Identifying Prognostic Factors for Toxic Epidermal Necrolysis

Chun-Te Lu[1,2], Chih-Sheng Lai[1], Wen-Hsiang Chien[1], I-Chen Chen[1], Jung-Hsing Yen[1], Ding-Yu Song[1], Yu-Wen Tang[1], and Yeo Kai-Jieh [3,4,*]

[1]Division of Plastic Surgery, Taichung Veterans General Hospital, Taiwan, Republic of China
[2]Division of Plastic Surgery, Chiayi Branch, Taichung Veterans General Hospital, Veterans Affairs Commission, Executive Yuan, Taiwan, Republic of China
[3]Division of Allergy-Immunology-Rheumatology, and Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan, Republic of China
[4]Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan, Republic of China
dryeokj@yahoo.com.tw

Abstract: Toxic epidermal necrolysis (TEN) is a rare, but life-threatening drug allergy that results in death in approximately 25-50 % of patients. There is still controversy over whether the performance of a severity-of-illness score specified TEN (SCORTEN) accurately predicts mortality or if treatment interventions such as corticosteroid or intravenous immunoglobulin (IVIg) could alter mortality. Our purpose was to identify prognostic factors and to assess SCORTEN. Charts of 26 patients aged 54.1 years, admitted to the hospitals (2004–2012) with toxic epidermal necrolysis were reviewed. SCORTEN was associated with a higher mortality rate and the areas under the receiver-operating characteristic curves were 94.5%. The presence of comorbidity, and/or gout, diabetes, higher SCORTEN, statistically significantly increased risk of death. The corticosteroids therapies had the trend to increase the mortality for TEN. IVIg and surgical debride did not significantly alter mortality.
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Keywords: Toxic epidermal necrolysis (TEN), Seven independent prognostic factors of toxic epidermal necrolysis (SCORTEN), mortality, complications.

1. Introduction

Toxic Epidermal Necrolysis (TEN) is a drug-related skin conditions with epidermal detachment of the skin and mucosal erosions (Figure 1) caused by sudden apoptosis of keratinocytes [1-3]. TEN with a mortality rate of 25-50% [4]. A severity-of-illness score specified for TEN, SCORTEN, was developed in 2000 [5]. The investigations of SCORTEN conducted in Asian with TEN were still sparse and whether the IVIg or corticosteroids have the therapeutic effectiveness is still in question [6,7]. The goal of this study is to identify the prognostic factors, to investigate the therapeutic efficacy of corticosteroids and IVIg, and to evaluate the performance of SCORTEN in two medical centers in Taiwanese patients with TEN.

2. Methods

Patients and data collection

Medical charts of all consecutive patients admitted to the burn unit at Taichung Veterans General Hospital and intensive care unit at Chung Shan Medical University Hospital, Taiwan from January 2004 to January 2012 were retrospectively reviewed. Patients were eligible if the discharge diagnosis was toxic epidermal necrolysis. The diagnosis was confirmed by clinical manifestations, or skin biopsy showing full thickness necrosis of the epidermis and a negative direct immunofluorescence test.

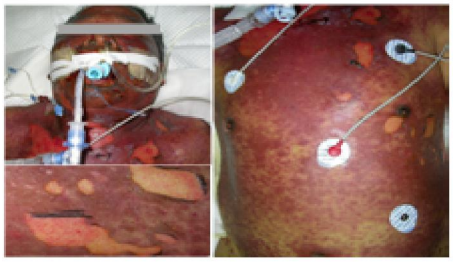

Figure 1: Clinical pictures of toxic epidermal necrolysis

Table 1 Demographic variables for patients in this study (n=26)

Demographic criteria	No. (%)
Female	9 (34.6)
Male	17 (65.4)
Survive	15 (57.7)
Dead	11 (42.3)
Age*	54.1 (24.6)
Body surface area involved (%)*	57.7 (15.8)
SCORTEN*	3.1 (1.3)
Days in hospital*	19.2 (13.6)
Comorbidity	15 (57.7)
Corticosteroids	4 (15.4)
IVIg	1 (3.8)
Surgical debride	13 (50)
Supportive	21 (80.8)

*mean (standard deviation)

Table 2. Patient detail characteristics in this study

No.	Age (yrs)	Sex	Cause	Onset (day)	Hospital Stay(day)	Treatment	SCORTEN	Mortality
1	84	F	Allopurinol	1	7	Supportive	5	yes
2	73	M	Sulpyrine	0	15	Supportive	3	yes
3	66	M	Acetylsalicylic acid	1	9	Supportive	5	yes
4	55	M	Piperacillin	1	2	Supportive	4	yes
5	62	M	Chinese herbal medicine	0	7	Corticosteroid	5	yes
6	83	M	Allopurinol	0	5	Supportive	5	yes
7	44	M	Sulfonamide	1	15	Corticosteroid	3	yes
8	62	F	Thalidomide	0	29	Supportive	5	yes
9	67	F	Cephalexin	0	45	Corticosteroid	4	yes
10	75	M	Carbamazepine	1	9	Supportive	4	yes
11	82	M	Mefenamic acid	1	9	Supportive	4	yes
12	75	F	Allopurinol	0	17	Supportive	3	no
13	81	M	Ketorolac tromethamine	0	10	Corticosteroid	3	no
14	20	M	Ketorolac tromethamine	0	13	IVIg*	1	no
15	89	M	Mefenamic acid	0	14	Supportive	2	no
16	34	F	Ibuprofen	0	35	Supportive	3	no
17	23	F	Chinese herbal medicine	0	20	Supportive	2	no
18	31	F	Ibuprofen	0	27	Supportive	3	no
19	10	M	Ibuprofen	0	30	Supportive	2	no
20	49	M	Carbamazepine	0	10	Supportive	2	no
21	69	M	Ketoprofen	0	42	Supportive	4	no
22	16	F	Naproxen	0	19	Supportive	1	no
23	38	F	Carbamzepine	0	15	Supportive	1	no
24	62	M	Penicillin	0	58	Supportive	2	no
25	11	M	Chinese herbal medicine	1	21	Supportive	3	no
26	46	M	Phenytoin	16	3	Supportive	0	no

*IVIg: Intravenous immunoglobulin

Statistical analysis

Data were analyzed using SAS 9.1.3 (SAS Institute, Cary, NC, USA) and SPSS 13.0 (SPSS Inc., Chicago, IL, USA) software. Patients who died during hospitalization were compared with those who did not by using Fisher's exact probability test for nominal variables, and unpaired two-tailed *t* test for continuous variables. Differences were considered significant at $p < 0.05$. The expected mortality rate predicted by the SCORTEN was calculated using the formula: P (death) = $e^{logit}/1 + e^{logit}$ where logit = −4.448 + 1.237(SCORTEN) [5]. The standardized mortality ratio (standardized mortality ratio = Σ observed deaths/Σ expected deaths) was used to determine whether there was a significant difference between observed and expected mortality on the first day of admission. Predictive accuracy of the logistic regression models was assessed by receiver-operating characteristic (ROC) curves and the area under the curve (AUC). Kaplan-Meier curves were constructed to evaluate the actuarial risk of death relative to treatment regimen. The log-rank test was used to compare treatment regimens relative to survival.

3. Results and Discussions

A total of 26 patients (9 female, 17 male) with mean age 54.1 years old were enrolled (Table 1). Four (15.4%) received corticosteroids, 13 (50%) received surgical debride, and 1 (3.8%) received treatment with IVIg. As in Table 2, 11 patients (42.3%) died of TEN, which is comparable to the average TEN mortality rate published in the literature [8-11]. Seven independent prognostic factors of toxic epidermal necrolysis was calculated (SCORTEN) (Table 3) [5,7].

Table 3. SCORTEN*

Prognostic factor	1	0
Age (yr)	≧40	＜40
Heart rate (/min)	≧120	＜120
Detached body surface (%)	＞ 10	≦10
Serum glucose (mg/dL)	＞ 252	≦252
Serum urea nitrogen (mg/dL)	＞ 27	≦ 27
Serum bicarbonate (mmol/L)	＜ 20	≧20
Malignancy	Yes	No

*Seven independent prognostic factors of toxic epidermal necrolysis (SCORTEN)

One patient had SCORTEN of 0, three patients had SCORTEN of 1, five patients had SCORTEN of 2, seven patients had SCORTEN of 3, five patients had SCORTEN of 4, and five patients with a SCORTEN of 5 (Table 4). In order to analyze how accurately SCORTEN predicted mortality in our study, we compared the probability of death for each patient to a logistic model of the patient's actual death status. The probability of death for each patient was calculated using the same logistic regression equation created by Bastuji-Garin *et al.* [4,5].

Table 4 SCORTEN on admission

		Predicted mortality ¥		Actual mortality	
	No. of patients	%	No. of deaths	%	No. of deaths
SCORTEN					
0	1	1.2	0.01	0	0
1	3	3.9	0.12	0	0
2	5	12.2	0.61	0	0
3	7	32.4	2.27	28.6	2
4	5	62.2	3.11	80.0	4
5	5	85.0	4.25	100.0	5
6	0	95.1	0	0	0
7	0	98.5	0	0	0
Total	26		10.37		11

¥ Values predicted by the SCORTEN with the formula P (death)=$e^{logit}/1+e^{logit}$ where logit=-4.448+1.237(SCORTEN).

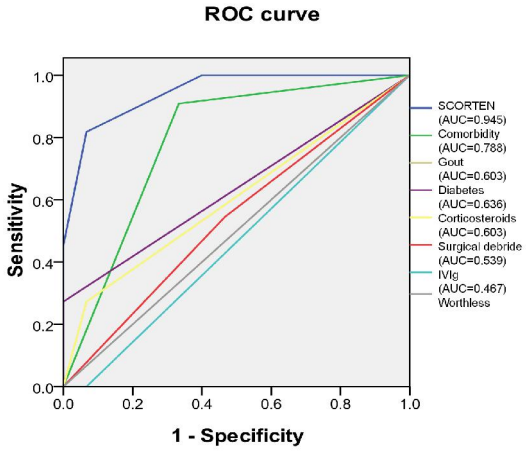

Figure 2: ROC curve for SCORTEN, comorbidity, diabetes, gout, corticosteroids, surgical debride, and IVIg.

Figure 2 shows an ROC curve. An AUC of 1 indicates a perfect test, or perfect accuracy (100%), whereas an AUC of 0.5 means that the test is no better than a random guess (50%-50%). In this study, the AUC for the variable SCORTEN on admission was 0.945, showing excellent correspondence between observed and predicted mortality. The AUC was 0.788 (comorbidity), 0.636 (diabetes mellitus), 0.603 (gout), 0.603 (corticosteroids), 0.539 (surgical debride), and 0.467 (intravenous immunoglobulin). Although the corticosteroids therapies that were reported to reduce morbidity and improve outcome of TEN patients [12,13], we found that corticosteroids had the trend to deteriorate the mortality of patients with TEN (p=0.17) (Figure 3).

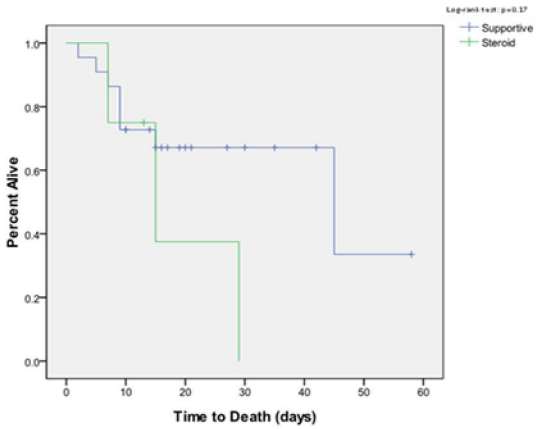

Figure 3: Kaplan-Meier survival curves by corticosteroids treatment

4. Conclusion

In conclusion, mortality in our retrospective case-control study was similar to what has been described in the literature. SCORTEN was confirmed as an accurate predictor of mortality in our study. New information from this analysis shows worse mortality if patients had the presence of additional comorbidities including diabetes and gout; the addition of these comorbidities to SCORTEN also improved its predictive ability. The corticosteroids therapies might increase the mortality for TEN. Surgical debride and IVIg did not significantly alter mortality.

Conflict of interest

The authors state no conflict of interest.

Corresponding Authors:
Yeo Kai-Jieh, M.D.
Division of Allergy-Immunology-Rheumatology, and Department of Internal Medicine, Chung Shan Medical University, Taiwan.
Institute of Medicine, Chung Shan Medical University,Taiwan
No.110,Sec.1,Chien-Kuo N.Rd.,Taichung City 402,Taiwan
E-mail: dryeokj@yahoo.com.tw

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