Distinguishing Stevens-Johnson syndrome/toxic epidermal necrolysis from clinical mimickers during inpatient dermatologic consultation—A retrospective chart review

Allison Weinkle, MD,[a] Cory Pettit, BS,[b] Aditi Jani, BS,[c] Jesse Keller, MD,[d] Yuanyuan Lu, MS,[e] Stephen Malachowski, MD, MS,[a] John C. Trinidad, MD,[b] Benjamin H. Kaffenberger, MD,[b] Elizabeth N. Ergen, MD,[c] Lauren C. Hughey, MD,[c] David Smith, MD,[f] and Lucia Seminario-Vidal, MD, PhD[a]
Tampa, Florida; Columbus, Ohio; Birmingham, Alabama; and Portland, Oregon

Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening conditions that may present with similar findings to other severe dermatologic diseases.

Objective: The primary objective of this exploratory study was to explore factors associated with SJS/TEN and develop a model that provides the predicted probability of SJS/TEN for patients for whom the diagnosis of SJS/TEN is considered.

Methods: Retrospective review of consultations for patients with suspected SJS, TEN, or overlap at 4 academic dermatology consultation services.

Results: Overall, 208 patients were included; 59 (28.4%) had a final diagnosis of SJS/TEN, and 149 (71.6%) were given a different diagnosis. The most common mimickers were drug hypersensitivity syndrome (n = 21, 10.1%), morbilliform drug eruption (n = 18, 8.7%), erythema multiforme (n = 15, 7.2%), and acute generalized exanthematous pustulosis (n = 13, 6.2%). Nikolsky sign, atypical targets, fever, and lymphopenia were included in a model for predicting the probability of SJS/TEN.

Limitations: All cases were obtained from academic centers, which may limit the generalization of findings to community-based settings. This was an exploratory study with a small number of cases, and external validation of the model performance is needed.

Conclusion: Early dermatologic evaluation of patients with suspected SJS/TEN is key to separating patients with this condition from those who ultimately receive diagnoses of other serious skin diseases. (J Am Acad Dermatol 2019;81:749-57.)

Key words: dermatology consultation; inpatient; severe cutaneous adverse reaction; Stevens-Johnson syndrome; toxic epidermal necrolysis.

Alan Lyell first introduced the term *toxic epidermal necrolysis* (TEN) in 1956.[1] It was used to describe 4 patients with life-threatening mucocutaneous diseases associated with systemic symptoms. The spectrum of disease ranges from involvement of less than 10% of the body

From the Department of Dermatology, University of South Florida Health Morsani College of Medicine, Tampa, Florida[a]; Wexner Medical Center, Ohio State University, Columbus, Ohio[b]; Department of Dermatology, University of Alabama at Birmingham, Birmingham, Alabama[c]; Oregon Health and Science University, Portland, Oregon[d]; School of Public Health, University of South Florida, Tampa, Florida[e]; and Department of Plastic Surgery, University of South Florida Health Morsani College of Medicine, Tampa, Florida.[f]

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Correspondence to: Lucia Seminario-Vidal, MD, PhD, 13330 USF Laurel Dr, 6th Floor, Tampa, FL 33612. E-mail: luciasem@health.usf.edu.

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surface area, referred to as *Stevens-Johnson syndrome* (SJS) to greater than 30% for TEN, with the zone in between referred to as *SJS/TEN overlap*. Dr. Lyell characterized TEN by extensive epidermal cell death resembling a first-degree burn. Later on, he acknowledged that his initial report had inadvertently included 2 patients with generalized bullous fixed drug eruption and staphylococcal scalded skin syndrome.[2] This initial report highlights the difficulty of diagnosing SJS/TEN and distinguishing it from clinically similar diseases.

CAPSULE SUMMARY

- Stevens-Johnson syndrome/toxic epidermal necrolysis is difficult to distinguish from its most common mimickers—drug reaction with eosinophilia and systemic symptoms, morbilliform drug eruption, erythema multiforme, and acute generalized exanthematous pustulosis.
- Nikolsky sign, atypical targets, fever, and lymphopenia aid in predicting the probability of true Stevens-Johnsons syndrome/toxic epidermal necrolysis.

The reported incidences of SJS, overlap, and TEN range from 1.6 to 9.2 cases per million per year in the United States and 1 to 2 cases per million per year in Europe.[3-8] With mortality rates reported between 23% and 49%,[9,10] it is critical to accurately diagnose SJS/TEN and distinguish it from other vesiculobullous and severe dermatologic conditions such as erythema multiforme (EM), linear immunoglobulin A bullous disease, acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), bullous lupus, acute graft-versus-host disease, staphylococcal scalded skin syndrome, and others because their management and prognoses are quite different. This task proves challenging because all of these conditions may present with desquamation, bullae, erosions, mucosal involvement, and systemic symptoms. Misdiagnosis of SJS/TEN may result in unjustified admissions to the intensive care unit, lead to increased costs, and expose patients to unnecessary treatments.

Rather than confirming a specific hypothesis, the primary aim of this study was to explore factors associated with SJS/TEN and to provide a prediction model for the probability of SJS/TEN for patients for whom SJS/TEN is considered versus a mimicker.

METHODS

This multi-institutional retrospective chart review includes data from 4 academic dermatologic consultation services: Tampa General Hospital, associated with the University of South Florida; University of Alabama Birmingham Hospital; Oregon Health and Science University Hospital; and Ohio State University Medical Center. Each hospital is staffed with at least 1 full-time dermatology hospitalist who evaluated each consultation with a resident team. Each dermatology hospitalist keeps a consultation database with "reason for consultation" and "final diagnosis." After institutional review board approval, these databases were reviewed from January 1, 2015, through December 31, 2017, and cases with "reason for consultation" of SJS, overlap, or TEN were identified, their charts were reviewed, and selected cases were included in the analysis.

Diagnosis of SJS/TEN was based on clinical presentation. Histologic evidence of epidermal necrosis was used to confirm diagnosis in most cases, and the results of direct immunofluorescence studies were used to identify autoimmune blistering conditions. Laboratory tests were used to calculate Score of Toxic Epidermal Necrosis (ie, SCORTEN) in patients with SJS/TEN and European Registry of Severe Cutaneous Adverse Reactions (ie, RegiSCAR) score in patients with DRESS and to aid in the diagnosis mimickers and direct management. Detailed collection of data was performed on initial evaluation by the consulting team through history, chart review, and thorough drug exposure review.

Because this was an observational study, traditional power and sample size estimates are not likely to be valid, given unmeasured confounding. Therefore, a goal was determined to have sufficient data to fit a model with adequate statistical properties.[11,12] The chi-square test and Fisher exact test were applied to compare categorical covariates between true SJS/TEN and mimickers, and the *t* test was used to compare continuous covariates; a Bonferroni correction was applied to each test with a nominal α of .05 allocated across the tests. Variable selection was completed with a forward stepwise logistic regression based on likelihood ratio tests; an α of .05 was used for model entry, and an $\alpha$of .10 was used for removal. Multivariable logistic regression was then fit with the selected variables to predict the probability of SJS/TEN. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were reported. The dermatology hospitalist team final diagnosis was taken as the criterion standard. Model performance was assessed by using sensitivity, specificity, positive predictive value, and negative predictive value. An area under the receiver operating characteristic

Abbreviations used:

AGEP: acute generalized exanthematous pustulosis
AUC: area under the receiver operating characteristic curve
CI: confidence interval
DRESS: drug reaction with eosinophilia and systemic symptoms
EM: erythema multiforme
OR: odds ratio
SJS: Stevens-Johnson syndrome
TEN: toxic epidermal necrolysis

curve (AUC) and a model calibration curve were used to assess the model's discriminative ability and absolute accuracy, respectively.[13,14] The AUC ranges from 0.5 for a test with no discriminative ability at all to 1.0 for a test with perfect discrimination.[15] A nomogram was created to visually represent the model and aid as a quick reference for bedside estimation of the probability of SJS/TEN. Unless otherwise specified, an α of .05 was used. Both SPSS software, version 24 (IBM, Armonk, NY), and R, version 1.1.453, RMS package (R Core Team, Vienna, Austria), were used to perform all analyses.

RESULTS

A total of 4001 inpatient dermatology consultations were requested at the 4 academic centers over the study inclusion periods and reviewed for consultation reason. Of these, 209 (5.2%) were requested for suspected cases of SJS, SJS/TEN, or TEN. In 1 patient, the consulting team could not differentiate between SJS or EM because at times, these diseases can be indistinguishable both clinically and histologically, and the patient was excluded from the analysis. Out of the 208 included patients, 149 (71.6%) patients were given a diagnosis that was not SJS/TEN, and 59 patients were given a final diagnosis of SJS/TEN (Table I). Skin biopsy samples were obtained in all patients with SJS/TEN, except in 3 patients for whom the dermatology team determined that biopsy samples were not needed to establish the diagnosis.

Secondary bivariate analyses of patient risk factors shed light on differences between SJS/TEN and those conditions that may mimic the disease (Tables II and III). More males were diagnosed with SJS/TEN than mimickers (62.7% vs 43.6%, respectively; $P = .01$). In general, patients with SJS/TEN were more critically ill, requiring transfer to tertiary referral centers included in the study (72.9% vs 45.0% of mimickers, $P < .01$) and admission to intensive care units or intensive care burn centers when available (61.0% vs 20.8% of mimickers, $P < .01$). Absence of drug exposure was seen in 38 patients (25.5%) with diagnoses other than SJS/TEN and only 2 patients with SJS/TEN (3.4%). Regarding the currently accepted high-risk preexisting conditions of malignancy, renal dysfunction, and HIV/AIDS, the proportion in patients with a final diagnosis of SJS/TEN compared with its mimickers[4,16] is presented in Table II.

Four conditions stood out as the most common mimickers of SJS/TEN: namely, DRESS, which made up 10.1% of all final diagnoses; morbilliform drug eruption (8.7%); EM (7.2%); and AGEP (6.2%). Analysis of clinical findings highlights differentiating factors between each of these conditions and SJS/TEN (Table III). In our sample, positive Nikolsky sign was seen in 79.7% of patients with SJS/TEN compared with no patients with DRESS or morbilliform eruption, only 1 patient with EM (6.7%), and 3 out of 13 patients with AGEP (23.1%). Macules/patches, papules/plaques, and erythroderma were never the primary lesions in patients with true SJS/TEN, and only 1 out of 59 patients had typical targets, defined as less than 3 cm in diameter, round with well-defined borders, and at least 3 distinct zones. Instead, SJS/TEN patients presented with atypical targets (64.4%) and vesicles/bullae (33.9%). Atypical targets were defined as 2-zone flat or elevated targetoid lesions with poorly defined borders with or without bulla/erosion. A

Table I. Distribution of final diagnoses

Diagnosis	n	%
SJS/TEN	59	28.4
DRESS	21	10.1
Morbilliform	18	8.7
EM	15	7.2
AGEP	13	6.2
Bullous pemphigoid	8	3.8
Staphylococcal scalded skin syndrome	6	2.9
Contact dermatitis	5	2.4
Fixed drug eruption	5	2.4
Small vessel vasculitis	5	2.4
Viral exanthem	5	2.4
Pemphigus	5	2.4
Serum sickness-like reaction	4	1.9
Atopic dermatitis	3	1.4
Linear IGA bullous dermatosis	3	1.4
Pustular psoriasis	3	1.4
Mycoplasma induced mucositis and rash	3	1.4
Urticaria multiforme	3	1.4
Other	24	11.5
Total	208	100

AGEP, Acute generalized exanthematous pustulosis; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *EM*, erythema multiforme; *IgA*, immunoglobulin A; *Morbilliform*, morbilliform drug eruption; *SJS/TEN*, Stevens-Johnson syndrome/toxic epidermal necrolysis.

Table II. Risk factors, epidemiologic differences, and clinical findings in patients with SJS/TEN compared with its mimickers

Risk factors and findings	SJS/TEN (n = 59)	Mimicker (n = 149)	*P* value
Risk factors			
Age in years, mean (SD)	48.0 (20.4)	49.7(20.1)	.60
Sex, males, n (%)	37 (62.7)	65 (43.6)	.01
Reason for admission, rash, n (%)	56 (95.0)	127 (85.2)	.053
Patient was transferred from outside hospital, n (%)	43 (72.9)	67 (45.0)	<.001
Admission location, n (%)*			
ICU (includes MICU and BICU)	36 (61.0)	31 (20.8)	<.001
Floor	23 (39.0)	110 (73.8)	<.001
Not admitted	0 (0.0)	8 (5.4)	.11
High-risk preexisting conditions†			
Malignancy	13 (22.0)	19 (12.8)	.09
Kidney disease	7 (11.9)	15 (10.1)	.70
HIV/AIDS	3 (5.1)	2 (1.3)	.14
More than 1	0 (0.0)	4 (2.7)	.10
None	36 (61.0)	109 (73.2)	.09
Use of high-risk medications, n (%)†			
Antibiotics	20 (33.9)	54 (36.2)	.75
Antivirals	2 (3.4)	2 (1.3)	.32
Allopurinol	1 (1.7)	0 (0.0)	.29
Anticonvulsants	5 (8.5)	13 (8.7)	.95
Nsaids	4 (6.8)	1 (0.7)	.02
More than 1	24 (40.7)	37 (24.8)	.03
Other	1 (1.7)	4 (2.7)	>.99
None	2 (3.4)	38 (25.5)	<.001
Length of stay in hospital, mean (SD)	14.5 (13.2)	10.1(15.1)	.05
Death, n (%)	7 (11.9)	11 (7.4)	.30
Clinical and laboratory findings, n (%)			
Fever	37 (62.7)	28 (18.8)	<.001
Painful skin	53 (89.8)	62 (41.6)	<.001
Positive Nikolsky sign	47 (79.7)	12 (8.1)	<.001
Primary lesion†			
Macule/Patch	0 (0.0)	20 (13.4)	.003
Papule/Plaque	0 (0.0)	34 (22.8)	<.001
Vesicle/Bullae	20 (33.9)	40 (26.8)	.31
Erythroderma	0 (0.0)	21 (14.1)	.002
Typical targets	1 (1.7)	25 (16.8)	.003
Atypical targets	38 (64.4)	9 (6.0)	<.001
CBC†			
Normal CBC level	9 (15.3)	34 (22.8)	.23
Leukocytosis	3 (5.1)	22 (14.8)	.05
Eosinophilia	4 (6.8)	8 (5.4)	.74
Atypical lymphocytes	2 (3.4)	0 (0.0)	.08
Lymphopenia	12 (20.3)	8 (5.4)	.001
Others	9 (15.3)	15 (10.1)	.34
>1 CBC abnormality	20 (33.9)	59 (39.6)	.45
No CBC laboratory result	0 (0.0)	3 (2.0)	.56
CMP†			
Normal CMP value	3 (5.1)	29 (19.5)	.01
Abnormal liver function	4 (6.8)	12 (8.1)	>.99
Abnormal kidney function	0 (0.0)	3 (2.0)	.56
Abnormal electrolyte level	12 (20.3)	24 (16.1)	.47
>1 CMP abnormality	33 (55.9)	63 (42.3)	.08
No CMP laboratory result	7 (11.9)	18 (12.1)	.97

Continued

Table II. Cont'd

Risk factors and findings	SJS/TEN (n = 59)	Mimicker (n = 149)	*P* value
Rash duration, n (%)[†,‡]			
<24	4 (6.8)	12 (8.1)	>.99
24-48	10 (16.9)	13 (8.7)	.09
48-120	12 (20.3)	22 (14.8)	.33
≥120	33 (55.9)	102 (68.5)	.09

BICU, Burn intensive care unit; *CBC*, complete blood count; *CMP*, complete metabolic panel; *ICU*, intensive care unit; *MICU*, medical intensive care unit; *NSAID*, nonsteroidal anti-inflammatory drug; *SD*, standard deviation; *SJS/TEN*, Stevens-Johnson syndrome/toxic epidermal necrolysis.

*P value $\leq \alpha$ after Bonferroni correction because P values are <.02.

†P value $\leq \alpha$ after Bonferroni correction because P values are <.01.

‡Rash duration refers to the time between the onset of the rash to the time of first evaluation by dermatology, in hours.

dusky macule (ie, a macule with a central dusky violaceous hue) was considered an atypical target. These distinct morphologic characteristics appeared more commonly in patients with SJS/TEN than in those with common mimickers. On laboratory analysis, lymphopenia was noted in 20.3% of patients with SJS/TEN and 5.4% of patients with its mimickers (P = .001), and complete metabolic panel results were rarely normal (5.1% vs 19.5% of mimickers, P = .01). Patients with SJS/TEN and those in the mimickers group frequently had more than 1 metabolic abnormality (55.9% and 42.3%, respectively), an isolated abnormality in electrolytes (20.3% and 16.1%, respectively) or only abnormal liver function (6.8% and 8.1%, respectively).

Stepwise regression selected 4 predictor variables, and a multivariable model was fitted with Nikolsky sign (adjusted OR, 78.3; 95% CI, 18.9-324.9; $P < .001$), atypical targets (adjusted OR, 44.1; 95% CI, 9.9-197.5; $P < .001$), fever (adjusted OR, 8.6; 95% CI, 2.4-30.8; P = .001), lymphopenia (adjusted OR, 6.5; 95% CI, 1.2-36.1; P = .033). This multivariable model for the probability of SJS/TEN is defined as follows:

$$\Pr\left(\frac{\text{SJS}}{\text{TEN}}\right) = \frac{e^{(-4.7 + 4.4 \times \text{Nikolsky sign} + 3.8 \times \text{atypical target} + 2.1 \times \text{fever} + 1.9 \times \text{lymphopenia})}}{1 + e^{(-4.7 + 4.4 \times \text{Nikolsky sign} + 3.8 \times \text{atypical target} + 2.1 \times \text{fever} + 1.9 \times \text{lymphopenia})}}$$

The reader may plug a value of 1 or 0 into the equation for each characteristic that is present or absent, respectively, to yield a predicted probability of SJS, pr(SJS). The final model yields a 76.3% sensitivity and 97.3% specificity, with corresponding positive and negative predictive values of 91.8% and 91.2%, respectively. The AUC for the final model is 0.96 (95% CI, 0.94-0.99; $P < .001$), indicating outstanding in-sample discrimination.[15]

Fig 1 displays the model calibration curve (n = 208) for the final model's absolute predictive accuracy. The diagonal line is perfect accuracy and is the theoretical ideal.[13,14] The bias-corrected solid line provides a better (ie, less prone to bias) look at how the model performs (compared with the apparent line). The bias-corrected line tracks the diagonal line and suggests high absolute accuracy at pr(SJS) of less than 0.15 or pr(SJS) of greater than 0.4, with underestimation of pr(SJS) between these values. With an AUC of 0.96 and the model calibration curve as discussed, the final model has strong promise for aiding the diagnosis of SJS/TEN versus a mimicker. Fig 2 is a nomogram that provides a visual representation of the relative contributions of each predictor to pr(SJS) and allows a quick, relatively accessible estimate of pr(SJS). The largest impact is from positive Nikolsky sign, and the smallest is presence of lymphopenia.

DISCUSSION

The use and availability of inpatient dermatology consultation vary nationwide, despite the immense number of patients admitted for dermatology-related diagnoses. In a study of 512 patients admitted for dermatology-related diagnoses, Hu and colleagues[17] discovered that dermatologic consultation changed

Table III. SJS/TEN findings compared with DRESS, AGEP, EM and Morbilliform drug eruption

	SJS/TEN (n = 59), n (%)	DRESS (n = 21), n (%)	*P* value	AGEP (n = 13), n (%)	*P* value	EM (n = 15), n (%)	*P* value	Morbilliform (n = 18), n (%)	*P* value
Fever	37 (62.7)	7 (33.3)	.02	3 (23.1)	.01	4 (26.7)	.01	3 (16.7)	.001
Painful skin	53 (89.8)	6 (28.6)	<.01	4 (30.8)	<.01	9 (60.0)	<.01	4 (22.2)	<.001
Positive Nikolsky sign	47 (79.7)	0 (0.0)	<.01	3 (23.1)	<.01	1 (6.7)	<.01	0 (0.0)	<.001
Primary lesion*									
Macule/Patch	0 (0.0)	2 (9.5)	.07	4 (30.8)	<.01	0 (0.0)	—	5 (27.8)	<.001
Papule/Plaque	0 (0.0)	10 (47.6)	<.01	4 (30.8)	<.01	0 (0.0)	—	3 (16.7)	.01
Vesicle/Bullae	20 (33.9)	1 (4.8)	.01	2 (15.4)	.32	2 (13.3)	.20	0 (0.0)	.004
Erythroderma	0 (0.0)	5 (23.8)	<.01	1 (7.7)	.18	1 (6.7)	.20	6 (33.3)	<.001
Typical targets	1 (1.7)	2 (9.5)	.17	2 (15.4)	.08	10 (66.7)	<.01	4 (22.2)	.01
Atypical targets	38 (64.4)	1 (4.8)	<.01	0 (0.0)	<.01	2 (13.3)	<.01	0 (0.0)	<.001
CBC*									
Normal CBC value	9 (15.3)	0 (0.0)	.10	1 (7.7)	.68	9 (60.0)	<.01	1 (5.6)	.44
Leukocytosis	3 (5.1)	2 (9.5)	.60	2 (15.4)	.22	1 (6.7)	>.99	4 (22.2)	.05
Eosinophilia	4 (6.8)	3 (14.3)	.37	0 (0.0)	>.99	0 (0.0)	.58	0 (0.0)	.57
Atypical lymphocyte value	2 (3.4)	0 (0.0)	>.99	0 (0.0)	>.99	0 (0.0)	>.99	0 (0.0)	>.99
Lymphopenia	12 (20.3)	1 (4.8)	.17	0 (0.0)	.11	0 (0.0)	.11	1 (5.6)	.28
Others	9 (15.3)	0 (0.0)	.10	1 (7.7)	.68	2 (13.3)	>.99	1 (5.6)	.44
More than 1 CBC abnormality	20 (33.9)	15 (71.4)	<.01	9 (69.2)	.02	3 (20.0)	.36	10 (55.6)	.10
No CBC laboratory value	0 (0.0)	0 (0.0)	—	0 (0.0)	—	0 (0.0)	—	1 (5.6)	.23
CMP*									
Normal CMP value	3 (5.1)	2 (9.5)	.60	0 (0.0)	>.99	6 (40.0)	<.01	3 (16.7)	.14
Abnormal liver function	4 (6.8)	6 (28.6)	.02	2 (15.4)	.30	1 (6.7)	>.99	0 (0.0)	.57
Abnormal kidney function	0 (0.0)	1 (4.8)	.26	0 (0.0)	—	0 (0.0)	—	0 (0.0)	—
Abnormal electrolytes	12 (20.3)	1 (4.8)	.17	2 (15.4)	>.99	2 (13.3)	.72	2 (11.1)	.50
More than 1 CMP abnormality	33 (55.9)	10 (47.6)	.51	8 (61.5)	.71	3 (20.0)	.01	13 (72.2)	.22
No CMP laboratory result	7 (11.9)	1 (4.8)	.67	1 (7.7)	>.99	3 (20.0)	.41	0 (0.0)	.19
Rash duration, H*,†									
<24	4 (6.8)	0 (0.0)	.57	1 (7.7)	>.99	1 (6.7)	>.99	3 (16.7)	.34
24-48	10 (16.9)	2 (9.5)	.50	2 (15.4)	>.99	1 (6.7)	.44	1 (5.6)	.44
48-120	12 (20.3)	2 (9.5)	.33	4 (30.8)	.47	2 (13.3)	.72	3 (16.7)	>.99
>120	33 (55.9)	17 (81.0)	.04	6 (46.2)	.52	11 (73.3)	.22	11 (61.1)	.70

AGEP, Acute generalized exanthematous pustulosis; *CBC*, complete blood count; *CMP*, complete metabolic panel; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *EM*, erythema multiforme; *Morbilliform*, referring to morbilliform drug rashes; *SJS/TEN*, Stevens-Johnson syndrome/toxic epidermal necrolysis.

*P value $\leq \alpha$ after Bonferroni correction as P values are <.01.

†Rash duration refers to the time between the onset of the rash to the time of first evaluation by dermatology.

the diagnosis made by admitting teams more than half the time (45%-80% of patients), often leading to treatment changes. Other studies have shown that inpatient dermatology services aid in the accurate diagnosis of skin conditions in hospitalized patients with cellulitis, pseudocellulitis, or opportunistic fungal infection.[18,19] Time to consultation with the dermatology service was almost 3 times longer among those who died during the hospital stay with opportunistic fungal infections.

Here, we showed that dermatologic evaluation is similarly helpful for diagnosing SJS/TEN and its mimickers. Patients with severe cutaneous eruptions frequently present to their local medical centers. When drug exposure is elicited on history and skin denuding, bulla formation, and/or systemic symptoms are present, providers develop appropriate concern for the most severe form of cutaneous drug reaction, SJS/TEN. Through our study of 208 consultations, we discovered that only 59 patients (28.4%) had the life-threatening condition SJS/TEN. Classic SJS/TEN presentation includes skin denuding with active pressure to previously intact lesions or positive Nikolsky sign.[20] From this exploratory study, we additionally suggest the presence of fever, atypical targets, and lymphopenia as clinical features

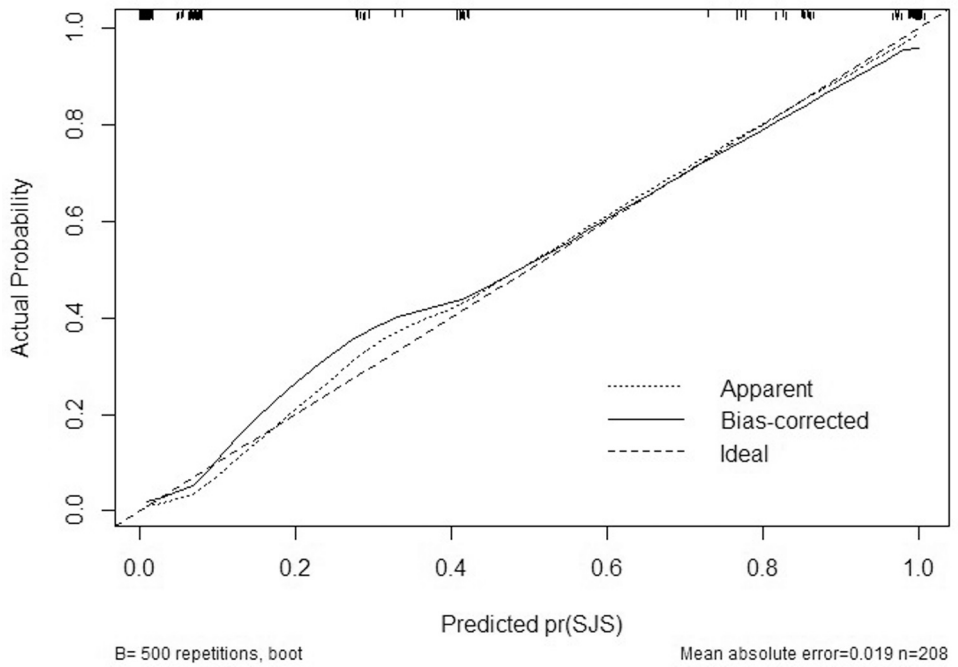

Fig 1. Model calibration curve for the final model absolute predictive accuracy (n = 208). The diagonal line represents perfect predictions (the ideal), and the bias-corrected line (500 bootstrap resamples) indicates that the model performs well overall (mean absolute error, 0.019; 90th percentile of absolute error, 0.038). The bias-corrected curve deviates upward between 0.15 and 0.40, suggesting that the model underestimates the probability of SJS in this range but estimates it well outside this range. The spike histogram across the top shows that there is a paucity of predictions between 0.15 and 0.25, for example, with more nearer the lower and higher ends. *pr(SJS)*, Predicted probability of Stevens-Johnson syndrome; *SJS*, Stevens-Johnson syndrome.

that may be present in SJS/TEN more frequently than in the most common mimickers. These disease characteristics are easily elicited from patient history and physical examination and may be useful for specialists and those first evaluating patients.

SJS/TEN is associated with a prolonged length of stay and higher costs of care (SJS: 9.8 days, $21,437; SJS/TEN: 16.5 days, $58,954; TEN: 16.2, $53,695) compared with all other admissions (4.7 days, $11,281).[4] Without dermatologic evaluation, patients with SJS/TEN mimickers may have unnecessary testing and care. In contrast to the usual evaluation and work-up performed by the dermatology inpatient consultation team before diagnosing SJS/TEN or a mimicker, directors of accredited burn units in the United States indicated that admission to the burn intensive care unit was based frequently on clinical suspicion of SJS/TEN (74%) and that biopsy and dermatologic evaluation were not required for admission (67% and 87%, respectively).[21] Two surveys of burn centers indicated that only 47% to 54% of them consulted a dermatologist for evaluation of patients with suspected SJS/TEN.[21,22] In 1 large burn center, 53.2% of patients with suspected SJS/TEN (n = 50) were assessed by a dermatologist with histopathologic evaluation, and 36% of those received alternative diagnoses.[23] Together, these studies and ours indicate that it is critical to diagnose SJS/TEN correctly and differentiate it from mimickers early in hospitalization to optimize patient care and allocation of medical resources.

Early evaluation of these patients should always include complete blood counts and metabolic panels because lymphopenia and metabolic derangements underscore concern for SJS/TEN. Careful attention must be paid to primary lesion morphology. We emphasize the difference between typical targetoid lesions with 3 distinct zones and the atypical targets seen here nearly exclusively in SJS/TEN.

Although the clinical findings should facilitate earlier and more accurate diagnosis, there have been reported incidents in which multidisciplinary teams could not distinguish between mimickers such as EM and SJS,[24] as was seen in 1 of our patients, who was excluded from final analysis. In a case-control study comparing 552 patients with EM or SJS/TEN with 1,720 control individuals to validate the

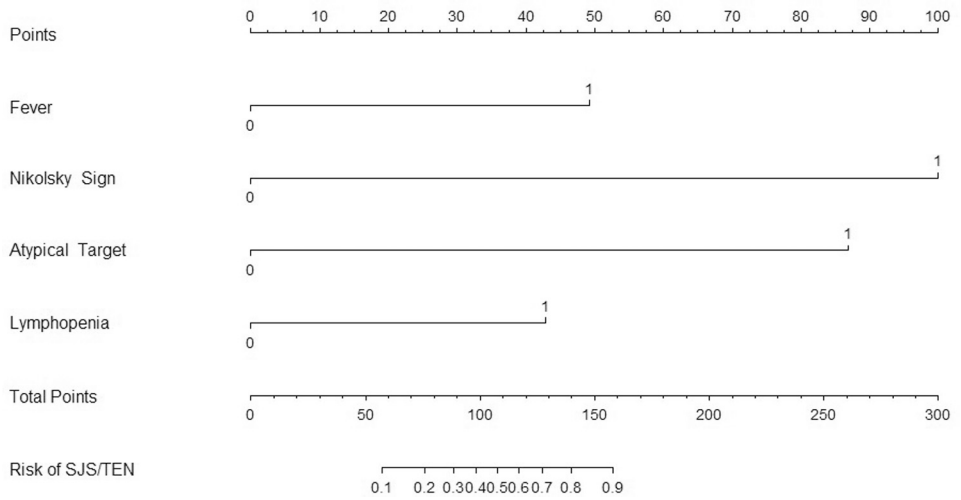

Fig 2. Nomogram used in understanding the prediction model and for estimating probabilities with the shown predictor variables. For example, for a patient with fever (1) and positive Nikolsky sign (1) but negative for atypical target lesions (0) and for lymphopenia (0), we can estimate the probability of SJS. Finding the value of the points associated with fever (1) traces directly to 50 on the "Total Points" line. Next, Nikolsky sign positive (1) corresponds to 100 points. No points are assigned for absent findings, so the "Total Point" line is used to see that a total points of 150 traces down to a pr(SJS) of roughly 0.85 (85%) on the "Risk of SJS/TEN" line. *pr(SJS)*, predicted probability of Stevens-Johnson syndrome; *SJS/TEN*, Stevens-Johnson syndrome/toxic epidermal necrolysis.

distinction between EM and the SJS/TEN spectrum, 92 patients had presentations that could not be distinguished between EM or SJS.[25] Although these diseases each have a unique pathogenesis and prognosis, they are at times impossible to differentiate both clinically and histologically—a diagnostic conundrum to even to most experienced clinician. Additionally, the dermatology literature fails to differentiate between the top 11 common mimickers in the differential diagnosis of SJS/TEN.[26] The data presented here highlight DRESS, morbilliform drug eruptions, EM, and AGEP as the most common diseases misdiagnosed early as SJS/TEN.

A limitation of this study is the number of cases available for examining associated factors and developing a prediction model. With a reported incidence as low as 1.6 cases per 1 million per year in the United States,[4] finding an adequate sample size proves challenging. With the identification of 208 consultations, we were able to notice many distinguishing factors; however, larger studies would show subtle differences in patients with other mimickers not emphasized here. For example, we had few patients with common mimickers such as staphylococcal scalded skin syndrome, acute graft-versus-host disease, pemphigus foliaceus, and severe cutaneous lupus, all of which can present with positive Nikolsky sign and prove to be diagnostically challenging.

Additionally, all of the tertiary care centers included in this study are equipped with academic dermatology services that are regularly involved in diagnosis and treatment when there is any suspicion of SJS/TEN. It is possible that the mimickers listed here may be more likely to be referred to a dermatologist to rule out SJS/TEN because the primary team was aware of some high-risk features (e.g., medication exposure), which may explain some of the lack of differences noted between groups.

Finally, the predictive model should be applied only to patients for which SJS/TEN is considered. Future efforts to externally validate the model performance on new patients should be undertaken. Clinicians who use the model should do so as an only adjunct to, rather than replacement of, clinical expertise and experience.

As in any nonrandomized study, the associations made cannot be misconstrued as causative. We recognize that the data gained from this study provide new information about the diagnostic challenges of severe cutaneous drug reactions but that more detailed comparisons of each individual mimicker and SJS/TEN is warranted. We encourage all medical professionals concerned about potential severe

cutaneous skin reactions to immediately remove all potential offending agents, stabilize the patient, and seek immediate dermatologic consultation.

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