the total body surface area, SJS-TEN overlap involves 10–30%, and TEN involves > 30% [1]. The severity-of-illness score for toxic epidermal necrolysis (SCORTEN) was first described by Bastuji-Garin et al. to assess the severity and prognosis of the disease [2]. SCORTEN is the most commonly used scale for prognostication in SJS-TEN and its effectiveness as a tool has been confirmed in several studies [3, 4]. The incidence of SJS and TEN is estimated to be 1.2–6 per million and 0.4–1.2 per million, respectively [5, 6], with mortality rates varying but averaging 1–5% for SJS and 25–35% for TEN [5, 6].

The etiopathogenesis of SJS/TEN is not fully understood, but it is primarily triggered by drugs. The most implicated drugs include sulfonamides, anticonvulsant agents, non-steroidal anti-inflammatory drugs, and allopurinol [7]. SJS/TEN is thought to be a type IV hypersensitivity reaction mediated by T cells. One of the accepted hypotheses regarding how drugs lead to the immunological reaction in SJS/TEN is the hapten/prohapten concept. According to this concept, small molecular drugs covalently bind to proteins in the serum, are recognized by certain HLA molecules, and activate T cells to produce an immune response [8, 9].

The cornerstone of treatment includes immediate discontinuation of the offending drug and multidisciplinary supportive care. Supportive care encompasses monitoring renal functions, fluid and electrolyte levels, ensuring adequate nutrition, pain control, maintaining skin integrity, and preventing infections. Treatment may need to be continued in a burn unit or intensive care unit [8]. Ensuring and maintaining enteral nutrition is crucial. Prophylactic antibiotics are not recommended, but appropriate wound care is critical in preventing secondary infections [8]. There is currently no consensus on immunomodulatory treatment for SJS-TEN. Systemic agents used in treatment include systemic steroids, intravenous immunoglobulin (IVIG), etanercept, infliximab, thalidomide, and cyclosporine [10, 11].

The primary objective of this study is to assess the factors influencing mortality among patients with SJS-TEN. Additionally, we aimed to provide a comprehensive description of the demographic and clinical characteristics of the patients included in our study.

MATERIALS AND METHODS

Study Design

Our study is a retrospective cohort study where data were collected from a total of 12 tertiary care centers between April 2012 and April 2022. Demographic and clinical characteristics, treatments received, and outcome of all adult patients aged ≥ 18 followed up with diagnoses of SJS-TEN were recorded. The factors affecting survival were analyzed.

Ethical Approval

The Ethics Committee of Ankara Bilkent City Hospital approved the study (date: 17/08/2022, number E1-22–2781). Our study was conducted in accordance with the ethical principles in the Helsinki Declaration.

Statistical Analysis

IBM SPSS Statistics 22 software was used for statistical analysis of the obtained data. The suitability of parameters for normal distribution was assessed using the Kolmogorov-Smirnov test, and it was determined that the parameters did not exhibit a normal distribution. Descriptive statistical methods (mean, standard deviation, frequency) as well as Mann-Whitney U test and Wilcoxon signed-rank test were used for comparing quantitative data. For comparing qualitative data, the chi-square test, Fisher's exact chi-square test, and Yates' continuity correction were utilized. Logistic regression analysis

was applied for multivariate analysis. Statistical significance was assessed at $p < 0.05$ level.

For each medication, the mortality rates of patients who used and did not use that medication were compared in univariate analysis. The medications showing differing mortality rates between users and non-users in univariate analysis were further assessed in multivariate analysis, alongside other factors.

RESULTS

The study was conducted with a total of 166 patients, comprising 59 (35.5%) males and 107 (64.5%) females, with ages ranging from 18 to 91 years. The average age was 50.91 ± 21.25 years.

Disease classification was TEN in 50% of cases, SJS in 33.1%, and SJS-TEN overlap in 16.9%. The SCORTEN score within the first 24 h ranged from 0 to 6, with an average of 2.44 ± 1.42 and a median of 2. The median SCORTEN scores were 2 (IQR: 1–2) for patients with SJS, 2 (IQR: 1.25–3) for SJS-TEN overlap, and 3 (IQR: 2–4) for TEN. The SCORTEN score on day 3 also ranged from 0 to 6, with an average of 2.44 ± 1.482 and a median of 2 (Table 1).

Comorbidities were present in 77.1% of cases. The most common comorbidities were coronary artery disease (CAD) with 19.3%, diabetes mellitus with 15.7%, malignancy with 15.1%,

Table 1 Distribution related to disease severity and parameters comprising SCORTEN

		n	%
Disease classification	SJS	55	33.1
	SJS-TEN Overlap	28	16.9
	TEN	83	50
Heart rate/minute	< 120	127	76.5
	> 120	39	23.5
Urea (mg/dl)	< 28	89	53.6
	> 28	77	46.4
Bicarbonate (mEq/l)	> 20	126	75.9
	< 20	40	24.1
Glucose (mg/dl)	< 252	140	84.3
	> 252	26	15.7
Presence of fever	Absent	81	48.8
	Present	85	51.2
Blood culture	Absent	125	75.3
	Present	41	24.7
		Min–Max	Average ± SD (median)
First 24 h SCORTEN		0–6	2.44 ± 1.42 (2)
Day 3 SCORTEN		0–6	2.44 ± 1.48 (2)
Symptom duration (days)		1–21	5.96 ± 3.87 (5)

chronic renal disease with 13.3%, and epilepsy with 11.4% (Table 2).

When examining the distribution of implicated causes, the most common were antibiotics (41.6%), anti-epileptic drugs (23.5%), allopurinol (17.5%), non-steroidal anti-inflammatory drugs (12.7%), and other drugs (12.7%) (Table 3).

The time between the culprit medication use and symptom onset ranged from 2 to 45 days, with an average of 11.92 ± 8.56 days and a median of 10 days.

Treatments Administered

One hundred sixty-five (99.4%) patients received supportive care, and 101 patients (60.8%) received systemic antibiotics.

One hundred forty (84.3%) patients were treated with systemic corticosteroids. The percentage of patients receiving this therapy for SJS, SJS-TEN overlap, and TEN were 83.9%, 89.3%,

Table 3 Distribution of suspected causes

Causes	n	%
Antiepileptic drugs	39	23.5
Antibiotics	69	41.6
Non-steroidal anti-inflammatory drugs	21	12.7
Allopurinol	29	17.5
Other drugs	21	12.7
Mycoplasma pneumoniae infection	0	0
Herpes simplex virus infection	3	1.8
Other infections	4	2.4
Vaccines	2	1.2
Other causes	9	5.4

and 79.6%, respectively. The duration of treatment ranged from 2 to 120 days, with an average of 23.62 ± 21.58 days and a median of 20 days. Treatment initiation ranged from day 1 to 24, with an average of 5.06 ± 4.21 days and a median of 4 days. Of the patients using steroids, 7.1% received pulse steroids, while 92.9% took oral steroids. The median steroid dose for those taking oral steroids was 1 mg/kg/day (IQR: 0.1–2).

Eighty-two (49.4%) patients received IVIG (intravenous immunoglobulin) treatment. The percentages of patients receiving this therapy for SJS, SJS-TEN overlap, and TEN were 28.6%, 53.6%, and 66.7%, respectively. The duration of treatment ranged from 1 to 6 days, with a mean of 4.1 ± 1.16 days and a median of 5 days. The initiation of treatment ranged from day 1 to day 23, with a mean of 6.28 ± 3.92 days and a median of 5 days. The median dose of IVG was 2 g (IQR: 2–3).

Sixty-four (38.6%) patients received cyclosporine treatment. The percentages of patients receiving this therapy for SJS, SJS-TEN overlap, and TEN were 35.7%, 33.9%, and 46.3%, respectively. The duration of treatment ranged from 2 to 98 days, with a mean of 21.18 ± 16.14 days and a median of 20 days. The initiation of treatment ranged from day 1 to day 17, with a mean of 5.49 ± 3.01 days and a median of 5 days. The median dose of cyclosporine was 3 mg/kg/day (IQR: 3–4).

Table 2 The distribution of comorbidities

	n	%
Comorbidity		
Present	128	77.1
Absent	38	22.9
Comorbidities		
Diabetes mellitus	26	15.7
Malignancy	25	15.1
Chronic renal disease	22	13.3
Connective tissue diseases	10	6
Chronic liver disease	4	2.4
Coronary artery disease	32	19.3
Chronic obstructive pulmonary disease	4	2.4
Epilepsy	19	11.4
HIV infection	1	0.6
Hypertension	7	4.2
Other	48	28.9

Five (3%) of the cases received plasmapheresis treatment. Of these patients, two cases were diagnosed as SJS, and three were diagnosed as TEN. The initiation of treatment ranged from day 5 to day 20, with a mean of 13 ± 6.67 days and a median of 15 days.

Only one case received TNF-α (tumor necrosis factor-alpha) antagonist treatment. Etanercept was administered as a single dose (50 mg) on the 5th day, and the patient experienced significant improvement. The distribution of the treatments received is shown in Table 4.

Forty-one percent of the cases ($n = 68$) used a combination of IVIG + systemic corticosteroids, and 30.1% ($n = 50$) used a combination of cyclosporine and systemic corticosteroids.

Laboratory Findings

Of the cases, 90.4% had elevated erythrocyte sedimentation rate/C-reactive protein, 67.5% had neutrophilia, 53% had electrolyte imbalance, 49.4% had leukocytosis, 44.6% had liver function test abnormalities, 40.4% had kidney function test abnormalities, and 12% had eosinophilia.

Patient Outcomes

The complication rate was 51.8%. The most common complications were sepsis (14.5%), intubation (13.9%), acute renal failure (12.7%), urinary tract infection (11.4%), and bacteremia (11.4%).

One hundred ten (66.3%) patients were discharged, 40 (24.1%) patients died, and 16 (9.6%) had residual sequelae. The sequelae included ocular issues in ten cases, genitourinary issues in four cases, and respiratory issues in two cases.

The hospital stay for survivors ranged from 1 to 120 days, with an average of 19.98 ± 14.18 days and a median of 18 days.

The hospital stay for those who died ranged from 3 to 76 days, with an average of 21.80 ± 17.87 days and a median of 15 days.

The baseline skin detachment was $21.82 \pm 18.68\%$, while it progressed to $40.99 \pm 31.82\%$ during follow-up. The increase in the percentage of skin detachment from the initial to the follow-up visit was statistically significant ($p = 0.001$).

Survival-Related Parameters

Univariate Analysis

There was no statistically significant difference in terms of sex and age between surviving and deceased cases ($p > 0.05$).

Deceased cases have significantly higher SCORTEN scores within the first 24 h compared to surviving cases ($p = 0.001$) (Table 5).

Deceased cases have significantly higher SCORTEN scores on day 3 compared to surviving cases ($p = 0.001$) (Table 5). Those with higher day 3 SCORTEN scores have a 2.715-times higher risk of mortality (Table 6).

There is no statistically significant difference in symptom duration between surviving and deceased cases ($p > 0.05$) (Table 5).

Deceased cases have a significantly higher percentage of skin detachment at the onset compared to surviving cases ($p = 0.001$) (Table 5). Those with a higher percentage of skin detachment at the onset have a 1.037-times higher risk of mortality (Table 6).

Deceased cases have a significantly higher percentage of skin detachment during follow-up compared to surviving cases ($p = 0.001$) (Table 5).

Table 4 The distribution of treatments received

Treatments received	n	%
Supportive care treatment	165	99.4
Systemic antibiotics	101	60.8
Systemic corticosteroids	140	84.3
IVIG	82	49.4
Cyclosporine	64	38.6
Plasmapheresis	5	3.0
TNF alpha antagonists (etanercept)	1	0.6

Table 5 Survival-related evaluations

	Survived (n = 126) Average ± SD (median)	Deceased (n = 40) Average ± SD (median)	[1]p
SCORTEN first 24 h	2 ± 1.16 (2)	3.83 ± 1.26 (4)	0.001*
SCORTEN day 3	1.98 ± 1.15 (2)	3.88 ± 1.52 (4)	0.001*
Symptom duration (days)	5.95 ± 3.96 (5)	5.98 ± 3.63 (5)	0.759
Percentage of skin detachment	18.56 ± 17.11 (13.5)	32.1 ± 19.87 (35)	0.001*
Maximum percentage of skin detachment during follow-up	34.79 ± 30.19 (27.5)	60.5 ± 29.13 (64.5)	0.001*
	n (%)	n (%)	
Presence of fever	57 (45.2%)	28 (70%)	[2]0.011*
Blood culture	23 (18.3%)	18 (45%)	[3]0.001*
Comorbidity	92 (73%)	36 (90%)	[2]0.044*
Diabetes mellitus	11 (8.7%)	15 (37.5%)	[2]0.011*
Malignancy	9 (7.1%)	16 (40%)	[2]0.001*
Chronic renal disease	13 (10.3%)	9 (22.5%)	[2]0.087
Connective tissue diseases	7 (5.6%)	3 (7.5%)	[4]0.705
Chronic liver disease	2 (1.6%)	2 (5%)	[4]0.245
Coronary artery disease	22 (17.5%)	10 (25%)	[2]0.410
Chronic obstructive pulmonary disease	2 (1.6%)	2 (5%)	[4]0.245
Epilepsy	16 (12.7%)	3 (7.5%)	[4]0.569
HIV	1 (0.8%)	0 (0%)	[4]1.000
Smoking	1 (0.8%)	0 (0%)	[4]1.000
Hypertension	4 (3.2%)	3 (7.5%)	[4]0.361
Other diseases	37 (29.4%)	11 (27.5%)	[2]0.979
Supportive care treatment	125 (99.2%)	40 (100%)	[4]1.000
Systemic antibiotics	67 (53.2%)	34 (85%)	[2]0.001*
Systemic corticosteroids	110 (87.3%)	31 (77.5%)	[2]0.209
IVIG	59 (46.8%)	23 (57.5%)	[2]0.24
Cyclosporine	52 (41.3%)	13 (32.5%)	[2]0.421
Plasmapheresis	1 (0.8%)	4 (10%)	[4]0.012*
Systemic corticosteroids + IVIG	53 (42.1%)	15 (37.5%)	[3]0.609
Systemic corticosteroids + cyclosporine	40 (31.7%)	10 (25%)	[3]0.418

[1]Mann-Whitney U test, [2]continuity (Yates) correction, [3]Chi-square test, [4]Fisher's exact test

*$p < 0.05$

Table 6 Univariate and multivariate logistic regression results related to mortality

Univariate			Multivariate		
OR (95% CI)		*p*	**OR (95% CI)**		*p*
SCORTEN first 24 h	2.994 (2.092–4.284)	0.001*	SCORTEN: 0–1 versus SCORTEN: 2	2.182 (0.381–12.505)	0.38
			SCORTEN: 0–1 versus SCORTEN: 3	12.000 (2.363–60.948)	0.003*
			SCORTEN: 0–1 versus SCORTEN: 4	22.000 (4.293–112.740)	< 0.001*
			SCORTEN: 0–1 versus SCORTEN ≥ 5	84.000 (13.902–507.537)	< 0.001*
SCORTEN day 3	2.715 (1.952–3.777)	0.001*		–	
Percentage of skin detachment	1.037 (1.017–1.058)	0.001*		–	
Maximum percentage of skin detachment during follow-up	1.026 (1.014–1.038)	0.001*		–	
Presence of fever	2.825 (1.319–6.051)	0.011*		–	
Blood culture	3.664 (1.697–7.911)	0.001*		–	
Comorbidity	3.326 (1.101–10.046)	0.044*		–	
Diabetes mellitus	6.273 (2.576–15.277)	0.011*		–	
Chronic renal disease	2.524 (0.988–6.449)	0.087		–	
Systemic antibiotics	4.990 (1.958–12.721)	0.001*		–	
Plasmapheresis	13.889 (1.505–128.193)	0.012*		22 (1.96–247.2)	0.012*

OR odds ratio, *CI* confidence interval, *p* < 0.05

Those with a higher percentage of skin detachment during follow-up have a 1.026-times higher risk of mortality (Table 6).

The presence of fever was significantly higher in deceased cases (70%) compared to surviving cases (45.2%) (*p* = 0.001) (Table 5). Those with fever have a 2.825-times higher risk of mortality (Table 6).

The rate of positive blood cultures in deceased cases (45%) is significantly higher than in surviving cases (18.3%) (*p* = 0.001) (Table 5). Those with positive blood cultures have a 3.664-times higher risk of mortality (Table 6).

The rate of comorbidity in deceased cases (90%) is significantly higher than in surviving cases (73%) (*p* = 0.044) (Table 5). Those with comorbidities have a 3.326-times higher risk of mortality (Table 6).

The rate of diabetes in deceased cases (37.5%) is significantly higher than in surviving cases (8.7%) (*p* = 0.011) (Table 5). Those with diabetes have a 6.273-times higher risk of mortality (Table 6).

The rate of malignancy in deceased cases (40%) is significantly higher than in surviving cases (7.1%) (*p* = 0.001) (Table 5).

There is no statistically significant difference in the rates of chronic renal disease, connective

tissue diseases, chronic liver disease, coronary artery disease (CAD), chronic obstructive pulmonary disease, epilepsy, HIV, hypertension, and other diseases between surviving and deceased cases ($p > 0.05$) (Table 5).

The rate of systemic antibiotic use in deceased cases (85%) is significantly higher than in surviving cases (53.2%) ($p = 0.001$) (Table 5).

The rate of IVIG use in deceased cases (57.5%) was not significantly higher than in surviving cases (46.8%) ($p = 0.24$) (Table 5).

The rate of plasmapheresis use in deceased cases (10%) is significantly higher than in surviving cases (0.8%) ($p = 0.012$) (Table 5).

There is no statistically significant difference in the rates of use of other treatments (systemic steroids, IVIG, and cyclosporine) between surviving and deceased cases ($p > 0.05$).

Mortality was similar among patients using pulse and oral steroids ($p = 0.88$).

No significant correlation was found between steroid dose and mortality ($p = 0.34$).

No significant correlation was found between the dose of IVIG and mortality ($p = 0.11$).

No significant correlation was found between the cyclosporine dose and mortality ($p = 0.86$).

Multivariate Regression Analysis

When we assessed the effects of the parameters, including SCORTEN score in the first 24 h, SCORTEN score on the 3rd day, percentage of skin detachment, percentage of skin detachment at follow-up, presence of fever, positive blood culture, diabetes, presence of chronic renal disease, and use of systemic antibiotics, IVIG, and plasmapheresis, we found a statistically significant relationship with mortality using backward stepwise logistic regression analysis. The model was deemed significant ($p = 0.001$; $p < 0.05$), with a Negelkerke R-square value of 0.560. Furthermore, the explanatory coefficient of the model was found to be 85.5%, indicating a good level of explanation. The effects of SCORTEN scores within the first 24 h and plasmapheresis use were found to be statistically significant ($p < 0.05$). Compared to SCORTEN 0–1, SCORTEN 2 did not significantly increase mortality ($p = 0.38$). However, SCORTEN 3 elevated mortality by 12 times (OR [95% CI]: 2.363–60.948, $p = 0.003$),

SCORTEN 4 increased mortality by 22 times (OR [95% CI]: 4.293–112.740, $p < 0.001$), and SCORTEN 5–6 escalated mortality by 84 times (OR [95% CI]: 13.902–507.537, $p < 0.001$) compared to SCORTEN 0–1.

The mortality risk exhibited an exponential rise with each increment in SCORTEN. Furthermore, the utilization of plasmapheresis was associated with a 22-fold increase in mortality (OR [95% CI]: 1.96–247.2, $p = 0.012$) (Table 6).

DISCUSSION

Our study included 166 patients with a female/male ratio of 1.81, aligning with the reported female predominance in the literature [12]. The average age was 50.91 ± 21.25 years, similar to Micheletti et al.'s study, which reported an average age of 49 ± 19.2 years [13]. The SCORTEN scores within the first 24 h and on day 3 were similar in our study with a median of 2 but a statistically significant increase in the maximum percentage of skin detachment during follow-up was observed.

One hundred twenty-eight (77.1%) of our patients had comorbidities, with the most common being CAD, diabetes mellitus, malignancy, chronic renal disease, and epilepsy. Manvi et al.'s study found seizure disorder, hyperuricemia/gout, and HIV infection as the most common comorbidities [14]. Schroeder et al. evaluated 28 patients with SJS/TEN in a retrospective study of 11 years of experience in a high-complexity tertiary care hospital; 89.2% of 28 patients were reported to have comorbidities, and cardiovascular comorbidities were more common [15]. Taken together, the data highlight a remarkable proportion of patients to suffer from co-existent disorders, which also necessitate the use of multiple medications.

In our study, antibiotics (41.6%), antiepileptic drugs (23.5%), allopurinol (17.5%), and nonsteroidal anti-inflammatory drugs (12.7%) were the most frequently implicated causes. Abulatan et al.'s study compiled drugs associated with SJS-TEN, highlighting antibiotics, especially sulfonamides, as the most commonly associated [12]. Hsu et al. identified antiepileptics, particularly

carbamazepine, as most frequently associated with SJS-TEN [16].

Due to the rarity of the disease, most studies on SJS-TEN are retrospective and involve a small number of patients. Only a few prospective studies analyzing the efficacy of specific immunomodulatory treatments have been conducted [4, 6, 17]. The absence of large randomized controlled trials prevents the establishment of a standard pharmacological treatment for SJS-TEN. However, there are publications suggesting that immunomodulatory treatments and combinations could be beneficial because of the immunological nature of the disease [18–21]. Whether the observed outcomes are attributable to these treatments or the cessation of the triggering drug and supportive care leads to remission remains uncertain.

Nearly all of our patients received supportive care. The most frequently used systemic immunomodulatory treatments were systemic steroids in 84.3% of patients, IVIG in 49.3%, and cyclosporine in 38.6%. Numerous systematic reviews have attempted to standardize immunomodulatory treatments for SJS-TEN or to find the ideal treatment for SJS-TEN [22, 23]. Zimmermann et al.'s meta-analysis in 2017 compiled 96 studies (covering 3248 patients) and evaluated the immunomodulatory and supportive treatments administered. The treatments assessed included supportive care, glucocorticoids, intravenous immunoglobulin, cyclosporine, plasmapheresis, thalidomide, cyclophosphamide, hemoperfusion, tumor necrosis factor inhibitors, and granulocyte colony-stimulating factors. Their analysis reported that only glucocorticoids and cyclosporine appeared promising in improving survival [22]. Tsai et al.'s recent systematic review and network meta-analysis evaluated the effects of systemic immunomodulatory treatments on mortality in SJS-TEN overlap and TEN. Covering 2079 patients across 67 studies, the analysis of 10 studies found that immunomodulatory treatments did not demonstrate superiority in reducing mortality compared to supportive care, and thalidomide increased mortality. Analysis of 11 studies suggested that the combination of corticosteroids and IVIG could be beneficial for survival, with a SCORTEN-based standardized mortality ratio (SMR) of 0.53 (95% CI, 0.31–0.93).

Cyclosporine and etanercept were mentioned as promising treatments, but further research is needed [23]. As can be seen, the results obtained from these meta-analyses are not in harmony with each other. Due to the rarity of SJS-TEN and their high morbidity and mortality rates, conducting randomized controlled clinical trials is challenging. This makes it hard to determine a definitive "gold standard" treatment approach [24]. In general, systemic steroids, IVIG, and cyclosporine were used as first-line treatments in our study. The selection of these therapies was guided by the patients' comorbidities (such as diabetes mellitus, renal disease, immune suppression leading to increased risk of infection, chronic hepatitis, and hypertension) as well as laboratory findings (such as positive blood cultures, renal function results, and electrolyte levels). In our comparative analysis of survivors and deceased patients, we found that systemic steroids, IVIG, and cyclosporine treatments did not have an impact on mortality. Contrary to our findings, some studies in the literature have reported positive effects of cyclosporine on mortality [11, 17, 25]. Gilbert et al.'s review on the efficacy and safety of cyclosporine treatment in SJS-TEN suggested that using a daily dose of 3 mg/kg could have positive effects on mortality [11]. Kirchhoff et al., in their retrospective study of 64 patients with SJS/TEN/overlap, reported that cyclosporine might have a positive effect on survival compared to IVIG [25]. Valeyrie-Allanore et al.'s phase II open prospective study on 29 patients with SJS/TEN/overlap treated with cyclosporine found a lower death rate than predicted by SCORTEN, suggesting that cyclosporine could improve survival [17].

Five (3%) of our patients received plasmapheresis treatment. On average, treatment commenced on day 13 ± 6.67. Of the five patients who underwent plasmapheresis, three had a SCORTEN score of 2, one had a score of 4, and one had a score of 5. Two of the three patients with a SCORTEN score of 2 died. Plasmapheresis is a potential treatment option in SJS-TEN therapy, but its efficacy is uncertain. The rationale behind plasmapheresis is its ability to remove toxins, including drugs, drug metabolites, and other cytotoxic agents. However, plasmapheresis has potential disadvantages, such as depleting

immunoglobulin levels, which could potentially increase the risk of sepsis [26]. While some studies do not find the use of plasmapheresis in TEN beneficial [27, 28], others support its efficacy [29]. Senda et al.'s study analyzed outcomes of 38 patients treated with plasma exchange (PE) within the first 24 h of hospital admission and 218 patients who did not receive PE, finding no benefit of PE in reducing in-hospital mortality or length of stay [27]. In the study by Krajewski et al., 21 patients who were followed up in a burn center for TEN were treated with plasmapheresis and IVIG. Mortality was observed in 52% of patients. Severe concomitant diseases were observed in the group with mortality. They concluded that plasmapheresis and IVIG treatment should be used only in the group without severe comorbidities; otherwise, it may increase mortality [28]. Han et al.'s prospective observational study randomly applied plasmapheresis to 13 of 28 patients followed for SJS-TEN overlap and TEN, with the remaining 15 receiving systemic treatments other than plasmapheresis. Of the 13 patients who received plasmapheresis treatment, 7 were also receiving corticosteroid or IVIG treatment. This study suggested that plasmapheresis might have advantages over conventional treatments like IVIG and corticosteroids, and its use as monotherapy could be more beneficial [29]. Although the number of the patients receiving plasmapheresis is low in our study, our results do not justify the use of this treatment modality.

In our study, the complication rate was 51.8%, with the most common complications being sepsis (14.5%), intubation (13.9%), acute renal failure (12.7%), urinary tract infection (11.4%), and bacteremia. Micheletti et al.'s comprehensive retrospective study of 377 patients identified significant in-hospital complications of SJS/TEN, including acute renal failure (34.5%), intubation (23.6%), pneumonia (15.1%), urinary tract infection (14.6%), bacteremia (13.3%), sepsis (12.7%), major thromboembolic event/disseminated intravascular coagulation (8.2%), and skin infection (8.0%) [13]. Schroeder et al.'s study found systemic infections as the most common complication, with septic shock occurring in 10.7% of cases [15]. Although 60.8% of our patients used antibiotics, infection was the leading cause of mortality, which underlines the importance of supportive care and avoidance of unnecessary antibiotic use.

Forty (24.1%) of our patients died in hospital. Schroeder et al.'s study found a mortality rate of 17.8% [15]. In our study, the average hospital stay for survivors was 19.98±14.18 days, with a median of 18 days. The hospital stay for those who died ranged from 3 to 76 days, with an average of 21.80±17.87 days and a median of 15 days. Similarly, Micheletti et al.'s study reported an average hospital stay of 16.2 (SD=16.1) days for discharged patients. The overall hospital stay, including survivors, was 21.9 (SD=79.9) days [13].

One of the key objectives of our study was to analyze the factors affecting mortality in SJS-TEN. Therefore, we compared the characteristics of cases that resulted in exitus with those who survived. In the multivariate (adjusted) regression analysis, that beyond SCORTEN 2, the risk of mortality increased exponentially with each increment in SCORTEN, reaching an 84-fold increase in mortality at SCORTEN 5–6. These results affirm SCORTEN as a reliable tool for determining disease prognosis and a primary determinant of mortality. Similar to our study, Krajewski et al. reported SCORTEN as an essential element in stratifying the therapeutic process, allowing for the distinction between patients with a high risk of death at the outset and those expected to have a better prognosis [28]. Our findings also seem to confirm the conclusions of a recent review that an underestimation of mortality was found for SCORTEN values ≤ 3 and the opposite for those > 3 (SCORTEN range: 0–7) [3]. Multivariate analysis also revealed that plasmapheresis was associated with a 22-fold higher risk of mortality. Although plasmapheresis is generally implemented as a relatively late-stage rescue therapy, with only the most severe and unresponsive cases selected for this treatment, that was not the case in our study. As this is a retrospective study, we do not have comprehensive information on the criteria used for selecting patients for plasmapheresis. The fact that plasmapheresis was applied to patients with a lower SCORTEN in our study may be attributed to variations in physicians' treatment approaches. However, data from our regression analysis indicate that plasmapheresis is associated with an

increased risk of mortality, even independent of SCORTEN. We also consider the possibility that the increased mortality that we determined associated with plasmapheresis could be related to the timing of its administration. Similar to our study, several studies have analyzed mortality risk factors in SJS-TEN [30–32]. A recent national study by Wasuwanich et al. in the US evaluated potential factors causing an increase in mortality for SJS-TEN [30]. In their univariable model, increased age, diabetes mellitus, congenital urea cycle metabolism disorders, chronic kidney disease, pneumonia, sepsis, and malignancy presence were significantly associated with increased mortality. Being non-Hispanic white race/ethnicity and having conjunctivitis were associated with a decreased risk of mortality. In the multivariate model, increased age, chronic kidney disease, pneumonia, sepsis, and malignant neoplasia were associated with increased mortality, while being non-Hispanic white was associated with decreased mortality risk [30]. Sunaga et al.'s nationwide study in Japan, evaluating data from 489 patients with SJS-TEN, reported higher mortality rates in patients using systemic steroids. The rate of sepsis in the steroid-using group was higher compared to the non-steroid group, though this increase was not statistically significant. The study found that SJS-TEN patients who developed sepsis had a higher mortality rate in later follow-ups compared to those without sepsis [31]. Sekula et al.'s large-scale, multinational study followed 460 patients diagnosed with SJS/TEN for 1 year [32]. The 6-week mortality rate within this cohort was 23% (95% CI 19–27), with mortality continuing to increase after the 6th week, reaching an overall mortality of 34% (95% CI 30–39) at the end of 1 year. Various factors were found to influence mortality: age, severity of the reaction, recent malignancy, pre-existing severe kidney or liver disorders, and recent infections. Among these, severe liver and kidney disorders were identified as independent risk factors for mortality. Additionally, recent infection was also determined to be an independent risk factor for mortality [32].

The primary limitation of our study is its retrospective design. The majority of treatments being used in combination and the fact that almost all patients received supportive therapy alongside make it difficult to evaluate treatment responses, especially in groups with few patients (e.g., etanercept). There might be biases in the selection of different treatment options, and not all subjects received the same doses of systemic treatments, which complicates comparisons. Additionally, the potential for missing or incorrect data in our study, which compiled data over a lengthy period of 10 years, is a concern.

CONCLUSION

Our study found no impact of systemic corticosteroids, IVIG, and cyclosporine treatments on mortality. We determined that higher SCORTEN (>2) within the first 24 h and the use of plasmapheresis was related to increased mortality. We believe the data obtained from 12 tertiary care hospitals over a 10-year experience will contribute to the literature. The lack of large prospective, randomized controlled trials regarding SJS-TEN still hinders the establishment of a standard treatment protocol. Until effective treatment protocols are developed and integrated into daily practice, it is recommended to meticulously provide supportive care and to determine the most suitable individualized option for each patient based on the physicians' experience.

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REFERENCES

1. Downey A, Jackson C, Harun N, Cooper A. Toxic epidermal necrolysis: review of pathogenesis and management. J Am Acad Dermatol. 2012;66:995–1003.

2. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol. 2000;115:149–53.

3. Torres-Navarro I, Briz-Redón Á, Botella-Estrada R. Accuracy of SCORTEN to predict the prognosis of Stevens-Johnson syndrome/toxic epidermal necrolysis: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2020;34:2066–77.

4. Kanagarajan A, Murthy AB, Moni PK, Palanivel N. Clinicoetiological Study of Stevens-Johnson syndrome and toxic epidermal necrolysis spectrum and the correlation of SCORTEN with prognosis. Indian J Dermatol. 2023;68:25–33.

5. Yang MS, Lee JY, Kim J, et al. Incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis: a nationwide population-based study using national health insurance database in Korea. PLoS ONE. 2016;11: e0165933.

6. Farhat S, Banday M, Hassan I. Antecedent drug exposure aetiology and management protocols in Steven-Johnson syndrome and toxic epidermal necrolysis, a hospital based prospective study. J Clin Diagn Res. 2016;10:FC01-4.

7. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. J Am Acad Dermatol. 2013;69:173.e1-13.

8. Frantz R, Huang S, Are A, Motaparthi K. Stevens-Johnson syndrome and toxic epidermal necrolysis: a review of diagnosis and management. Medicina (Kaunas). 2021;57:895.

9. Hasegawa A, Abe R. Recent advances in managing and understanding Stevens-Johnson syndrome and toxic epidermal necrolysis. F1000Res. 2020;9:612.

10. Chen CB, Wang CW, Chung WH. Stevens-johnson syndrome and toxic epidermal necrolysis in the era of systems medicine. Methods Mol Biol. 2022;2486:37–54.

11. Gilbert M, Scherrer LA. Efficacy and safety of cyclosporine in Stevens-Johnson syndrome and toxic epidermal necrolysis. Dermatol Ther. 2019;32: e12758.

12. Abulatan IT, Ben-David SG, Morales-Colon LA, Beason E, Fakoya AO. A compilation of drug etiologies of stevens-johnson syndrome and toxic epidermal necrolysis. Cureus. 2023;15: e48728.

13. Micheletti RG, Chiesa-Fuxench Z, Noe MH, et al. Stevens-Johnson syndrome/toxic epidermal necrolysis: a multicenter retrospective study of 377 adult patients from the United States. J Invest Dermatol. 2018;138:2315–21.

14. Manvi S, Mahajan VK, Mehta KS, et al. The clinical characteristics, putative drugs, and optimal management of 62 patients with Stevens-Johnson syndrome and/or toxic epidermal necrolysis: a retrospective observational study. Indian Dermatol Online J. 2022;13:23–31.

15. Schroeder JW, Caputo V, Guida S, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: 11-year retrospective experience in a high-complexity tertiary hospital in Milan, Italy. Clin Dermatol. 2023;41:712–20.

16. Hsu TJ, Yeh HH, Lee CH, Liu KL. Stevens-Johnson syndrome and toxic epidermal necrolysis in a referral center in Taiwan. Int J Dermatol. 2021;60:964–72.

17. Valeyrie-Allanore L, Wolkenstein P, Brochard L, et al. Open trial of ciclosporin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol. 2010;163:847–53.

18. Chafranska L, Saunte DM, Behrendt N, et al. Pediatric toxic epidermal necrolysis treated successfully with infliximab. Pediatr Dermatol. 2019;36:342–5.

19. Coulombe J, Belzile E, Duhamel A, et al. Pediatric SJS/TEN subdued by a combination of dexamethasone, cyclosporine, and etanercept. J Cutan Med Surg. 2019;23:547–50.

20. Peng YT, Xiong JX, Wei B, et al. Tumor necrosis factor-α inhibitor for successful treatment of toxic epidermal necrolysis with severe infection: a case series. J Int Med Res. 2024;52:3000605231223059.

21. Fu Y, Xiao Y, Gao T, Zhang J, Wang T. Etanercept combined with glucocorticoid and gamma globulin for treating children with toxic epidermal necrolysis: a case report. Clin Cosmet Investig Dermatol. 2024;17:167–71.

22. Zimmermann S, Sekula P, Venhoff M, et al. Systemic immunomodulating therapies for Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. JAMA Dermatol. 2017;153:514–22.

23. Tsai TY, Huang IH, Chao YC, et al. Treating toxic epidermal necrolysis with systemic immunomodulating therapies: a systematic review and network meta-analysis. J Am Acad Dermatol. 2021;84:390–7.

24. Pisano C, Brown M, Jambusaria A. A comparison of international treatment guidelines for Stevens-Johnson syndrome and toxic epidermal necrolysis. Int J Dermatol. 2023;62:397–403.

25. Kirchhof MG, Miliszewski MA, Sikora S, Papp A, Dutz JP. Retrospective review of Stevens-Johnson syndrome/toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporine. J Am Acad Dermatol. 2014;71:941–7.

26. Wing EJ, Bruns FJ, Fraley DS, Segel DP, Adler S. Infectious complications with plasmapheresis in rapidly progressive glomerulonephritis. JAMA. 1980;244:2423–6.

27. Senda A, Fushimi K. Effectiveness of early treatment with plasma exchange in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. Sci Rep. 2024;14:2893.

28. Krajewski A, Mazurek MJ, Mlynska-Krajewska E, Piorun K, Knakiewicz M, Markowska M. Toxic epidermal necrolysis therapy with TPE and IVIG-10 years of experience of the burns treatment center. J Burn Care Res. 2019;40:652–7.

29. Han F, Zhang J, Guo Q, et al. Successful treatment of toxic epidermal necrolysis using plasmapheresis: a prospective observational study. J Crit Care. 2017;42:65–8.

30. Wasuwanich P, So JM, Chakrala TS, Chen J, Motaparthi K. Epidemiology of Stevens-Johnson syndrome and toxic epidermal necrolysis in the United States and factors predictive of outcome. JAAD Int. 2023;13:17–25.

31. Sunaga Y, Hama N, Ochiai H, et al. Risk factors for sepsis and effects of pretreatment with systemic steroid therapy for underlying condition in SJS/TEN patients: results of a nationwide cross-sectional survey in 489 Japanese patients. J Dermatol Sci. 2022;107:75–81.

32. Sekula P, Dunant A, Mockenhaupt M, et al. Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. J Invest Dermatol. 2013;133:1197–204.