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Original Article

Risk Factors for Mortality in Senile Patients with Toxic Epidermal Necrolysis in Taiwan

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SUMMARY

Background: Toxic epidermal necrolysis (TEN) is a rare and potentially fatal disorder that manifests as large areas of bullous skin lesions. Early diagnosis and appropriate management are essential for survival. It is associated with a high mortality rate, especially among elderly patients. However, there have been no specific reports targeting elderly TEN patients. The aim of this study was to determine risk factors for mortality in elderly patients with TEN.

Methods: A retrospective review of 19 patients with pathologically confirmed TEN in the burn unit (BU) of a tertiary medical center from January 2004 to December 2015 was conducted. Comparison between survivors and non-survivors was based on clinical findings, laboratory data, complications, and management strategies.

Results: The mortality rate among the 19 patients was 52.6%. The average duration of BU stay was 11.6 days. Significant differences between the two groups were observed in albumin level and delay of transfer to a BU.

Conclusion: Early transfer to a BU for supportive treatment is essential for elderly TEN patients. Patients with hypoalbuminemia have a high risk for mortality, and infection prevention is essential for survival.

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1. Introduction

First described by Lyell in 1956,¹ toxic epidermal necrolysis (TEN) is a rare disease and has an annual incidence of about 1–5 cases per million population.² Although there is a clear understanding of the pathophysiology of the disease in recent years, the resulting mortality remains high.³ The main symptom of the disease is fever with massive bullous skin lesions involving the whole body and sometimes including the mucosae of organs like the mouth, throat and urethra. Hematological abnormalities and ocular involvement may also occur.⁴ The commonly incriminated causes are drugs like chlorpromazine, allopurinol and some antibiotics. According to the definition of the World Allergy Organization, skin detachment lesions less than 10% body surface area (BSA) is termed as Stevens-Johnson syndrome. TEN is diagnosed if there is epithelial detachment involving more than 30% of the BSA. An overlap of SJS/TEN is diagnosed if the lesions involve 10–30% of the BSA. Several risk factors have been related to the high mortality rate associated with this disease. Kidney disease, liver disease and recent episode of infection or malignancy are possible reasons for such casualties.⁵ Although mortality in aged patients is high, no related study was found in the literature. Thus, the purpose of this study was to identify the possible risk factors associated with mortality in senile patients with TEN.

2. Materials and methods

From January 2004 to December 2015, patients older than 65

years diagnosed with TEN and admitted to the burn unit of a tertiary medical center were included in our study. The diagnosis of TEN was based on clinical cutaneous lesions with detachment involving > 30% total BSA (TBSA) and confirmed by pathologic examination after skin biopsy. All demographic data including gender, age, percentage TBSA affected, SCORTEN (SCORE of Toxic Epidermal Necrosis) score, laboratory data, complications, mode of treatment, and outcome were obtained if available. Comorbidities included renal disease, diabetes, chronic obstructive pulmonary disease, and cancer. The prognostic parameters of SCORTEN were calculated with the records obtained within 24 h of admission to our burn unit (BU). Univariate analyses were initially performed. Risk factors including gender, underlying disease, malignancy, tachycardia (> 120/min), epidermal detachment (> 60% TBSA), serum urea (> 10 mmol/L), serum glucose (> 14 mmol/L), serum bicarbonate (< 20 mmol/L), delayed admission to the BU (more than two days), usage of dressing containing silver (Ag), application of steroid, dialysis application, and ventilator support were compared using the chi square test. Fisher's exact test was used if the total number was less than 20 and any one group was less than 5. SCORTEN scores were compared using the two-tailed student's t-test. All variables with $p < 0.05$ in the univariate analyses were included in a binary logistic regression analysis. In-hospital mortality was used as the dependent variable. The adjusted odds ratios with 95% confidence intervals were calculated to explain relative risks of mortality. Statistical analyses were performed using SPSS version 19.0 (SPSS, Chicago, IL, USA). p values < 0.05 were considered statistically significant. This study was approved by the Institutional Review Board of our hospital.

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3. Results

A total of 19 senile patients diagnosed with TEN were admitted to our burn center during the study period (Table 1). The mean age of the patients was 80 years (range: 68 to 92 years). The sex ratio of males to females was about 3:2. The mean BSA affected by epidermal necrolysis was 47.5% (range: 30 to 97%). The mean duration of stay in the BU was 11.6 days. Three patients had malignancies, 7 had diabetes mellitus, 5 had chronic renal insufficiency, and 2 had chronic obstructive pulmonary disease (Table 2). The mean time from the onset of TEN to admission to our BU was 5.1 days. The incriminated drugs were allopurinol (32%), nonsteroidal anti-inflammatory drugs (21%), antibiotics (16%), and anticonvulsants (10%). No specific incriminating drugs could be identified for 4 patients (Table 3). The overall mortality rate in our series was 52.6%, and septic shock was the main cause of death (Table 4). No ocular complications or scar contracture were found. Ag-containing dressings had been used in 7 patients, 11 patients received steroid medications, and no patient underwent treatment with intravenous immunoglobulin (IVIG). The average SCORTEN score was 3.53, and there was no significant difference in average SCORTEN score between survivors and non-survivors. As shown in Table 1, univariate analyses found that albumin level and delayed admission to the BU were significant predictors of patients' survival. Survivors had higher albumin levels (2.9 vs. 2.5 g/dL) on admission and were admitted to the BU sooner (1.0 vs. 4.9 days).

4. Discussion

The mortality rate among our study participants was higher than that in the general population.⁶⁻⁸ The elderly constitute about 10% of the population in Taiwan,⁹ a figure that is increasing with the aging global population. Skin atrophy, immunosenescence, and comorbid diseases among elderly patients always present with atypical symptoms that hamper accurate diagnosis of diseases.¹⁰ Age more than 40 years is a bad predictor in the SCORTEN scoring system¹¹ and our results showed that the outcome of senile patients might be poorer than expected. Although TEN is distinctive, it is clinically difficult to distinguish it from other bullous lesions in older patients. Diseases like Staphylococcal scalded skin syndrome, toxic shock syndrome, pemphigus and bullous pemphigoid have similar early clinical symptoms and signs in aged patients. In the study conducted by Lim et al., the misdiagnosis rate of TEN was up to 20%

without skin biopsy.¹² Misdiagnosis may delay proper management such as cessation of the incriminated medication. Epidermal necrosis in early frozen sections has a high sensitivity and low specificity for detecting TEN. A skin biopsy specimen is useful for distinguishing between differential diagnoses and early initiation of treatment.

More than half of our patients died due to infection, including sepsis and pneumonia. TEN patients lose large areas of skin, mimicking large burn wounds, which expose them to various infections.¹³ Isolation from environmental infection is one of the major functions of a BU. Transfer of patients with TEN to a BU has become a standard of care.^{14,15} The combination of critical care expertise and experience with the management of large wounds makes BUs

Table 2
Comparison of comorbidities between survivors and non-survivors

	Survivors (n = 9)	Non-survivors (n = 10)	Mean	p-value
Kidney disease	11.1%	40.0%	26.3%	0.30
DM	33.3%	40.0%	36.8%	1.00
COPD	11.1%	10.0%	10.5%	1.00
Cancer	11.2%	20.0%	15.8%	1.00

Abbreviations: DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease.

Table 3
Comparison of incriminated agents between survivors and non-survivors

Incriminated agents	Survived	Died	Total	p-value
CPZ	1	1	2	0.91
Allopurinol	1	5	6	0.91
Antibiotics	0	3	3	0.09
NSAIDs	4	0	4	0.56
Unknown	3	1	4	0.55

Abbreviations: CPZ, chlorpromazine; NSAID, nonsteroidal anti-inflammatory drug.

Table 4
Comparisons of in-hospital complications between survivors and non-survivors

Complication	Survived	Died	p-value
Sepsis	2	1	0.91
Pneumonia	1	4	0.92
Acute renal failure	0	3	0.92
Other	0	1	0.94

Table 1
Clinical characteristics of 19 patients according to survivorship

	Survivors	Non-survivors	Mean	p-value
No	9	10		
Males	33.3%	50.0%	40.2%	1.00
Age (yrs)	82.6 ± 5.3	77.8 ± 6.6	80.1 ± 6.3	0.45
BSA (%)	38.3 ± 8.1	55.8 ± 31.1	47.5 ± 24.3	0.12
CRP (mg/dL)	7.8 ± 8.9	13.4 ± 11.4	10.8 ± 11.4	0.35
Fever	66.7%	100%	84.2%	0.09
Cr (mg/dL)	1.4 ± 0.5	3.7 ± 3.7	2.6 ± 2.9	0.29
Glucose (mg/dL)	141.3 ± 67.0	143.9 ± 73.1	142.7 ± 68.3	0.87
SCORTEN score	3.3 ± 1.0	3.7 ± 0.8	3.5 ± 0.9	0.33
Albumin	2.9 ± 0.5	2.5 ± 0.4	2.7 ± 0.5	0.02
Steroid administration	66.7%	50.0%	57.9%	0.65
Ag dressing	22.2%	50.0%	36.8%	0.35
Delayed admission to BU	1.0 ± 1.1	4.9 ± 1.9	3.1 ± 2.5	0.00
Burns	12.4 ± 9.0	10.9 ± 8.1	11.6 ± 8.3	0.60
Hospitalization	23.7 ± 21.1	39.2 ± 34.3	31.8 ± 29.1	0.26

Abbreviations: BSA, body surface area; CRP, C-reactive protein; Cr, creatinine; SCORTEN, SCORe of Toxic Epidermal Necrosis; BU, burn unit.

ideally suited to deal with such complex cases. A large multicenter retrospective comparison of the treatment of TEN at burn centers and non-burn centers found that burn centers had increased use of enteral nutrition, decreased steroid use, decreased use of empiric antibiotics, and more intensive wound management, all of which seemed to contribute to better outcomes.¹⁶ In our series, all patients were transferred to the BU within seven days, but the period of delay was significantly longer among non-survivors than among survivors. Since an accurate diagnosis must be based on pathological examination of a skin biopsy, patients may be admitted to non-burn centers for several days. Based on our finding, prompt transfer of patients with large skin lesions to a BU before confirmation of the diagnosis may be needed to save more senile TEN patients.

One striking finding among our TEN patients is the association of mortality rate with albumin level. The albumin level in the blisters of the TEN patients was found to be lower than that in burn patients, suggesting that TEN is less disruptive to the microvasculature of the dermis than burns. Theoretically, macromolecules like albumin will be retained in the intravascular compartment and should not be influenced by this disease.¹⁷ However, albumin is not only a nutritional indicator but also a major transporter with strong antioxidant properties.¹⁸ In recent years, albumin level has been identified to be associated with mortality in congestive heart failure, acute coronary heart disease, and several surgical procedures.^{19,20} Therefore, hypoalbuminemia may not be associated with the severity of TEN, but may be a possible risk indicator in geriatric patients.

We did not use IVIG or cyclosporine A in our patients. Steroids were administered to control disease progression according to individual conditions, and not as routine medication. Although steroids have been reported to be associated with a high rate of bacterial infection and sepsis in TEN patients,¹⁴ early initiation of steroid therapy seemed to decrease ocular complications.⁷ While our study could not prove the benefit of steroids in improving patient survival, we did not observe any ocular sequelae in our series.

Two major components of management were recently reported in the guidelines: cessation of any offending agents and BU supportive care.^{3,21} Immediate identification of the cause, cessation of the offending drug and replacement with an alternative agent were achieved by cross-communication among our pharmacological, dermatological and burn team members. Intensive supportive care was provided by a multidisciplinary team as occurs in the management of burn patients. However, the mortality rate among our elderly patients was still higher than 40%. Our findings suggest that earlier transfer to the BU and prioritization of patients with hypoalbuminemia may increase patient survival.

Our study has several limitations. First, our data were collected retrospectively, and the cohort included some cases with missing values. We could only do available data analysis. Potential factors affecting patient survival may also not be completely documented in the patients' charts. In addition, the number of patients was small and reflected the experiences of a single tertiary center. Because of the small number, no significant risk factor could be found by logistic regression. Our findings cannot be generalized to all elderly patients. Further nationwide studies will be needed. Likewise, because of the wide disparity in therapeutic modalities, a prospective randomized comparison is necessary for the establishment of a proper protocol.

In conclusion, the risk factors associated with mortality among senile patients with TEN were hypoalbuminemia and delayed ad-

mission to a BU. Early isolation and supportive treatment is essential for the aged TEN patients.

Declarations of interest

None.

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