The effect of comorbidities on overall mortality in Stevens-Johnson Syndrome: an analysis of the Nationwide Inpatient Sample

Harib Ezaldein MD, Mariam Totonchy MD, Christopher Chow BS, Andre Samuel MD, Alessandra Ventura MD

Affiliations: Yale School of Medicine Department of Dermatology, New Haven, Connecticut

Corresponding Author: Alessandra Ventura, MD, Yale School of Medicine Department of Dermatology, 333 Cedar St, LCI 501, PO Box 208059, New Haven, CT 06520-8059, E-mail: alessandra.ventura@yale.edu

Abstract

Background: Stevens Johnson Syndrome (SJS) is a life-threatening skin condition with an overall mortality rate of 5%. Although the causes and pathology of the disease have been well studied, the factors that significantly contribute to mortality remain unclear. Objective: To determine relevant risk factors that increase the likelihood of inpatient mortality after diagnosis of SJS. Methods: A retrospective cohort study of the 2010-2011 Healthcare Costs and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) database was conducted. This study included 1,811 patients who encountered inpatient hospital stays with a discharge diagnosis of SJS. Results: The primary outcome of our study was in-hospital mortality. We analyzed the prevalence and associated inpatient mortality of underlying critical illness in patients with SJS. Three age ranges of patients in this study showed significantly increased rates of inpatient mortality by odds-ratio with a 95% CI: 70-79 years (10.91% mortality, OR=4.57, p=0.001), 80-89 years (10.67% mortality, OR=4.48, p=0.001), and 90+ years (9.30% mortality, OR=4.22, p=0.028). Two comorbid conditions showed significant association with increased inpatient mortality in SJS by odds-ratio with a 95% CI: cirrhosis (14.58% mortality, OR=2.79, p=0.028) and metastatic disease (10.62% mortality, OR=1.87, p=0.031). Interpretation: Age (70+ years), cirrhosis, and metastatic disease were identified as significantly associated with inpatient mortality after diagnosis with SJS. These findings enhance current understanding of the pathology of this disease, as well as help improve clinical management of high-risk patients to reduce inpatient mortality.

Keywords: Stevens-Johnson syndrome, toxic epidermal necrolysis, National Inpatient Sample, risk factors, comorbidities

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are disorders of high morbidity and mortality, characterized by epidermal necrosis following drug exposure [1]. Classification as SJS or TEN depends on the extent of body surface area (BSA) affected by epidermal detachment (>30% in established TEN, 10-30% in SJS/TEN overlap, <10% in SJS,). A National Institutes of Health (NIH) working group agreed that mucous membrane erosions are present in all SJS/TEN patients [2]. Little is established regarding methods of predicting patient prognosis. Bastuji-Garin and colleagues proposed a unique severity of illness score in 2000 for TEN (SCORTEN: age, malignancy, pulse, blood urea nitrogen level, glucose level, bicarbonate level, and body surface area), which has since been evaluated and used as a prognostic score [3]. SJS/TEN are usually triggered by an immune reaction to a drug, including most commonly antibiotics, non-steroidal anti-inflammatory agents, anticonvulsants, and allopurinol [4, 5]. SJS related to mycoplasma pneumonia infection is observed predominantly in children. Other studies have implicated a genetic basis for the immune reaction [6-8]. The disease onset starts 8 to 12 days after drug exposure, typically as an acute macular exanthema with rapidly spreading necrosis involving the mucous membranes [8].

Although the exact pathophysiology of SJS/TEN remains unclear, immune-mediated apoptosis of keratinocytes followed by necrosis is believed to be the basis of the epidermal detachment. Keratinocyte death is presumed to be a result of soluble Fas ligand (FasL) or granulysin produced by activated cytotoxic T cells [9-11]. Chung et al. found a 10- to 20-fold increase in blister cell expression of granulysin, an eight-fold increase in granzyme B, a three-fold increase in perforin, and a two-fold increase in serum FasL [10]. Activated cytotoxic T cells express FasL on their surface and bind target cells, activating intracellular caspases and leading to the controlled destruction of the target cell. In an alternative pathway, metalloproteinases can cleave FasL, producing a soluble form of FasL, which retains the capacity to bind to the Fas receptor and trigger apoptosis. TNF and nitric oxide have also been implicated in the apoptosis of TEN, as TNF can activate the "death receptor" TNF-R1, causing caspase activation and cell death [11, 12].

The annual incidence of TEN is 0.5–1.2 cases per million, whereas the incidence of SJS is 1.2–6.0 cases per million [14, 15]. The overall mortality rate of Stevens Johnson syndrome varies between 1% and 5%, whereas TEN ranges from 25% to 30% [16]. The most common causes of death are epithelial loss, bacterial and fungal infections, and sepsis. A universally accepted drug treatment regimen has not been established, though corticosteroids, intravenous immunoglobulin (IVIG), cyclosporine, and TNF inhibitors have been studied [16, 17].

There is evidence that infiltrates of cytotoxic T lymphocytes contain an increased amount of TNF, which is hypothesized to induce apoptosis at the level of the keratinocyte via its TNF- receptor [18, 19]. The potential to treat SJS/TEN with biological agents is also currently under investigation. Paradisi et al. treated 10 patients affected by TEN with a single dose of etanercept (50 mg subcutaneously). The patients responded to treatment and attained complete re-epithelialization within a mean of 8.5 days (range, 7-20 d) [20]. Another study demonstrated remarkable efficacy in treating TEN in an HIV-positive patient with mucocutaneous lesions and extensive truncal targetoid lesions and epidermal detachment [21, 22]. Infliximab has also shown significant effects in a number of cases, with one instance of TEN resolution within 24 hours of a first dose (5mg/kg) [23, 24]. Adverse effects have yet to be reported regarding the use of biologics in SJS/TEN cases, highlighting the changing landscape of therapeutic possibilities.

In this study, we examined a population of patients, from the Nationwide Inpatient Sample, diagnosed with SJS with the aim of identifying potential risk factors that might increase the likelihood of inpatient mortality following SJS. By analyzing factors such as age and comorbidities, we hope to further elucidate the mechanisms by which SJS can lead to inpatient mortality, as well as to improve the ways in which SJS patients are treated.

Methods

Study Design and Setting

A retrospective cohort study of the 2010-2011 Healthcare Costs and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) database was conducted. NIS, developed by the U.S. Agency for Healthcare Research and Quality (AHRQ), is a stratified systematic sample from all HCUP hospitals equivalent to 20% of all discharges from U.S. hospitals [25].

Participants/Study Subjects

All patients aged 18 or greater with a diagnosis of SJS were identified. SJS was identified using International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes (695.13).

Data elements

Age and medical comorbidities were analyzed as possible risk factors for inpatient mortality. Age is reported in NIS as a continuous variable. Medical comorbidities were determined based on ICD-9 diagnosis coding. Medical comorbidities analyzed were alcoholism (ICD-9 303.00-303.99), cirrhosis (ICD-9 571.00-571.99), diabetes mellitus (ICD-9 250.00.250.99), end-stage renal disease (ESRD; ICD-9 585.60-585.69), epilepsy (ICD-9 345.00.345.99), human immunodeficiency virus (HIV; ICD-9 42.00-42.99), and metastatic cancer (ICD-9 140.00-210.99).

Statistical analysis, study size

The primary outcome measure of this cohort study was inpatient mortality. First, the overall rate of

inpatient mortality was determined based on inpatient outcomes in NIS. Second, multivariate logistic regression was used to identify risk factors for inpatient mortality. Age was converted into a categorical variable for multivariate analysis (18-29, 30–39, 40-49, 50-59, 60-69, 70–79, 80 +). All statistical analyses were performed using Stata® version 13.0 (StataCorp, LP, College Station, Texas, USA). All statistical tests were two-tailed and an α level of 0.05 was considered as statistically significant.

Results

Demographic data included gender, age, and comorbidity data for the 1,811 SJS patients in this study. Gender distribution showed 729 males (40.3%) and 1,082 females (59.8%). The mean age of patients studied was 56.4 years, with the most populated age range being 50-59 years (353 patients, 19.5%). Six hundred thirty nine patients fall below that range (18-49 years, 35.3%) and 819 patients fall above that range (>59 years, 45.2%). The most commonly occurring comorbidity among patients was diabetes (460 patients, 25.4%), followed by metastatic disease (160 patients, 8.8%) and epilepsy (149 patients, 8.2%). Additional studied comorbidities include end-stage renal disease, cirrhosis, alcoholism, and HIV occurred in 227 patients (12.3%). In total, 996 patients (55.0%) expressed a comorbid condition alongside SJS. This is conveniently summarized in **Table 1**.

Length of inpatient stay for SJS diagnoses was limited to a range of 0 to 30 days. The median length of inpatient stay was 5 days, and mean length of stay was 8.4 days. This is graphically depicted in **Figure 1**.

Comorbidities were analyzed as risk factors for SJS inpatient mortality. The overall inpatient mortality rate for SJS patients included in this study was 5.91%. Three age ranges showed significantly higher rates of mortality: 70-79 years (10.91% mortality, OR=4.57, p=0.001), 80-89 years (10.67% mortality, OR=4.48, p=0.001), and 90+ years (9.30% mortality, OR=4.22, p=0.028). These three age ranges encompass all patients greater than 70 years of age. We also examined the inpatient mortality rate among patients displaying different comorbidities. Two comorbid conditions showed significant association with increased inpatient mortality after SJS: cirrhosis (14.58% mortality, OR=2.79, p=0.028) and metastatic disease (10.62% mortality, OR=1.87, p=0.031). The remaining comorbidities presenting among patients with SJS did not demonstrate any significant increase in mortality rate (**Table 2**).

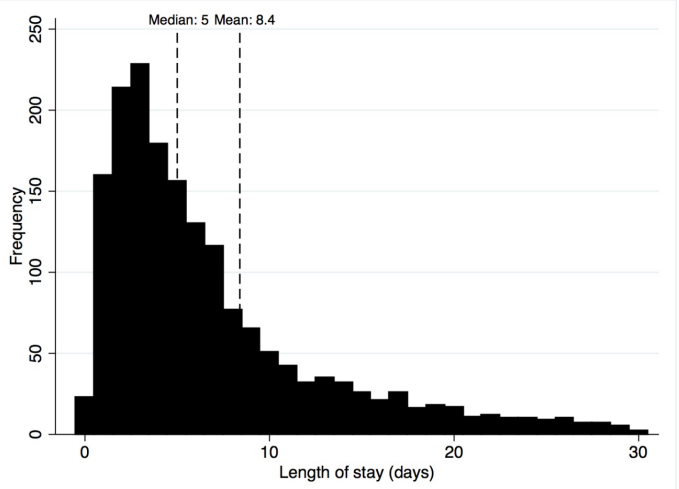

Figure 1. *Steven Johnson Syndrome. Length-of-stay distributions (in days) across all SJS inpatient cases. The overall distribution of overall inpatient stays across the analyzed time period. Mean and median inpatient stay are* **8.***4 and 5 days, respectively.*

Discussion

Interpretation

In this retrospective study, we report an overall rate of inpatient mortality of 5.91% with an average hospital length of stay between 8 and 9 days. Although this figure falls within the expectations of overall mortality, several key findings help improve our notion of characterizing overall risk [26, 27]. For one, older age extensively increases patient risk, perhaps owing to the potentially multiple comorbidities that can develop over time and hamper a patient's capability to respond to aggressive treatment. Age also portends a greater exposure risk to iatrogenic antigens, which can predispose such patients to developing immunological conditioning against the hundreds of drugs associated with SJS [28]. Our study showed an incremental augmentation of inpatient mortality risk, with the greatest percentage of death seen between 70 and 89 years of age.

When stratifying by comorbidities that increase patient exposure to SJS-causing agents, we learned that only patients with cirrhosis and metastatic disease had significantly higher mortality. These findings could represent cases in which patients

Table 1. *Patient demographics.*

N = 1811	Frequency	Incidence
Gender		
Male	729	40.3%
Female	1,082	59.8%
Age, in years (mean: 56.4)		
18 - 29	204	11.3%
30 - 39	174	9.6%
40 - 49	261	14.4%
50 - 59	353	19.5%
60 - 69	323	17.8%
70 - 79	275	15.2%
80 - 89	178	9.8%
90 +	43	2.4%
Comorbidities		
Diabetes	460	25.4%
Metastatic disease	160	8.8%
Epilepsy	149	8.2%
End-stage renal disease	106	5.9%
Cirrhosis	48	2.7%
Alcoholism	42	2.3%
HIV	31	1.7%

are unable to clear medications effectively or are exposed to large numbers of prophylactic agents due to immunocompromised states, both scenarios leading to increased antigen formation, drug-drug interactions, or risk for toxic serum drug levels. The contribution of these two conditions seems particularly relevant in light of the fact that 30-50% of SJS cases are linked to administration of medications [29]. The presence of metastatic disease may also cause a heightened immune sensitivity through the production of cytokines such as IFN, potentially contributing to the progression of SJS [30]. HIV, ESRD, alcoholism, type 2 diabetes, and epilepsy were all associated with higher rates of inpatient mortality compared to our overall patient sample, though the effect was not as powerful. With end-stage renal disease in particular, it may be that such patients are getting dialyzed regularly, masking an expected effect. Therefore, we reason that a lacking effect results from improvement in management and a larger prevalence of chronic diseases, namely diabetes mellitus, metastatic disease, and epilepsy in our cohort.

One of the drawbacks of the NIS database lies in the inability to achieve proper follow-up studies, as most of the data is restricted to inpatient hospital stays [31]. There were far fewer entries listed as the

Table 2. *Stevens Johnson Syndrome. Multivariate analysis of risk factors for mortality.*

Outcome: Mortality	Mortality rate (Overall: 5.91%)	Odds ratio (95% C.I.)	P-value
Age			
18 - 29	0.98%	0.41 (0.08 - 1.99)	0.266
30 - 39	4.02%	1.54 (0.53 - 4.53)	0.430
40 - 49	2.68%	Reference	-
50 - 59	5.38%	1.90 (0.78 - 4.62)	0.159
60 - 69	5.88%	2.08 (0.85 - 5.09)	0.108
70 - 79	10.91%	4.57 (1.94 - 10.78)	0.001
80 - 89	10.67%	4.48 (1.82 - 11.07)	0.001
90 +	9.30%	4.22 (1.17 - 15.29)	0.028
Comorbidities			
Cirrhosis	14.58%	2.79 (1.11 - 7.00)	0.028
Metastatic disease	10.62%	1.87 (1.06 - 3.31)	0.031
HIV	6.45%	1.79 (0.40 - 7.95)	0.445
End-stage renal disease	8.49%	1.60 (0.77 - 3.34)	0.207
Alcoholism	9.52%	1.59 (0.49 - 5.18)	0.441
Diabetes	7.17%	1.06 (0.68 - 1.66)	0.792
Epilepsy	4.03%	0.79 (0.33 - 1.85)	0.580

Significant values appear in bold text.

SJS/TEN overlap or TEN cases, which restricted our ability to decipher trends over the entire spectrum of emergent epidermolytic adverse reactions. This is possibly related to the nuanced dermatological definitions of SJS/TEN overlap based on body surface area, which may not be known to most practitioners on a nationwide scale. It is also useful to note that a recent NIH working group has stated that SJS and TEN are considered a single disease [2]. Another complication involves the fact that characterizing a primary neoplasm for the metastatic cases included in the study is not possible owing to the reliance on ICD-9 codes within the database. Although our primary outcome is inpatient mortality, if a significant portion of the cases represents re-hospitalizations, this could falsely elevate the importance of a particular comorbidity or exposed risk. Additionally, comorbidities were assumed to exist prior to admission, making it difficult to interpret if they were diagnosed within a hospital stay especially since NIS data cannot provide diagnostic timelines of each inpatient case. Coding errors along with bias from missing or unreported data can also potentially limit the study, a common issue with databases requiring administrative input. The database lacks information regarding the lag between patient presentation and initiation of offending agent, which can also be affected by comorbidities.

It is reassuring that our findings are confirmatory of other studies. Sekula and colleagues demonstrated in a mortality risk factor study that severe liver or kidney disorders, along with recent malignancy or infection, were all associated with increased mortalities with varying degrees of significance [32]. This was corroborated in another recent study that showed an overall 39% prevalence of such associated conditions in an SJS/TEN cohort [33]. Malignancy was further

shown to be associated with a higher mortality rate of SJS in a recent study that also demonstrated the effect of malignancy-related risk factors, such as chemotherapy treatment [34]. A recent joint-institutional study demonstrated some evidence that corticosteroids, which are prevalent in use, may increase the time until onset for SJS and prolong duration of symptoms, but did not affect severity or mortality [35]. Our study has many implications for patients and practicing dermatologists, from preventative and therapeutic standpoints. An analysis of over 3,000 drug descriptions showed that a number of discrepancies existed in drug dictionaries regarding their warnings of SJS risk associated with certain drugs [36]. Improving such reporting can help raise physician awareness and patient education as an additional preventative measure. Further studies need to shed light on other diseases that may increase the mortality among our older patients, as such details will ultimately help clinicians develop a risk-stratifying differential to treat patients with SJS and avoid its lethal complications and progression.

Conclusion

An analysis of the Nationwide Inpatient Sample revealed a preponderance of Stevens-Johnson syndrome among female patients and a larger risk of mortality with increased age, cirrhosis, and metastatic disease, perhaps related to greater exposures to offending agents or dysregulated immune sensitivity.

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