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Assessment of Mortality among Inpatient Cases with Severe Dermatologic Diseases: Infection and Sepsis, the Most Common cause of Mortality

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Background: Dermatologic diseases are generally managed at an outpatient clinic and most cases have very low mortality rates. However, some dermatologic diseases are life-threatening and only a few studies have assessed their mortality rates and associated factors.

Objective: To investigate the mortality of inpatients with dermatological diseases.

Methods: This retrospective study was conducted by reviewing the medical records of patients who died in the dermatology ward at a tertiary hospital in Korea in a period of 17 years. Patient demographics, dermatologic diseases, immediate cause of death, comorbidities, and clinical factors related with mortality were investigated.

Results: The total number of inpatients in the dermatology ward during the study period was 740. Thirteen patients (1.76%, 5 men and 8 women) expired while they were admitted in the hospital. The median age of the patients was 63.8 years (range, 18 to 86), and the maximum number of deaths occurred in patients over 70 years old (7 out of 13 patients, 53.8%). Drug reactions were the most common dermatologic complication resulting in admission, followed by bullous disease, generalized pustular psoriasis, and dermatomyositis. Most patients had multiple comorbidities, including hypertension, diabetes mellitus, kidney disease, and angina. Sepsis due to infection was the most common cause of death.

Conclusion: Infection was the most important factor contributing to mortality. Old age, immunosuppression, and comorbidities were important factors that contributed to mortality in dermatologic inpatients.

Key Words: Death, Dermatology, Infection, Mortality, Sepsis

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INTRODUCTION

Most dermatologic diseases have very low mortality rates and are generally managed on an outpatient basis. Nevertheless, some dermatologic diseases can be life-threatening and require intensive care as a result of the disease itself or its complications. Analysis of dermatologic diseases and their associated risk factors could provide information to predict or prevent patient death. However, only a few studies have assessed the mortality rates among patients with dermatologic diseases.

We have recorded 13 patient deaths in the dermatology ward from 1998 to 2014. The aim of this study is to investigate dermatologic diseases and the associated factors that lead to death by analyzing these cases.

MATERIALS AND METHODS

1. Data collection

This is a retrospective study conducted at a tertiary hospital in Korea (Department of Dermatology at Pusan National University Hospital, Republic of Korea). All data were collected from the medical records of dermatologic inpatients from 1998 to 2014. Patients who died from malignancy, including melanoma and non-melanoma skin cancer, were excluded. This study was approved by the Institutional Review Board of the Pusan National University Yangsan Hospital (IRB No. 05-2022-094).

Patient medical records and death certificate data were retrospectively reviewed. We analyzed the clinical findings according to the following: (1) patient demographic data, including age, sex, and comorbidities; (2) diagnosis of dermatologic disorders resulting in admission; (3) treatments and progression including length of hospital stay (LoS); (4) cause of death; (5) and laboratory findings, including bacteriological profile and radiologic findings.

2. Statistical analysis

We compared the clinical parameters between expired and recovered patients with Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN). Statistical analyses were performed using SPSS ver. 21.0 (IBM Co., Armonk, NY, USA). Comparisons of clinical parameters between the groups were performed using Fisher's exact test for categorical variables and Mann-Whitney U test for numerical variables. *p*-values less than 0.05 were considered statistically significant.

Table 1. †The top twenty conditions resulting in dermatology inpatient admission at Pusan National University Hospital, Republic of Korea between 1998 and 2014 (Total N = 740)

No	Diagnosis	N (%)
1	Herpes zoster	247 (33.4)
2	Drug reaction	75 (9.9)
3	Psoriasis‡	36 (4.9)
4	Atopic dermatitis	34 (4.6)
5	Contact dermatitis	31 (4.2)
6	Cellulitis/Erysipelas	31 (4.2)
7	Eczema hepeticum	26 (3.5)
8	Pemphigus vulgaris/foliaceus	23 (3.1)
9	Exfoliative dermatitis	22 (3.0)
10	Varicella	21 (2.9)
11	Erythema multiforme	20 (2.7)
12	Urticaria/Angioedema	20 (2.7)
13	Pyoderma/Abscess/Impetigo	19 (2.6)
14	Vasculitis	16 (2.2)
15	Bullous pemphigoid	15 (2.0)
16	Staphylococcal scalded skin syndrome	15 (2.0)
17	Eczematous dermatitis	12 (1.6)
18	Hidradenitis suppurativa	11 (1.5)
19	Pyoderma gangrenosum	9 (1.2)
20	Miscellaneous	57 (7.7)

†Admission for surgical treatment of malignant or benign cutaneous tumor, laser treatment, and aesthetic treatment was excluded
‡Psoriasis included psoriasis vulgaris, generalized pustular psoriasis, pustulosis palmaris et plantaris, and acrodermatitis continua of Hallopeau

RESULTS

A total of 740 patients were hospitalized in the dermatologic ward from 1998 to 2014 (Table 1, admission for the surgical treatment of malignant or benign cutaneous neoplasia, laser treatment, and aesthetic treatment was excluded). Thirteen patients who eventually died during hospitalization were enrolled in this study. The proportion of expired cases was 1.76% (13 deaths/740 dermatologic inpatients) during the study period. Table 2 shows the patient demographics,

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Table 2. Summary of expired patients

Patient	Dermatologic disease	Sex	Age	Admission-death (day)	Treatment	Underlying disease	Cause of Transfer	Cause of death
1	SJS/TEN	F	62	11	Systemic steroid (PO)	HTN, Angina	–	Myocardial infarction
2	SJS/TEN	F	18	99	Systemic steroid (IV/PO) Systemic antibiotics	–	Pneumonia	Sepsis
3	SJS/TEN	F	76	12	Systemic steroid (IV/PO)	HTN, DM, CKD	Sepsis	Sepsis
4	Drug reaction (n=7) SJS/TEN	M	76	7	Systemic steroid (IV/PO) Systemic antibiotics	DM, Angina	Sepsis	Sepsis
5	SJS/TEN	M	58	46	Systemic steroid (PO) Systemic antibiotics	HTN	AKI	Respiratory failure diffuse alveolar hemorrhage
6	SJS/TEN	M	86	33	Systemic steroid (IV/PO) Systemic antibiotics	HTN	Pneumonia	Respiratory failure from pneumonia
7	Exanthematous drug eruption	F	73	40	Systemic steroid (PO)	HTN, DM, Pneumonia	Pneumonia	Respiratory failure from pneumonia
8	Bullous pemphigoid (n = 2)	F	56	53	Systemic steroid (IV/PO) Systemic antibiotics	DM	Sepsis	Sepsis
9		M	71	43	Systemic steroid (IV/PO) Systemic antibiotics	DM, HTN, Psoriasis	Pneumonia	Respiratory failure from pneumonia
10	Exfoliative dermatitis (n = 2)	F	81	29	Topical steroid Systemic antibiotics	HTN	Pneumonia	Sepsis
11		F	81	17	Cyclosporine	HTN, DM	AKI	Respiratory failure from pneumonia
12	Generalized pustular psoriasis (n = 1)	F	37	8	Methotrexate	–	–	Sepsis
13	Dermatomyositis (n = 1)	M	55	31	Systemic steroid (PO) Hydroxychloroquine	–	Increased liver enzyme	Sepsis

AKI: acute kidney injury, CKD: chronic kidney disease, DM: diabetes mellitus, HTN: hypertension, SJS/TEN: Stevens-Johnson syndrome and toxic epidermal necrolysis

comorbidities, and dermatological disorders causing mortality.

1. Demographics

Fig. 1 shows the age distribution of the patients. The mean age was 63.8 years (range, 18~86). Eleven of out 13 patients (84.6%) were older than 55 years, and the highest mortality was recorded in patients older than 70 years (7 out of 13 patients, 53.8%). A slight female dominance among the patients was observed (male : female ratio, 1:1.6). Ten of 13

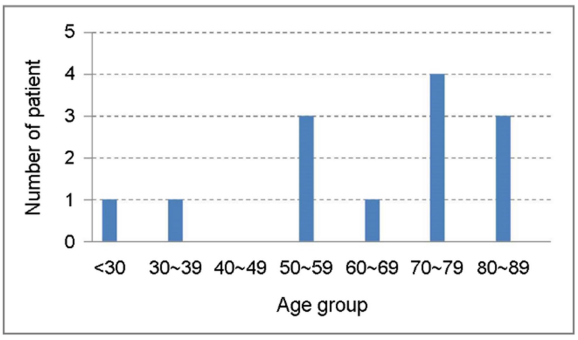

Fig. 1. Age distribution of expired patients

patients (76.9%) had more than one comorbidity, including hypertension (n = 8), diabetes mellitus (n = 6), angina pectoris (n = 2), and chronic kidney disease (n = 1). None presented with HIV infection.

2. Diagnosis of dermatologic disorders

Dermatologic complications responsible for admissions were drug reactions, including SJS/TEN and exanthematous drug eruption (n = 7), as well as bullous pemphigoid (BP, n = 2), exfoliative dermatitis (n = 2), generalized pustular psoriasis (GPP, n = 1), and dermatomyositis (n = 1).

The offending medications responsible for drug reactions were antibiotics in two patients, non-steroidal anti-inflammatory drugs in two patients, allopurinol in two patients, and "unknown" in one patient.

SJS/TEN was the most common dermatologic disorder in this study (n = 6). The mean detached body surface area (BSA) was 42.0 ± 19.2% (range, 20~70), and the mean SCORTEN was 2.8 ± 1.3 (range, 1~4) points upon admission. Compared with the recovered patients with SJS/TEN during the same period (n = 58), expired patients had significantly lower serum albumin levels (expired patients 3.0 ± 0.5 vs. recovered patients 3.9 ± 0.6, Mann-Whitney *U* test, $p = 0.002$) and higher blood urea nitrogen levels (expired patients 49.6 ± 39.7 vs. recovered patients 18.9 ± 9.6, Mann-Whitney *U* test, $p = 0.016$). Other laboratory findings, SCORTEN, and BSA were not significantly different between the two groups (data not shown).

3. Treatments and progression

Twelve patients (92.3%) were treated with immunosuppressive agents, such as systemic steroids (n = 10, 76.9%), cyclosporine (n = 1, 7.7%), and methotrexate (n = 1, 7.7%).

Table 3. Bacteriological isolates in culture-positive patients among the patients with severe dermatologic diseases

Pathogen	Number
Pseudomonas aeruginosa	6
Staphylococcus aureus (including methicillin-resistant *Staphylococcus aureus*)	2
Klebsiella pneumonia	1
Acinetobacter baumannii	1
Vancomycin-resistant *Enterococcus faecalis* (VRE)	1
Candida albicans	1

Antibiotics were administered in seven patients (53.8%) from admission. None of the expired patients with SJS/TEN were treated with intravenous immunoglobulin.

Two patients (15.4%) died in the dermatology ward, and 11 patients (84.6%) were transferred to another department or an intensive care unit. A total of 11 patients were transferred because of suspected sepsis (n = 6), continuous fever (n = 2), renal dysfunction (n = 2), or abnormal liver function (n = 1). The average LoS in hospital (from admission to expiration) of all patients was 31.6 ± 24.7 days (range, 7~99). The mean LoS in dermatology wards (from admission to expiration or transfer) was 9.5 ± 8.5 days.

4. Cause of death

Seven of 13 patients (53.8%) developed septic shock and died as a result. Five patients (38.5%) died from acute respiratory failure caused by pneumonia (n = 4) or diffuse alveolar hemorrhage (n = 1). One patient (7.7%) died from acute myocardial infarction.

5. Laboratory findings

Abnormal laboratory findings upon admission included leukocytosis (n = 5), electrolyte imbalance (n = 3), thrombocytopenia (n = 2), anemia (n = 2), abnormal kidney function (n = 2), and abnormal liver function (n = 2).

Infection developed in 11 patients (84.6%). The most common infection site was the respiratory tract (pneumonia), followed by the kidneys (acute pyelonephritis) and skin (soft tissue infection). Table 3 summarizes the results of the blood cultures. Twelve microorganisms in 7 patients were identified

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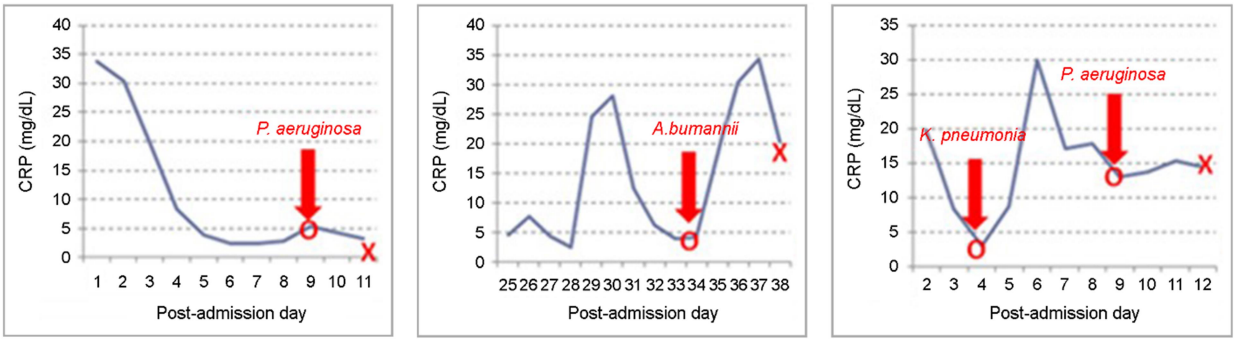

Fig. 2. CRP reversal from a decrease to an increase with positive blood cultures (X: patient death)

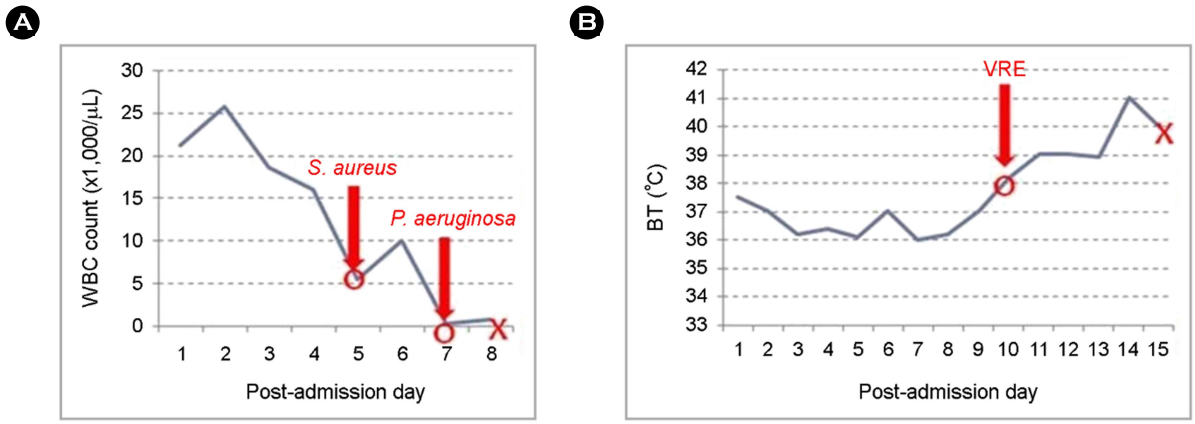

Fig. 3. Sudden-onset neutropenia (A) and sudden-onset fever (B) (VRE: vancomycin-resistant *Enterococcus faecalis*, X: patient death)

using bacterial cultures from blood. The most common pathogens were well-known microorganisms causing hospital-acquired infections (HAI), such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*. In most cases, the results of the blood cultures were reported after the patient's death. Among the patients who died from infection, a reversal of C-reactive proteins (CRP) from decreasing to increasing levels with positive microbial growth in the blood cultures was observed in three patients (Fig. 2). Sudden-onset neutropenia (Fig. 3A) and sudden-onset fever (Fig. 3B) with positive microbial growth in the blood cultures were observed in one patient.

DISCUSSION

The frequency of dermatologic diseases causing death is different for each country. The most common diseases were autoimmune blistering diseases in Brazil[1] and India[2], chronic ulcers and cellulitis in the United States[3], and SJS/TEN in the United Kingdom[4]. In the present study, SJS/TEN was the most common disorder resulting in death, followed by BP, exfoliative dermatitis, GPP, and dermatomyositis in dermatologic inpatients.

SJS/TEN is a well-known, life-threatening disorder. The overall hospital mortality rate of SJS/TEN is 22~25%[5]. In our study, the mortality rate of SJS/TEN was 9.4% (6 out of 64 patients with SJS/TEN). The prognosis score of SJS/TEN (SCORTEN) is useful, but the SCORTEN upon admission was not significantly different between the expired and recovered patients (expired patients 2.8 vs. recovered patients 2.0, Mann-Whitney *U* test, $p = 0.224$) in the present study. BP is the most common autoimmune blistering disease. Old age, poor general health, and the presence of anti-BP180 antibodies have been associated with a poor prognosis[5]. Exfoliative dermatitis is potentially life-threatening because of complications, including fluid and electrolyte imbalance, thermoregulatory disturbance, fever, tachycardia, high-output failure,

and hypoalbuminemia. GPP can potentially result in life-threatening complications, such as hypocalcemia, bacterial superinfection, sepsis, and dehydration. Death occurred in 2% of the GPP cases[6]. The overall mortality rate of dermatomyositis and polymyositis was 22%. Variables associated with poor outcomes of dermatomyositis and polymyositis were older age, pulmonary and esophageal involvement, and cancer[7].

It is well-known that old age contributes to increased mortality in diseases. In a population-based study examining death from non-neoplastic skin disease in the United States, most deaths occurred in patients aged 65 years and older[3]. Similarly, in the present study, 85% of deaths occurred in patients aged 55 years and older, and the highest mortality was reported in patients aged 70~79.

Infection developed in 11 patients (84.6%) and 7 patients (53.8%) died from septic shock. Inflammation, fissuring, and excoriation of the diseased skin increase susceptibility to bacterial colonization and infection in dermatologic diseases, such as SJS/TEN, exfoliative dermatitis, and blistering diseases[5]. Immunosuppressive agents are the mainstay of treatment in severe inflammatory skin diseases, but they can also predispose patients to infections[8]. Most patients (92.3%) were treated with immunosuppressive agents in the present study.

The most common pathogens were *P. aeruginosa*, *S. aureus* (including MRSA), *K. pneumoniae*, and *E. coli*, which are important microorganisms in HAI. Tao et al.[9] reported that *P. aeruginosa*, *K. pneumoniae*, and *E. coli* are common pathogens in HAI. Vijayamohan et al.[10] reported a high prevalence of methicillin-resistant *S. aureus* (MRSA) infection among dermatology inpatients. Prolonged duration of illness, prolonged antibiotic and steroid therapy, and diabetes were relative risk factors for acquiring MRSA. In another study, prolonged LoS was an important factor in hospital-acquired MRSA[11]. Therefore, precautions against HAI during hospitalization, such as hand decontamination, personal hygiene, disinfection of patient equipment, and safe injection practices[12], could decrease mortality among patients with severe dermatologic disease.

Among the patients who died from sepsis, sudden-onset fever, neutropenia, and CRP elevation were observed. Bor et al.[13] reported a fourfold increase in the mortality rate of patients with fever compared with those without fever. CRP is an acute-phase reactant, suggesting that its levels rise in response to inflammation. In sepsis, IL-6, TNF-a, and IL-1b stimulate the release of CRP during the inflammatory cascade[14,15]. Therefore, the reversal of CRP from decreasing to increasing levels could be a marker of infection, and serial CRP measurement could be a valuable tool in patients with severe dermatologic disorders. Leukopenia (defined as a white blood cell count of <4,000/μL) can be seen in sepsis as one of the criteria of systemic inflammatory response syndrome. Leukopenia indicates anomalies in the host's inflammatory response and is associated with poor outcomes[16]. Therefore, although fever, CRP elevation, and neutropenia can be observed without infection, such as those with connective tissue disease, malignancy, and cardiovascular disease[17,18], efforts should be made to identify any infection sites in these situations.

The limitations of this study include its retrospective design, small cohort size, and the single center nature of the study.

CONCLUSION

In conclusion, our study revealed that drug reactions, such as SJS/TEN, were the most common dermatologic disease leading to mortality that is associated with infection and sepsis. Factors including old age, epithelial loss by dermatologic diseases, and immunosuppression could predispose infection in these patients. Infection, especially during hospitalization, was the most important factor contributing to mortality. Therefore, efforts to prevent HAI could contribute to decreasing mortality. This study aims to improve the understanding of severe dermatologic diseases and contributes to the prevention of deaths in patients with dermatologic disorders.

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CONFLICT OF INTEREST

In relation to this article, we declare that there is no conflict of interest.

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ETHICAL APPROVAL STATEMENT

The study was approved by the Institutional Review Board of (IRB No. 05-2022-094). This study was conducted in accordance with the principles of the Declaration of Helsinki.

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