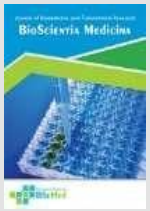
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Drug-Induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Retrospective Study on Causative Agents and Patient Profiles in an Indonesian Hospital Setting

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ARTICLE INFO

Keywords:
Adverse drug reaction
Drug eruption
SCORTEN
Stevens-Johnson syndrome
Toxic epidermal necrolysis

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v9i7.1327

A B S T R A C T

Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) represent rare, severe mucocutaneous adverse drug reactions characterized by extensive epidermal necrosis and significant morbidity and mortality. Understanding the specific causative agents and patient profiles within local populations is crucial for early diagnosis and management. This study aimed to characterize SJS/TEN cases in a tertiary hospital setting in Indonesia. **Methods:** A retrospective descriptive study was conducted using secondary data from medical records of patients diagnosed with SJS, SJS/TEN overlap, and TEN admitted to the inpatient installation of Dr. Moewardi General Hospital, Surakarta, Indonesia, between January 2022 and December 2024. Data collected included demographics (age, gender), comorbidities, diagnosis classification (SJS, SJS/TEN overlap, TEN), suspected causative drugs, length of hospital stay, SCORTEN score, and patient outcome (discharged alive or deceased). Total sampling was employed, excluding records with incomplete data. Data were compiled and analyzed descriptively. **Results:** Fifty-one patients were included, with a slight female predominance (52.94%). The largest age group affected was 19-59 years (60.78%). The distribution of diagnoses was SJS (41.18%), SJS/TEN overlap (31.37%), and TEN (27.45%). The mean SCORTEN score for the cohort was 2. The most common suspected causative drug classes were antibiotics (25.71%), followed by analgesic-antipyretics (24.29%), and anticonvulsants (22.86%). Carbamazepine (11.43%) and amoxicillin (10%) were frequent individual culprits. Epilepsy (13.73%) and diabetes mellitus (11.76%) were common comorbidities, although a significant portion (33.33%) had no recorded comorbidity. The mean length of stay was 9 days. Overall mortality was 15.68%, with higher rates observed in TEN (28.57%) compared to SJS (9.52%) and SJS/TEN overlap (12.5%). **Conclusion:** SJS/TEN affected predominantly adults, with antibiotics, analgesics, and anticonvulsants being the most implicated drug classes. While mortality was considerable, it appeared lower than some international reports, particularly for TEN. Recognizing common causative agents and patient risk factors, such as specific comorbidities like epilepsy and diabetes, can aid clinicians in early identification and prompt management of these life-threatening conditions.

1. Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are categorized as rare, acute, and life-threatening mucocutaneous reactions that are predominantly triggered by medications. These conditions are characterized by extensive necrosis and detachment of the epidermis, involving both the skin and mucous membranes, and are associated with significant morbidity and mortality. The classification of SJS, SJS/TEN overlap, and TEN is primarily based on the extent of body surface area (BSA) affected by epidermal detachment. Specifically, SJS involves detachment of less than 10% BSA, SJS/TEN overlap involves 10-30% BSA detachment,

and TEN involves detachment of greater than 30% BSA. Despite the shared pathophysiology, the degree of skin involvement significantly influences the prognosis of these conditions. The global incidence of SJS and TEN is estimated to be low. For SJS, the incidence ranges from 1 to 6 cases per million person-years, while for TEN, it ranges from 0.4 to 1.2 cases per million person-years. However, it is important to note that the associated mortality rates remain alarmingly high. Mortality rates have been reported as 1-9% for SJS and escalate to 30-50% for TEN in various studies. It is important to acknowledge that some reports suggest potentially lower rates, which may depend on the specific setting and advancements in supportive care. The primary causes of mortality in SJS/TEN include complications such as sepsis, electrolyte imbalances, and multi-organ failure. These factors highlight the critical importance of early diagnosis and specialized management for these conditions. Medications are implicated in over 80% of SJS/TEN cases. A wide range of medications has been associated with SJS/TEN, but certain classes are considered high-risk. These high-risk classes include anticonvulsants (e.g., carbamazepine, lamotrigine, and phenytoin), antibiotics (particularly sulfonamides), allopurinol, and non-steroidal anti-inflammatory drugs (NSAIDs) of the oxicam type. The pathogenesis of SJS/TEN is complex and not yet fully understood. However, it is recognized as an immune-mediated process, likely involving a delayed-type hypersensitivity reaction (Type IV) with drug-specific T lymphocytes. The activation of cytotoxic T cells (CTLs) and natural killer (NK) cells leads to the release of mediators such as granulysin, perforin/granzyme B, and Fas-Ligand (FasL), which induce widespread keratinocyte apoptosis.[1-3]

Genetic predisposition plays a significant role in the risk of developing SJS/TEN, particularly with certain drugs. Specific Human Leukocyte Antigen (HLA) alleles, such as HLA-B*15:02 (associated with carbamazepine in Southeast Asians) and HLA-B*58:01 (associated with allopurinol), have been strongly linked to an increased risk. In addition to genetic factors, other risk factors may include systemic lupus erythematosus, active malignancy, infections (especially Human Immunodeficiency Virus - HIV), and potential abnormalities in T-cell function or regulation, which can be associated with aging or certain diseases. The clinical presentation of SJS/TEN typically begins with a prodromal phase characterized by non-specific symptoms. These symptoms may include fever, malaise, cough, and sore throat, often mimicking an upper respiratory tract infection. This prodromal phase usually precedes the development of the mucocutaneous eruption by 1-3 days. The cutaneous manifestations classically start as ill-defined erythematous macules, sometimes with atypical targetoid features, predominantly on the trunk and face. These lesions rapidly coalesce, progressing to flaccid blisters and extensive epidermal detachment, often elicited by gentle pressure (Nikolsky's sign). Mucosal involvement is a hallmark feature of SJS/TEN, affecting two or more sites in the majority of patients. Oral mucositis, characterized by painful erosions and hemorrhagic crusting of the lips, is nearly universal. Ocular involvement is also frequent, ranging from conjunctival hyperemia to severe pseudomembrane formation, and can lead to long-term sequelae such as blindness, thus requiring urgent ophthalmologic consultation. Furthermore, genital and, less commonly, respiratory and gastrointestinal mucosal involvement can occur.[4-6]

Given the severity and rapid progression of SJS/TEN, prompt recognition, immediate withdrawal of the suspected causative drugs, and the institution of intensive supportive care are of utmost importance. Management typically occurs in specialized units, such as intensive care or burn units. The focus of management includes wound care, fluid and electrolyte management, nutritional support, pain control, temperature regulation, and the prevention or treatment of secondary infections. The use of systemic immunomodulatory therapies, such as systemic corticosteroids, intravenous immunoglobulin (IVIG), cyclosporine, or TNF-alpha inhibitors, remains a topic of debate. There is varying evidence regarding their

efficacy in halting disease progression or improving mortality, and treatment decisions are often individualized. Prognostication tools, most notably the SCORTEN score, are used to predict mortality risk. The SCORTEN score is calculated within the first 24-72 hours of admission and is based on seven clinical and laboratory parameters. This score can help guide management decisions, including determining the level of care required. While there is a substantial body of global research on SJS/TEN, there is a relative lack of data on the specific epidemiological characteristics, causative drug patterns, associated comorbidities, and outcomes of these conditions within the Indonesian population. Regional variations in drug prescribing habits, genetic predispositions (HLA allele frequencies), and access to healthcare can significantly influence the presentation and management outcomes of SJS/TEN. Therefore, it is essential to understand the local context to optimize prevention strategies, improve early detection, and refine management protocols. Previous reports from Indonesia have identified anticonvulsants, NSAIDs, and antibiotics as important causative agents and have noted the occurrence of adverse drug reactions (ADRs) in hospitalized patients. However, continuous surveillance and updated profiles are necessary to maintain a current understanding of the evolving nature of SJS/TEN in this population.[7-10] This study was conducted to provide a contemporary descriptive profile of SJS, SJS/TEN overlap, and TEN cases managed at a major tertiary referral hospital in Surakarta, Central Java, Indonesia, over a recent three-year period (January 2022-December 2024). The study focuses on patient demographics, clinical severity, implicated medications, comorbidities, and treatment outcomes. The findings are expected to contribute valuable local data to the understanding of SJS/TEN in Indonesia and inform clinical practice.

2. Methods

This study was meticulously designed and executed as a descriptive retrospective analysis. The fundamental purpose of this retrospective approach was to conduct a thorough and in-depth examination of the clinical and epidemiological characteristics exhibited by patients diagnosed with Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) within a defined healthcare setting. The core strength of a retrospective study lies in its ability to leverage existing clinical data, which provides a window into real-world medical practice. By analyzing data that was previously recorded as part of routine patient care, this study aimed to capture the nuances of how SJS/TEN presents, how it is managed, and what the outcomes are in a specific context. This approach allowed the researchers to investigate a cohort of patients who had already completed their treatment course, enabling the study of the entire clinical trajectory from presentation to discharge (or other outcome).

The research was strategically carried out at Dr. Moewardi General Hospital. This hospital is not just any healthcare facility; it holds the distinguished position of being a large, tertiary referral center. In the healthcare hierarchy, tertiary referral centers occupy the highest level, providing specialized and advanced medical care that goes beyond the capabilities of primary or secondary care facilities. Dr. Moewardi General Hospital plays a pivotal role in the healthcare ecosystem of Surakarta and the surrounding regions. It serves as a central hub, receiving patients with complex and challenging medical conditions that necessitate a high degree of medical expertise, cutting-edge technology, and a wide array of specialized services. The hospital's affiliation with the Faculty of Medicine, Universitas Sebelas Maret, further amplifies its significance. This affiliation signifies that the hospital is actively involved in the training and education of future physicians and other healthcare professionals. It also fosters a culture of academic inquiry and research, ensuring that medical practices are evidence-based and continuously improving. The selection of Dr. Moewardi General Hospital as the specific site for this study was a well-considered decision. It was based on the understanding that a tertiary referral center would likely manage a

substantial volume of SJS/TEN cases, providing a rich dataset for analysis and enhancing the representativeness of the study findings.

The study was carefully designed to encompass a defined period of three years, specifically from January 1, 2022, to December 31, 2024. This specific timeframe was not arbitrary; it was chosen with the explicit purpose of capturing recent trends in the occurrence of SJS/TEN. The rationale behind this lies in the dynamic nature of medical practice and disease patterns. Factors such as changes in the availability and prescribing of medications, the emergence of new risk factors, and evolving diagnostic and treatment approaches can all influence the epidemiology and clinical presentation of SJS/TEN over time. By focusing on this contemporary period, the researchers aimed to minimize the risk of including outdated or irrelevant data that might not reflect current clinical realities. This approach ensures that the study's findings are as relevant and applicable as possible to current medical practice, providing clinicians with the most up-to-date information to guide their decision-making.

The study population was rigorously defined to ensure clarity and precision in case selection. It comprised all patients who were admitted to the inpatient wards of Dr. Moewardi General Hospital during the three-year study period and received a diagnosis of Stevens-Johnson Syndrome (SJS), SJS/TEN overlap, or Toxic Epidermal Necrolysis (TEN). This focus on inpatient wards is crucial. SJS/TEN are severe and potentially life-threatening conditions that typically necessitate hospitalization for intensive medical management. These patients require close monitoring of their vital signs, meticulous wound care, management of fluid and electrolyte imbalances, pain control, and prompt intervention for any complications that may arise. Therefore, by limiting the study population to inpatients, the researchers specifically targeted cases that were serious enough to warrant hospital-level care, ensuring that the findings are relevant to the management of severe SJS/TEN.

The process of identifying eligible patients for inclusion in the study was systematic and rigorous, relying on the established framework of the International Classification of Diseases, 10th Revision (ICD-10). The ICD-10 is a globally recognized system used by healthcare professionals to classify and code diseases and health conditions. It provides a standardized language that ensures consistency and uniformity in the recording and reporting of diagnoses. In this study, researchers meticulously searched the hospital's medical record system, which includes both electronic and paper-based records, using the specific ICD-10 codes assigned to SJS/TEN. The use of both electronic and paper records is essential to ensure that all eligible cases are captured, regardless of the format in which the patient's information is stored. The specific ICD-10 codes used were: L51.1 for Stevens-Johnson syndrome, L51.2 for Toxic epidermal necrolysis [Lyell], and L51.3 for Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome. These codes are internationally recognized and widely used in epidemiological studies and healthcare statistics, facilitating comparisons with other research conducted in different parts of the world.

A total sampling method was employed in this study. This approach, also known as a census, means that every single patient who met the inclusion criteria and was identified within the defined study period was included in the final analysis. The decision to use total sampling was a deliberate one, driven by the desire to maximize the representativeness of the study findings. By including all eligible cases, the researchers aimed to create the most complete and accurate picture possible of SJS/TEN within the specific hospital setting. This method eliminates the potential for sampling bias, which can occur when only a subset of the population is selected for study. Sampling bias can distort the results and limit the generalizability of the findings. Total sampling, by contrast, ensures that the results are based on the totality of available data, making them more robust and reliable.

The study employed a set of carefully defined inclusion and exclusion criteria to ensure the selection of appropriate cases and maintain the quality of the data. The primary inclusion criterion was a documented final diagnosis of SJS, SJS/TEN overlap, or TEN. This criterion emphasizes the importance of a definitive diagnosis made by the attending physicians, who were responsible for the patient's care during their hospitalization. These physicians, often specialists in dermatology or internal medicine, used their clinical expertise and knowledge of diagnostic criteria to determine the specific diagnosis for each patient. To further strengthen the reliability of case selection, the inclusion criterion also required that the physician's diagnosis be corroborated by the presence of the corresponding ICD-10 codes (L51.1, L51.2, or L51.3) within the patient's medical record. This dual requirement, involving both clinical diagnosis and standardized coding, provided a robust mechanism for confirming cases and minimizing the risk of misclassification. Conversely, several exclusion criteria were applied to exclude cases that might compromise the integrity of the study. The most important exclusion criterion was the unavailability of complete medical records. This included situations where the records were missing entirely or, more commonly, where there were significant gaps in the data related to the key variables under investigation. These key variables were: patient demographics (age and gender), the definitive diagnosis of SJS, SJS/TEN overlap, or TEN, the patient's outcome (discharged alive or deceased), and the history of suspected drug exposure prior to the onset of the reaction. The exclusion of incomplete records was essential to prevent bias and ensure the accuracy of the analysis. Analyzing cases with substantial missing data could lead to inaccurate conclusions, as researchers might be forced to make assumptions or estimations to fill in the gaps. Another exclusion criterion involved patients whose initial diagnosis of SJS/TEN was subsequently revised to an alternative condition that can mimic these reactions. Several dermatological conditions can present with symptoms that resemble SJS/TEN, making accurate differential diagnosis critical. These conditions include Erythema Multiforme Major, Staphylococcal Scalded Skin Syndrome, and Generalized Bullous Fixed Drug Eruption. To address this, the study excluded cases where the treating physicians explicitly documented a revision of the initial diagnosis to one of these alternative conditions. This requirement for explicit documentation is important. It ensures that the exclusion is based on a clear and definitive change in diagnosis made by the medical professionals caring for the patient, rather than on any ambiguity or uncertainty in the records.

The process of data extraction, which involves retrieving the necessary information from the patients' medical records, was conducted retrospectively. This means that the data collection occurred after the events of interest (the patients' hospitalizations and treatment) had already taken place. This approach is a common and efficient way to study medical conditions using existing clinical data. The data extraction was carried out by trained researchers or clinicians who were directly involved in the study. These individuals possessed the medical knowledge and research skills necessary to accurately interpret the medical records and extract the relevant information. To maintain consistency and uniformity in the data extraction process, a standardized data collection form was specifically designed for this study. This form served as a template, guiding the researchers on what specific information to extract from each patient's record. The use of a standardized form is a crucial methodological step, as it minimizes variability in how different researchers collect and record the data, enhancing the reliability of the extracted information. Throughout the data extraction process, the researchers adhered to strict principles of patient confidentiality and anonymity. All information was transcribed carefully and accurately from the medical records to the data collection form. Furthermore, all patient identifiers, such as names, addresses, and unique identification numbers, were either removed from the data or replaced with codes, ensuring that the extracted data could not be linked

back to individual patients.

The data collected for each patient included a range of carefully selected variables designed to provide a comprehensive description of SJS/TEN cases. These variables were; Demographics: Age and gender were recorded for all patients. Age was categorized into four groups: <10 years, 10-18 years, 19-59 years, and ≥ 60 years. This categorization allows for analysis of SJS/TEN across the lifespan; Clinical Diagnosis: The final diagnosis was recorded as SJS, SJS/TEN overlap, or TEN. This was based on the physician's assessment, with the understanding that it correlates with the extent of body surface area (BSA) detachment; Severity Score: The SCORTEN score, a predictor of mortality risk, was recorded if available in the patient's records; Causative Drugs: Suspected causative drugs were recorded as identified by the treating physicians. These drugs were categorized by pharmacological class, and specific drug names were also noted. The study acknowledges that formal causality assessment was not routinely performed; Comorbidities: Pre-existing medical conditions were recorded and categorized by organ system. A category of "Without Comorbidity" was used for patients without other significant medical issues; Length of Stay: The duration of the patient's hospital stay was recorded in days; Outcome: The patient's status at discharge was recorded as either "Discharged Alive" or "Deceased."

The collected data were organized and analyzed using spreadsheet software. Descriptive statistics were used to summarize the data. Categorical variables were presented as frequencies (n) and percentages (%). Continuous variables were presented as mean ± standard deviation (SD) or range and mean. The results were presented in tables with accompanying narrative descriptions. Case fatality rates (CFR) were calculated to assess mortality within each diagnostic group and overall.

The study protocol underwent rigorous ethical review and was granted approval by the relevant institutional review board or ethics committee. Given the retrospective nature of the study and the use of anonymized data, individual patient consent was typically waived, in accordance with institutional policies and ethical guidelines. To ensure patient confidentiality, all patient identifiers were removed or anonymized during the data handling processes.

3. Results

Table 1 presents the baseline characteristics of the 51 patients included in the study, categorized by their diagnoses: Stevens-Johnson Syndrome (SJS), SJS/TEN Overlap, and Toxic Epidermal Necrolysis (TEN); Diagnosis Distribution: SJS was the most frequent diagnosis, comprising 41.18% (n=21) of the patients. SJS/TEN Overlap accounted for 31.37% (n=16) of the cases. TEN was diagnosed in 27.45% (n=14) of the patients. This distribution indicates a higher prevalence of SJS compared to the more severe forms, SJS/TEN Overlap and TEN, within this cohort; Gender: There was a slight female predominance in the overall cohort, with 52.94% (n=27) being female and 47.06% (n=24) being male. This trend was observed across all diagnostic groups, with a slightly higher percentage of females in both SJS (52.38%) and SJS/TEN Overlap (56.25%), while the gender distribution was balanced in the TEN group (50% each); Age Distribution: The majority of patients fell within the 19-59 years age group, representing 60.78% (n=31) of the total cohort. SJS had the highest proportion of patients in this age group (80.95%), followed by SJS/TEN Overlap (75.00%). TEN showed a much smaller proportion in this group (14.29%). The elderly (≥60 years) constituted the second-largest group (19.61%), with a higher proportion in the TEN group (35.71%) compared to SJS (14.28%) and SJS/TEN Overlap (12.50%). Children (<10 years) and adolescents (10-18 years) made up smaller proportions, with TEN having the highest representation in these younger age groups; Age Range (Overall): The overall age range of the patients in the study was 3 to 85 years, indicating that the conditions affected individuals across a broad age spectrum; SCORTEN Score: The mean SCORTEN score for the entire cohort was 2 (±1 SD). SJS had the

lowest mean SCORTEN score of 1 (±1 SD), while both SJS/TEN Overlap and TEN had a mean score of 2 (±1 SD). This suggests that TEN and SJS/TEN Overlap cases tended to be more severe than SJS cases, as the SCORTEN score is a predictor of mortality risk; Length of Stay: The mean length of hospital stay increased with the severity of the diagnosis: 7 days for SJS, 10 days for SJS/TEN Overlap, and 11 days for TEN. The overall range for the length of stay was 1 to 28 days, highlighting the variability in the duration of hospitalization; Outcome at Discharge: The majority of patients (84.31%, n=43) were discharged alive. Mortality was 15.68% (n=8) for the entire cohort. Mortality rates increased with the severity of the condition: 9.52% for SJS, 12.50% for SJS/TEN Overlap, and 28.57% for TEN.

Table 1. Baseline characteristics of patients with SJS, SJS/TEN overlap, and TEN (N=51).

Characteristic	Category	SJS (n=21)	SJS/TEN overlap (n=16)	TEN (n=14)	Total cohort (N=51)
Diagnosis Distribution		n=21 (41.18%)	n=16 (31.37%)	n=14 (27.45%)	**N=51 (100%)**
Gender	Male	10 (47.62%)	7 (43.75%)	7 (50.00%)	24 (47.06%)
	Female	11 (52.38%)	9 (56.25%)	7 (50.00%)	27 (52.94%)
Age distribution	< 10 years	1 (4.76%)	0 (0.00%)	3 (21.43%)	4 (7.84%)
	10 - 18 years	0 (0.00%)	2 (12.50%)	4 (28.57%)	6 (11.76%)
	19 - 59 years	17 (80.95%)	12 (75.00%)	2 (14.29%)	31 (60.78%)
	≥ 60 years	3 (14.28%)	2 (12.50%)	5 (35.71%)	10 (19.61%)
Age range (Overall)	Minimum - Maximum	---	---	---	3 - 85 years
SCORTEN score	Mean (± SD)	1 (± 1)	2 (± 1)	2 (± 1)	2 (± 1)
Length of stay	Mean (days)	7 days	10 days	11 days	9 days
	Range (Overall)	---	---	---	1 - 28 days
Outcome at discharge	Discharged Alive	19 (90.48%)	14 (87.50%)	10 (71.43%)	43 (84.31%)
	Deceased	2 (9.52%)	2 (12.50%)	4 (28.57%)	8 (15.68%)

Notes: SJS: Stevens-Johnson Syndrome (<10% Body Surface Area detachment); SJS/TEN Overlap: Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis Overlap (10-30% Body Surface Area detachment); TEN: Toxic Epidermal Necrolysis (>30% Body Surface Area detachment); SCORTEN: Severity-of-Illness Score for Toxic Epidermal Necrolysis; n: Number of patients; SD: Standard Deviation.

Table 2 details the comorbidities observed in the 51 patients, categorized by the primary diagnosis (SJS, SJS/TEN Overlap, and TEN) and organized by comorbidity category; Psychiatric: Bipolar Disorder was the only psychiatric comorbidity reported, found in 1 patient (1.96% of the total cohort). This comorbidity was present only in the SJS/TEN Overlap group (1 patient, 6.25% of that group); Respiratory System: Pneumonia was present in 2 patients (3.92% of the total cohort), both within the SJS group (9.52% of that group). Tuberculosis was reported in 1 patient (1.96% of the total cohort), also only in the SJS group (4.76% of that group); Nervous System: Epilepsy was the most common specific comorbidity, found in 7 patients (13.73% of the total cohort). Epilepsy was observed across all groups: 4 patients in the SJS group (19.05% of that group), 2 in the SJS/TEN Overlap group (12.50% of that group), and 1 in the TEN group (7.14% of that group). Stroke was present in 2 patients (3.92% of the total cohort), with 1 patient in the SJS/TEN Overlap group (6.25% of that group) and 1 patient in the TEN group (7.14% of that group). Meningioma and Subarachnoid Hemorrhage were each reported in 1 patient (1.96% of the total cohort), both in the SJS/TEN Overlap group (6.25% of that group); Cardiovascular System: Hypertension was present in 2 patients (3.92% of the total cohort), with 1 patient in the SJS group (4.76% of that group) and

1 patient in the SJS/TEN Overlap group (6.25% of that group). Hypertensive Heart Disease and Dyslipidemia were each reported in 1 patient (1.96% of the total cohort), both in the SJS group (4.76% of that group); Gastrointestinal System: Hepatitis was reported in 1 patient (1.96% of the total cohort), in the SJS group (4.76% of that group). Hepatoblastoma was reported in 1 patient (1.96% of the total cohort), in the TEN group (7.14% of that group); Uroreproduction System: Acute Kidney Injury (AKI) was reported in 1 patient (1.96% of the total cohort), in the SJS group (4.76% of that group). Chronic Kidney Disease (CKD) was present in 5 patients (9.80% of the total cohort), with 3 patients in the SJS group (14.29% of that group) and 2 patients in the TEN group (14.29% of that group); Endocrine System: Diabetes Mellitus was present in 6 patients (11.76% of the total cohort), with 3 patients in the SJS group (14.29% of that group) and 3 patients in the TEN group (21.43% of that group); Immune System: HIV Infection was reported in 1 patient (1.96% of the total cohort), in the SJS group (4.76% of that group); No Comorbidity: A significant proportion of patients, 17 in total (33.33% of the total cohort), had no documented comorbidity. This was most frequent in the SJS/TEN Overlap group (8 patients, 50.00% of that group) and the TEN group (6 patients, 42.86% of that group), compared to the SJS group (3 patients, 14.29% of that group).

Table 2. Comorbidities in patients with SJS, SJS/TEN overlap, and TEN (N=51).

Comorbidity category	**Specific comorbidity**	**SJS (n=21)**	**SJS/TEN overlap (n=16)**	**TEN (n=14)**	**Total cohort (N=51)**
		n (%)	n (%)	n (%)	n (%)
Psychiatric	Bipolar Disorder	0 (0.00%)	1 (6.25%)	0 (0.00%)	1 (1.96%)
Respiratory system	Pneumonia	2 (9.52%)	0 (0.00%)	0 (0.00%)	2 (3.92%)
	Tuberculosis	1 (4.76%)	0 (0.00%)	0 (0.00%)	1 (1.96%)
Nervous system	**Epilepsy**	**4 (19.05%)**	**2 (12.50%)**	**1 (7.14%)**	**7 (13.73%)**
	Stroke	0 (0.00%)	1 (6.25%)	1 (7.14%)	2 (3.92%)
	Meningioma	0 (0.00%)	1 (6.25%)	0 (0.00%)	1 (1.96%)
	Subarachnoid Hemorrhage	0 (0.00%)	1 (6.25%)	0 (0.00%)	1 (1.96%)
Cardiovascular system	Hypertension	1 (4.76%)	1 (6.25%)	0 (0.00%)	2 (3.92%)
	Hypertensive Heart Disease	0 (0.00%)	1 (6.25%)	0 (0.00%)	1 (1.96%)
	Dyslipidemia	1 (4.76%)	0 (0.00%)	0 (0.00%)	1 (1.96%)
Gastrointestinal system	Hepatitis	1 (4.76%)	0 (0.00%)	0 (0.00%)	1 (1.96%)
	Hepatoblastoma	0 (0.00%)	0 (0.00%)	1 (7.14%)	1 (1.96%)
Uroreproduction system	Acute Kidney Injury (AKI)	1 (4.76%)	0 (0.00%)	0 (0.00%)	1 (1.96%)
	Chronic Kidney Disease (CKD)	3 (14.29%)	0 (0.00%)	2 (14.29%)	5 (9.80%)
Endocrine system	**Diabetes Mellitus**	**3 (14.29%)**	**0 (0.00%)**	**3 (21.43%)**	**6 (11.76%)**
Immune system	HIV Infection	1 (4.76%)	0 (0.00%)	0 (0.00%)	1 (1.96%)
No comorbidity	---	3 (14.29%)	8 (50.00%)	6 (42.86%)	17 (33.33%)

Notes: SJS: Stevens-Johnson Syndrome; SJS/TEN Overlap: Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis Overlap; TEN: Toxic Epidermal Necrolysis; HIV: Human Immunodeficiency Virus; n: Number of patients.

Table 3 presents the suspected causative drugs implicated in cases of SJS, SJS/TEN Overlap, and TEN, categorized by drug class. It shows the number of instances each drug was suspected in each diagnostic category and the total instances and percentage of total instances for each drug class; Anticonvulsants (Overall: 22.86%): This class of drugs was implicated in 22.86% of the total suspected drug instances (16 out of 70). Carbamazepine was the most frequently suspected individual anticonvulsant (8 instances, 11.43% of total), with cases across all diagnostic categories (3 in SJS, 4 in SJS/TEN Overlap,

1 in TEN). Valproic Acid and Lamotrigine were each suspected in 3 instances (4.29% each), primarily in SJS and SJS/TEN Overlap. Phenytoin was suspected in 2 instances (2.86%), both in SJS; Antipsychotics (Overall: 10.00%): This class accounted for 10.00% of the suspected drug instances (7 out of 70). Lithium and Trifluoperazine were each suspected in 2 instances (2.86% each), exclusively in SJS cases. Other antipsychotics (Haloperidol, Risperidone, Aripiprazole) were each suspected in 1 instance; Sedatives/Anxiolytics (Overall: 8.57%): This class represented 8.57% of the suspected drug instances (6 out of 70). Fluoxetine was suspected in 2 instances (2.86%), both in SJS. Other sedatives/anxiolytics (Alprazolam, Lorazepam, Benzodiazepine (unspec.), Trihexyphenidyl) were suspected in 1 instance each; Antihistamines (Overall: 1.43%): Dimenhydrinate was the only antihistamine suspected, with 1 instance (1.43% of total), in SJS; Antibiotics (Overall: 25.71%): This was the most frequently implicated drug class, accounting for 25.71% of the suspected drug instances (18 out of 70). Amoxicillin was the most frequently suspected individual antibiotic (7 instances, 10.00% of total), with cases across all diagnostic categories. Cefadroxil was suspected in 5 instances (7.14%), also across all categories. Levofloxacin was suspected in 2 instances (2.86%), in SJS. Other antibiotics (Metronidazole, Cefixime, Cotrimoxazole, Chloramphenicol) were suspected in 1 instance each; Antihypertensives (Overall: 2.86%): Ramipril was the only antihypertensive suspected, with 2 instances (2.86% of total), in SJS and SJS/TEN Overlap; Antidepressant (Overall: 1.43%): Maprotiline HCL (Sandepril) was the only antidepressant suspected, with 1 instance (1.43% of total), in SJS; Analgesic-Antipyretics (NSAIDs & others) (Overall: 24.29%): This class was the second most frequently implicated, accounting for 24.29% of the suspected drug instances (17 out of 70). Paracetamol was the most frequently suspected analgesic (5 instances, 7.14% of total), with cases across all categories. Ibuprofen was suspected in 3 instances (4.29%), also across all categories. Metamizole was suspected in 4 instances (5.71%), across all categories. Other analgesics (Diclofenac Sodium, Meloxicam, Tramadol, Mefenamic Acid) were suspected in 1 or 2 instances each; Antituberculosis (Overall: 1.43%): One instance (1.43%) of an unspecified antituberculosis drug was suspected, in SJS; Mucolytic-Expectorant (Overall: 1.43%): One instance (1.43%) of an unspecified mucolytic-expectorant drug was suspected, in SJS/TEN Overlap; Antiretrovirals (Overall: 1.43%): Efavirenz was the only antiretroviral suspected, with 1 instance (1.43% of total), in SJS.

4. Discussion

The demographic analysis of the patient cohort revealed several noteworthy patterns. Firstly, the study observed a slight predominance of female patients, with 52.94% of the cases occurring in women compared to 47.06% in men. This finding aligns with some previous research that has suggested a potential, albeit not universally consistent, trend towards a higher susceptibility to SJS/TEN among females. While the exact reasons for this potential gender disparity remain unclear, it is possible that hormonal factors, differences in drug metabolism, or variations in immune responses may play a role. However, it is important to emphasize that this observation was not statistically significant in this particular study, and further research with larger sample sizes is needed to confirm or refute this trend in the Indonesian population. The age distribution of the patients in this study spanned a wide range, from 3 to 85 years, underscoring the fact that SJS/TEN can affect individuals across the entire age spectrum. However, the majority of cases (60.78%) were concentrated in the 19-59 year age group, which represents the adult population. This finding is consistent with many other studies that have identified adulthood as the period of highest risk for developing SJS/TEN.

Table 3. Suspected causative drugs implicated in SJS, SJS/TEN overlap, and TEN cases.

Drug class	Specific drug	SJS (n)	SJS/TEN overlap (n)	TEN (n)	Total instances (N=70)	% of Total instances
Anticonvulsants	**(Overall: 22.86%)**				**16**	**22.86%**
	Valproic Acid	1	2	0	3	4.29%
	Phenytoin	2	0	0	2	2.86%
	Carbamazepine	**3**	**4**	**1**	**8**	**11.43%**
	Lamotrigine	3	0	0	3	4.29%
Antipsychotics					**7**	**10.00%**
	Lithium	2	0	0	2	2.86%
	Trifluoperazine	2	0	0	2	2.86%
	Haloperidol	1	0	0	1	1.43%
	Risperidone	0	0	1	1	1.43%
	Aripiprazole	1	0	0	1	1.43%
Sedatives/Anxiolytics					**6**	**8.57%**
	Alprazolam	1	0	0	1	1.43%
	Lorazepam	1	0	0	1	1.43%
	Benzodiazepine (unspec.)	0	1	0	1	1.43%
	Trihexyphenidyl	1	0	0	1	1.43%
	Fluoxetine	2	0	0	2	2.86%
Antihistamines					**1**	**1.43%**
	Dimenhydrinate	1	0	0	1	1.43%
Antibiotics	**(Overall: 25.71%)**				**18**	**25.71%**
	Amoxicillin	**2**	**2**	**3**	**7**	**10.00%**
	Levofloxacin	2	0	0	2	2.86%
	Metronidazole	0	0	1	1	1.43%
	Cefadroxil	1	1	3	5	7.14%
	Cefixime	1	0	0	1	1.43%
	Cotrimoxazole	0	1	0	1	1.43%
	Chloramphenicol	0	1	0	1	1.43%
Antihypertensives					**2**	**1.43%**
	Ramipril	0	1	0	1	1.43%
Antidepressant						**1.43%**
	Maprotiline HCL (Sandepril)	1	0	0	1	1.43%
Analgesic-antipyretics (NSAIDs & others)	**(Overall: 24.29%)**				**17**	**24.29%**
	Paracetamol	**2**	**2**	**1**	**5**	**7.14%**
	Ibuprofen	2	0	1	3	4.29%
	Diclofenac Sodium	1	1	0	2	2.86%
	Meloxicam	1	0	0	1	1.43%
	Metamizole	1	2	1	4	5.71%
	Tramadol	1	0	0	1	1.43%
	Mefenamic Acid	1	0	0	1	1.43%
Antituberculosis	(Specific drug not listed)	1	0	0	1	1.43%
Mucolytic-expectorant	(Specific drug not listed)	0	1	0	1	1.43%
Antiretrovirals					**1**	**1.43%**
	Efavirenz	1	0	0	1	1.43%

Notes: SJS: Stevens-Johnson Syndrome; SJS/TEN Overlap: Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis Overlap; TEN: Toxic Epidermal Necrolysis; n: Number of instances the drug was suspected as a causative agent; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

Several factors may contribute to this pattern. Adults, compared to children or the elderly, are more likely to be prescribed a wider variety of medications, including those with a higher propensity to trigger SJS/TEN. Additionally, adults may be more likely to have certain underlying medical conditions or lifestyle factors that increase their susceptibility to adverse drug reactions. Interestingly, while the adult age group was the most affected, the study also found that a significant proportion of cases occurred in the elderly (≥60 years), accounting for 19.61% of the total. This finding is particularly relevant given the increasing global population of older adults, who often have multiple comorbidities and require polypharmacy, placing them at elevated risk for adverse drug reactions. The occurrence of SJS/TEN in children and adolescents, although less frequent (combined 19.60%), highlights the importance of vigilance in this population as well. While SJS/TEN may be less common in younger individuals, it can still occur, particularly in association with certain medications.[11-13]

The classification of SJS/TEN cases based on the extent of body surface area (BSA) involvement is a critical aspect of understanding the severity of these conditions. In this study, SJS, which involves less than 10% BSA detachment, was the most frequent diagnosis (41.18%), followed by SJS/TEN overlap (10-30% BSA detachment) at 31.37%, and TEN, the most severe form with greater than 30% BSA detachment, at 27.45%. This distribution is generally consistent with the understanding that SJS is more common than TEN. However, the relative proportions of each category can vary across different studies and populations, depending on factors such as the study setting, patient demographics, and the specific causative drugs involved. The Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN) is a widely used and validated tool for predicting mortality risk in patients with SJS/TEN. In this study, the mean SCORTEN score for the entire cohort was 2. When analyzed by diagnostic category, the mean SCORTEN score was lowest for SJS (1), and higher for both SJS/TEN overlap and TEN (2). This finding suggests a correlation between the extent of skin involvement and the predicted severity of the condition, as reflected by the SCORTEN score. However, it is important to note that the mean SCORTEN scores for SJS/TEN overlap and TEN were similar in this cohort, which may indicate that other factors beyond BSA involvement, such as age, comorbidities, and the presence of complications, also play a significant role in determining disease severity and prognosis. The duration of hospitalization is another important indicator of the severity and impact of SJS/TEN. In this study, the average length of stay for the entire cohort was 9 days, with a range of 1 to 28 days. As expected, the mean length of stay tended to increase with the severity of the diagnosis 7 days for SJS, 10 days for SJS/TEN overlap, and 11 days for TEN. This finding underscores the fact that more extensive skin involvement is associated with a more prolonged and complicated clinical course, often requiring more intensive medical management and a longer recovery period.[14,15]

The ultimate outcome of SJS/TEN, particularly the risk of mortality, is a major concern for both patients and healthcare providers. In this study, the overall mortality rate was 15.68%. However, this rate varied significantly depending on the severity of the condition. The case fatality rate was lowest for SJS (9.52%), increased for SJS/TEN overlap (12.50%), and was highest for TEN (28.57%). This clear trend confirms the well-established principle that the extent of epidermal detachment is a major determinant of prognosis in SJS/TEN. Patients with TEN, who have the most extensive skin involvement, are at the highest risk of developing life-threatening complications such as sepsis, multi-organ failure, and severe electrolyte imbalances. It is important to compare the mortality rates observed in this study with those reported in other studies. While some older literature has reported mortality rates as high as 30-50% for TEN, more recent studies have suggested that these rates may be lower, particularly with advancements in supportive care. The mortality rate

of 28.57% for TEN in this study falls within the range reported in some of these more recent studies, but it is still substantial and highlights the serious nature of this condition. Several factors can influence mortality rates in SJS/TEN, including patient age, the presence of comorbidities, the specific causative drugs involved, the time to diagnosis and drug withdrawal, and the quality of supportive care provided.[16,17]

Identifying the medications that are most likely to trigger SJS/TEN is crucial for preventing future cases. In this study, the analysis of suspected causative drugs revealed that antibiotics were the most frequently implicated class overall, accounting for 25.71% of the total recorded drug exposures potentially linked to the reaction. Within the antibiotic class, amoxicillin was the most commonly suspected agent, followed by cefadroxil. This finding is somewhat unexpected, as sulfonamide antibiotics have traditionally been considered the highest-risk antibiotics for SJS/TEN. However, the high frequency of amoxicillin and cefadroxil as suspected causative agents in this study may reflect their widespread use in the Indonesian population. Analgesic-antipyretics were the second most common class implicated, accounting for 24.29% of suspected exposures. Paracetamol (acetaminophen) was the most frequent drug in this group, followed by metamizole (dipyrone) and ibuprofen. Paracetamol is generally considered a relatively safe analgesic, and its frequent implication in this study warrants further investigation. While causality can be difficult to establish due to its common use for prodromal symptoms, it has been reported as a trigger in some cases. Metamizole is another analgesic that has been associated with SJS/TEN, and its use varies across different countries. Anticonvulsants constituted the third major class of drugs implicated, accounting for 22.86% of suspected exposures. Carbamazepine was the single most frequently suspected anticonvulsant and one of the most common drugs overall. This finding is consistent with numerous international studies that have identified carbamazepine as a high-risk drug for SJS/TEN, particularly in Asian populations due to the higher prevalence of the HLA-B*15:02 allele, a known genetic risk factor. It is important to acknowledge that in this study, the determination of causative drugs was based on clinical suspicion documented in the medical records by the treating physicians. Formal causality assessment tools, such as the ALDEN algorithm, and confirmatory tests, such as patch testing or lymphocyte transformation tests (LTT), were not routinely implemented. This represents a limitation of the study, as it makes it difficult to definitively confirm the causative agent, especially in cases where patients were taking multiple medications.[18-20]

5. Conclusion

In conclusion, this retrospective study provides valuable insights into the epidemiological and clinical characteristics of SJS/TEN in a tertiary hospital setting in Indonesia. The findings highlight that SJS/TEN predominantly affects adults, with a slight female predominance observed in this cohort. The most common causative drug classes implicated were antibiotics, analgesics-antipyretics, and anticonvulsants, with specific drugs such as amoxicillin, paracetamol, and carbamazepine frequently suspected. The severity of the conditions, as indicated by the SCORTEN score and length of hospital stay, generally correlated with the extent of body surface area involvement, with TEN cases demonstrating the highest mortality rate. While the overall mortality rate in this study was considerable, it appeared to be lower than some international reports, particularly for TEN. The identification of common causative agents and the recognition of patient risk factors, including specific comorbidities like epilepsy and diabetes mellitus, are crucial for early diagnosis and prompt management of SJS/TEN. These findings emphasize the importance of continued surveillance and research to further refine our understanding of SJS/TEN and improve patient outcomes.

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