

## Profile of Stevens-Johnson syndrome and toxic epidermal necrolysis patients in the inpatient hospital installation of Dr. Soetomo general hospital Surabaya from January 2019 – December 2021

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### Abstract

**Background:** Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis are significant health issues due to their severe complications. Factors like age, clinical symptoms, and underlying etiology play crucial roles in patient management. Therefore, it is important to review further the background or profile of the patients. This is the basis for conducting this study. This research aims to provide an overview of patients with SJS-TEN in the Inpatient Installation of RSUD Dr. Soetomo Surabaya, aiming to aid in prevention and management.

**Aim:** Providing an overview of the profile of patients with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in the Inpatient Installation of Dr. RSUD. Soetomo Surabaya

**Methods:** The study analyzed medical records of patients with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis at RSUD Dr. Soetomo Surabaya from 2019-2021, analyzing parameters such as gender, age, symptoms, etiology, comorbidities, and length of stay.

**Results:** The study found 28 cases of SJS-TEN, with 15 males (53.6%) and 13 females (46.4%). The highest prevalence was in the age group 19-44 years old as we called adult (35.7%). Most patients had multiple comorbidities, with common clinical symptoms including palpebral edema, multiple erythematous macules, conjunctival erythema, and fever. Most patients were classified as SCORTEN 1, with 71.4% taking multiple drugs. Most patients experienced multiple complications but experienced improvement and continued treatment through outpatient care (57.1%).

**Keywords:** Stevens-Johnson Syndrome; Toxic Epidermal Necrolysis; SCORTEN; Profile of SJS-TEN Patients; Human & Medicine; Human & Mortality; Immunology

### 1. Introduction

Stevens-Johnson Syndrome is a skin disorder resulting from a hypersensitivity reaction mediated by an immune complex. Stevens-Johnson Syndrome is a variant of erythema multiforme that can be caused by various aspects, from medications, infections, to malignancies [1]. The manifestations experienced by patients are on the skin and mucous

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membranes, on the layers of the eyeball, in the mouth, and genitals. This disease was first discovered by pediatrician Albert M. Stevens and Frank C. Johnson in 1922 after diagnosing a child who came with a disease that manifested in severe ocular involvement accompanied by oral involvement triggered by a drug reaction. Patients with this syndrome can experience death if they experience fatal conditions and do not receive quick and appropriate treatment [2].

The early course of this disease is often marked by flu symptoms, which will then manifest on the skin in the form of painful red or purple rashes due to blistering of the mucous membrane and ends with peeling of the mucosa, if it can be handled properly and well will end in healing [3]. Erythema multiforme is divided into three groups, namely Erythema multiforme minor, Erythema multiforme major or Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) [4]. SJS has similarities with TEN in terms of histopathology, clinical indications, triggers, risk factors, as well as its pathogenesis. Both are only distinguished from the extent of epidermolysis affected or the percentage of body surface involved.

The incidence of SJS-TEN cases is approximately 1-6 cases and 0.4-1.2 per one million population per year, SJS-TEN events can occur anywhere in the world because this case can affect all races in the world [5]. The highest incidence is reported in the age group of 46-63 years and most often in women with a prevalence of 61-64% compared to men, making drugs the most common major cause [6]. The incidence of SJS-TEN in the United States and European countries is estimated to be as much as 2-3% per million population each year. According to a study in South Africa from 2004 to 2006 [7], the incidence increased from 40% to 69% due to the increasing incidence of HIV (Human Immunodeficiency Virus), thus increasing drug use, in this case antiretroviral (ARV) drugs that can make the incidence higher. Meanwhile, the incidence of Stevens-Johnson Syndrome cases in Indonesia reaches about 12 cases per year with different conditions and causes. Differences mainly in the incidence and etiology each year directly tend to make a difference in the patient profile affected by SJS-TEN cases in various places. Although with unclear causes and linked to specific immune responses, the consequences of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in patients are something that must be considered. Various effects ranging from systemic symptoms such as fever to peeling of the epidermis on parts of the patient's body experiencing this disease make this disease enter into skin emergencies. Different complications, although rarely found in patients who are handled quickly and accurately, but make this even more important because the initial condition (release of epidermis) increases vulnerability and triggers various different disorders in the body such as respiration, digestion, to very fatal things/death is a serious matter. Various things above make SJS and TEN an important health burden to be researched considering the incidence rate, etiology, effects/impacts, up to complications for the patients.

From this background, the author is interested in understanding the patient profile of SJS and TEN in the Inpatient Installation at Dr. Soetomo Hospital, Surabaya, for the period of January 2019 – December 2021. It is hoped that this research will add information about the picture of SJS case prevalence based on several things and the background of SJS patients as a reinforcement of references or comparisons for the prevalence of previous studies regarding the SJS-TEN patient profile. This study aims to describe the profile of patients with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in the Inpatient Installation at Dr. Soetomo Hospital, Surabaya, for the period of January 2019 – December 2021.

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## 2. Material and methods

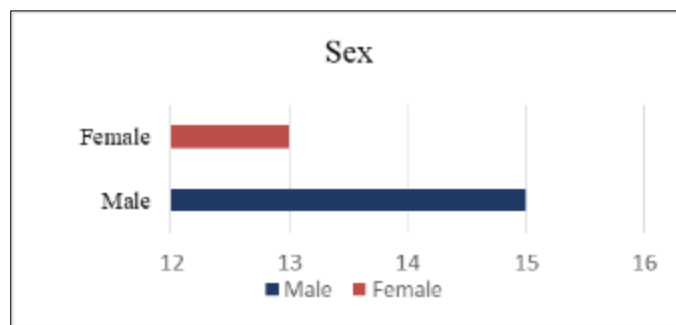
This study is a descriptive study using secondary data in the form of medical records of all patients with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in the Inpatient Installation at Dr. Soetomo Hospital, Surabaya, for the period of January 2019 – December 2021. The sampling technique used is total sampling with 28 SJS-TEN patient samples. Variables in this study include: etiology, examination results or classification of SJS-TEN, age group, gender, suspected causative drugs, patient's comorbidity history, clinical symptoms, SCORTEN results, management, complications, patient's final condition after management, mortality, and length of treatment. The study was conducted from December 2022 - August 2023 at the Medical Records Installation at Dr. Soetomo Hospital, Surabaya. Data were processed with SPSS 25.0 and interpreted in the form of narrative and tables.

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## 3. Results

### 3.1. Distribution of research subjects based on sex

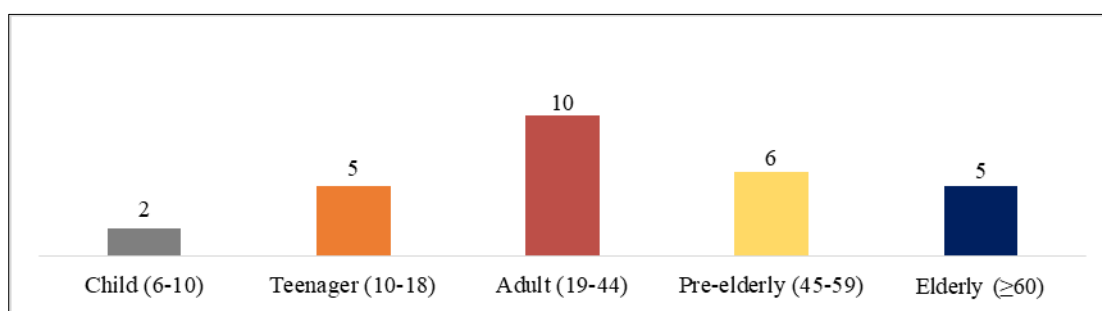
The results of this study show that there are 15 male research subjects (53.6%) and 13 female research subjects (46.4%).



**Figure 1** Distribution of research subjects based on sex

### 3.2. Distribution of research subjects based on age

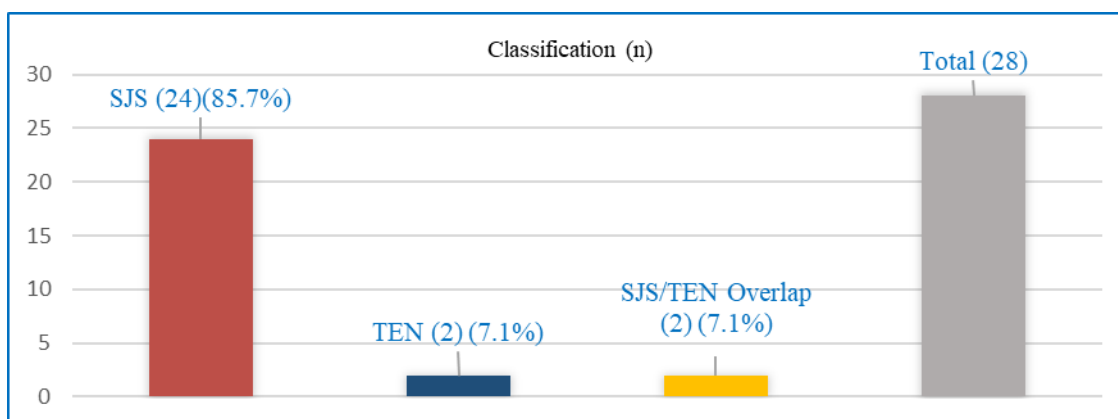
In this study, it was found that 35.7% of the research subjects were aged 19-44 years (adults), 21.4% of the research subjects were aged 45-59 years (pre-elderly), 17.9% of the research subjects were aged 10-18 years (teenagers), 17.9% of the research subjects were aged 60 years and above (elderly), and 7.1% of the research subjects were aged 6-10 years (children).



**Figure 2** Distribution of research subjects based on age [8]

### 3.3. Distribution of research subjects based on SJS/TEN classification

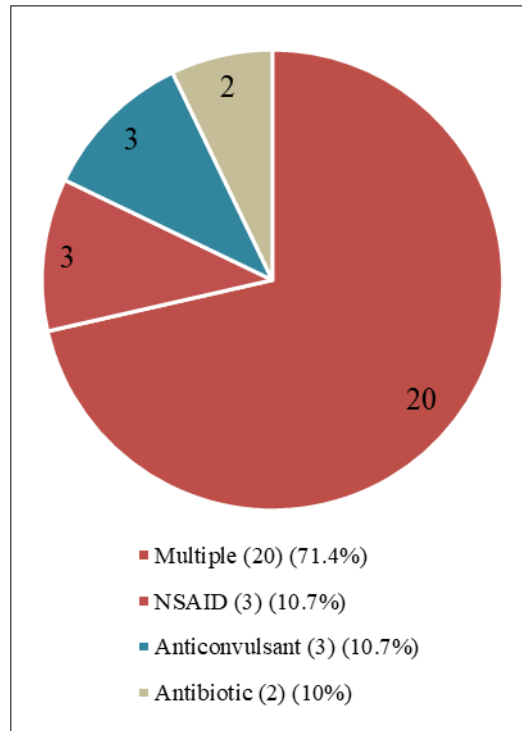
There were 85.7% classified as SJS, 7.1% classified as TEN, and 7.1% classified as SJS/TEN overlap.



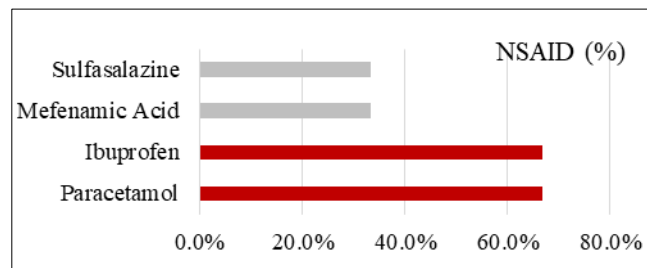
**Figure 3** Distribution of research subjects based on SJS/TEN classification

### 3.4. Distribution of research subjects based on drug usage

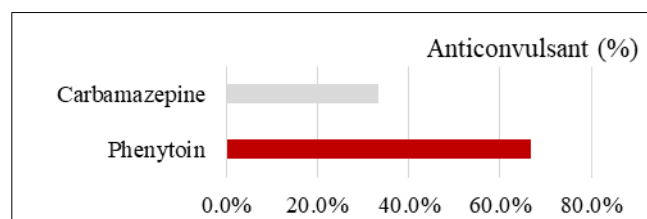
There were 71.4% of multiple drug users, which refers to the consumption of various types of drugs simultaneously (including interactions from the aforementioned drugs), but various unmentioned drugs include NSAID, antibiotics, anticonvulsant, antihistamine, antihypertensive, diuretics, statins, antihistamines, antigout, corticosteroid, vitamin to herbal drink. Then 10.7% of drug users only used NSAID, similar as anticonvulsant it shows 10.7% drug users only used anticonvulsant, and 7.1% of drug users only used antibiotics.



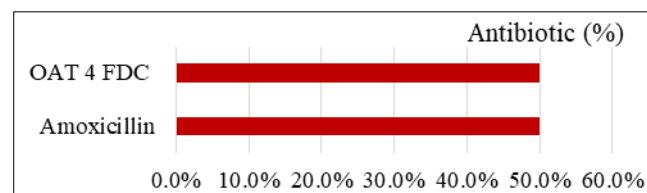
**Figure 4** Distribution based on drug usage



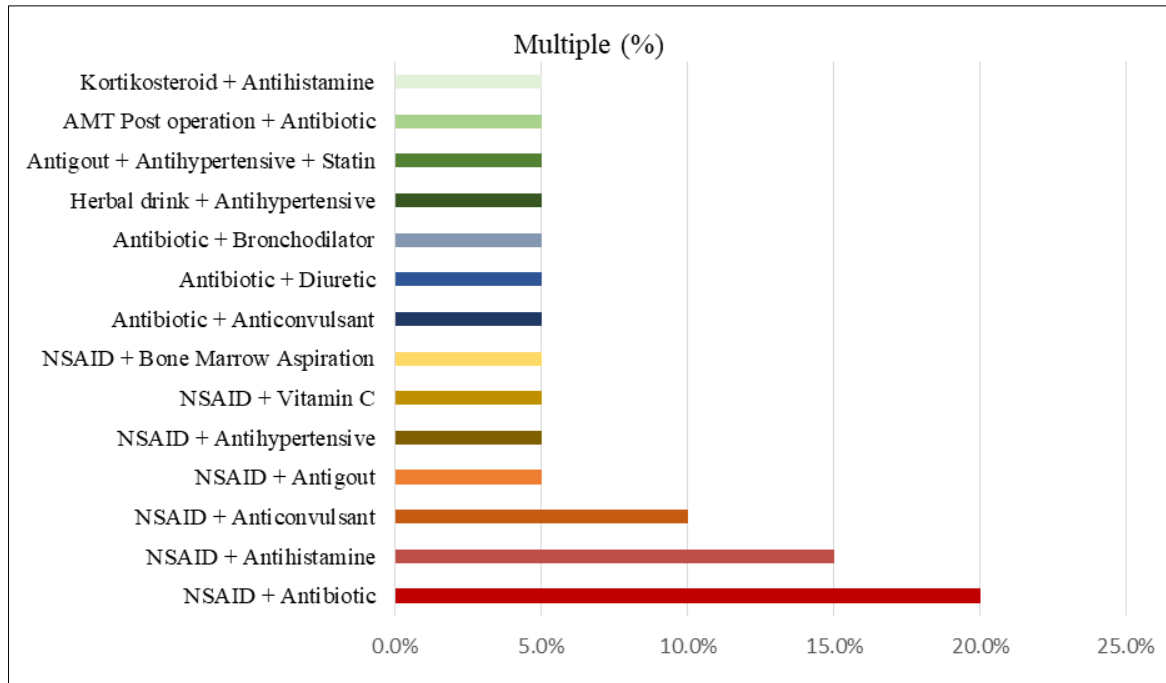
**Figure 5** Distribution based on NSAIDs drug usage



**Figure 6** Distribution based on Anticonvulsants drug



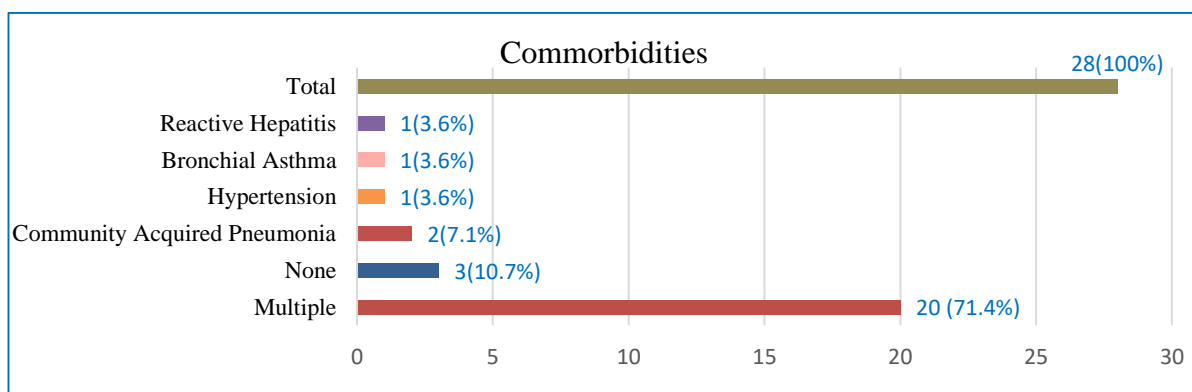
**Figure 7** Distribution based on Antibiotics drug usage



**Figure 8** Distribution of research subjects based on Multiple drug usage

### 3.5. Distribution of research subjects based on comorbidities

The results of this study show that 71.4% of patients had multiple comorbidities including Type I and II Diabetes Mellitus, autoimmune diseases such as vulgaris psoriasis and SLE, kidney diseases such as AKI (Acute Kidney Injury) and CKD (Chronic Kidney Disease), blood disorders such as anemia, ITP (Idiopathic Thrombocytopenic Purpura), ascites, splenomegaly, TBC (tuberculosis), acute pharyngitis, pancreatitis, epilepsy, chronic gastritis, hyperthyroidism, mature cataracts, post-operative AMT (Amniotic Membrane Transplantation) due to limbal stem cell deficiency in the eye, skin infections such as tinea cruris and scabies, to trigeminal neuralgia. 10.7% had no comorbidities, 7.1% had CAP (Community Acquired Pneumonia) as a comorbidity, 3.6% had hypertension as a comorbidity, 3.6% had bronchial asthma as a comorbidity, and 3.6% had reactive hepatitis as a comorbidity.



**Figure 9** Distribution of research subjects based on comorbidities

### 3.6. Distribution of research subjects based on SCORTEN

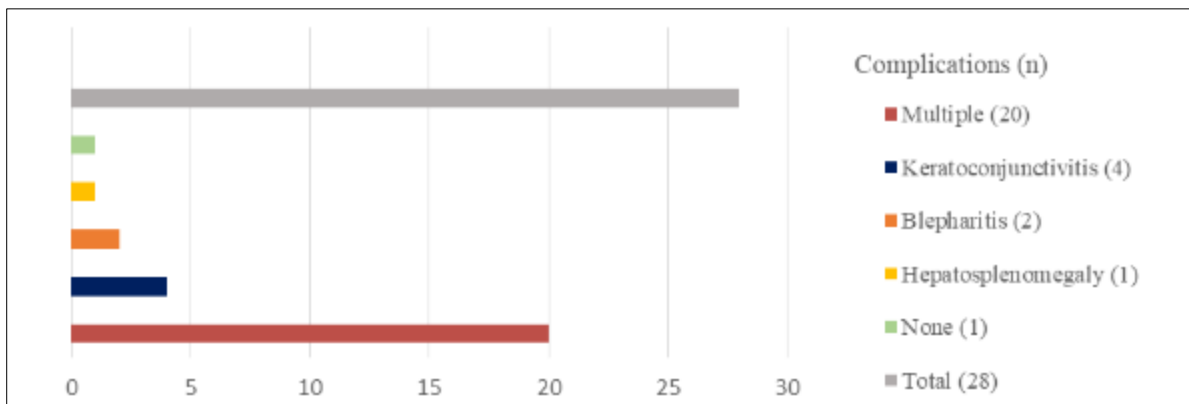
The research subjects were classified according to the SCORTEN scale as follows: 39.3% were classified as SCORTEN 1, 32.1% as SCORTEN 0, 17.9% as SCORTEN 3, and 10.7% as SCORTEN 2.

**Table 1** Distribution of research subjects based on SCORTEN

SCORTEN	Frequency (n)	%
0	9	32.1
1	11	39.3
2	3	10.7
3	5	17.9
Total	28	100

**3.7. Distribution of research subjects based on complications**

The study found that 71.4% of the subjects had multiple complications, which are a combination of several diseases or complex conditions in one patient, both those mentioned above and those not mentioned such as respiratory failure, septic shock, anemia, blepharoconjunctivitis, blepharitis, symblepharon, conjunctival hyperemia, various conditions of electrolyte imbalance in the body (hypoglycemia, hyperglycemia, hypokalemia, hypoalbuminemia, hypokalemia, hypocalcemia, hyponatremia, hypochloride, hypotonic, hypovolemic, metabolic acidosis, respiratory acidosis), pneumonia, AKI (Acute Kidney Injury), CKD (Chronic Kidney Disease), type II diabetes mellitus, pancreatitis, bronchial asthma, sudden cardiac death, cardiovascular event, atopic dermatitis, CNV (Cytomegalovirus) infection, prolonged diarrhea to knee abscess. There were also 14.3% of subjects with Keratoconjunctivitis complications, 7.1% with blepharitis complications, 3.6% with Hepatosplenomegaly complications and 3.6% without complications.

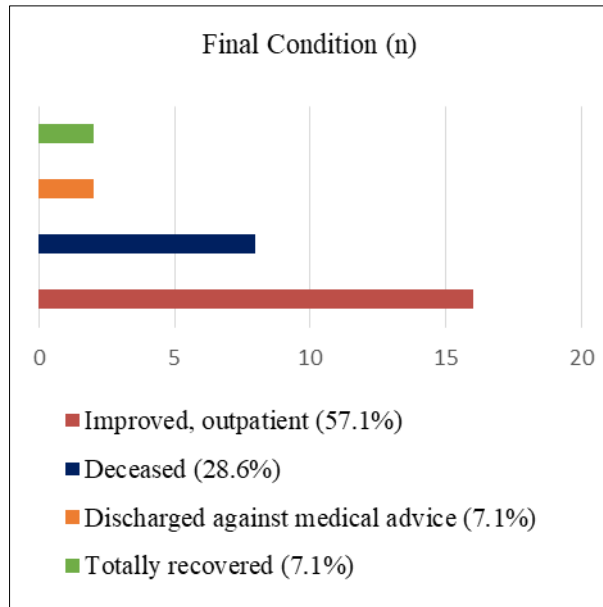


\*Multiple (various disease complications that cannot be detailed in the table one by one)

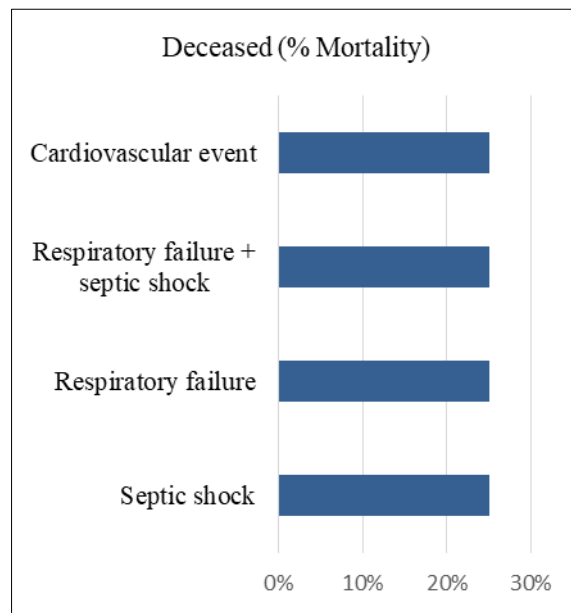
**Figure 10** Distribution of research subjects based on complications

**3.8. Distribution of research subjects based on final condition**

It was found that 57.1% of the subjects showed improvement and were treated as outpatients, 28.6% of the subjects died, 7.1% of the subjects were discharged against medical advice, and 7.1% of the subjects recovered.



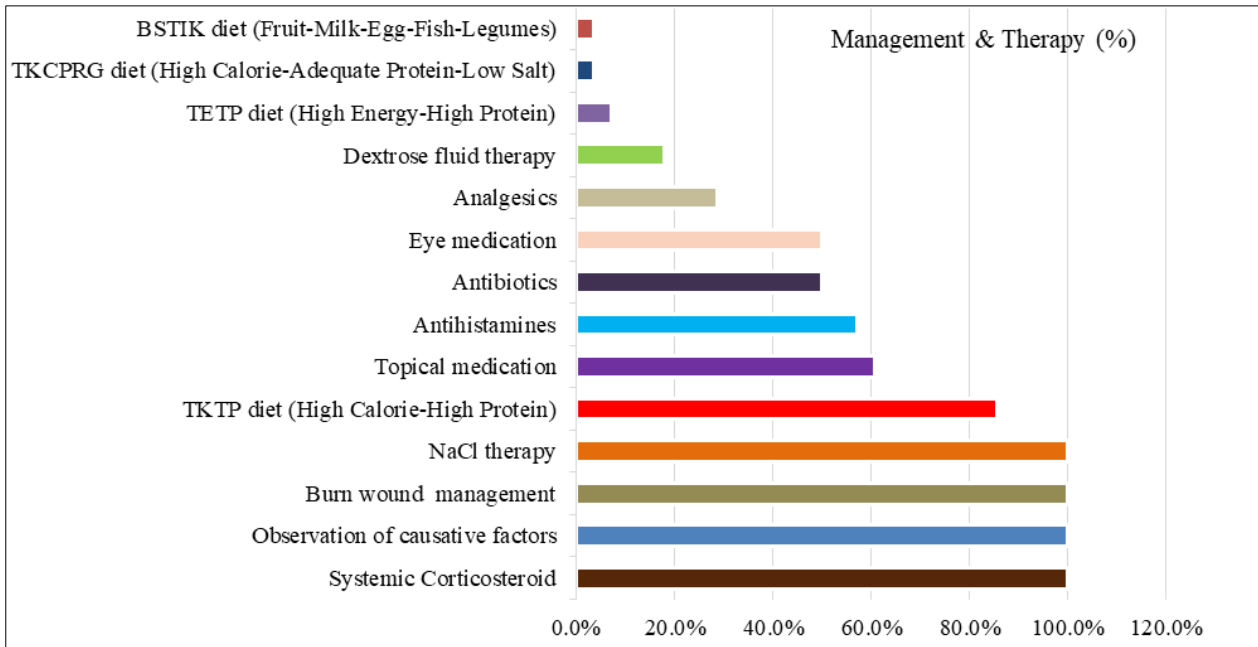
**Figure 11** Distribution of research subjects based on final condition



**Figure 12** Distribution of the mortality of SJS-TEN (deceased patients).

### 3.9. Distribution of research subjects based on therapy and management

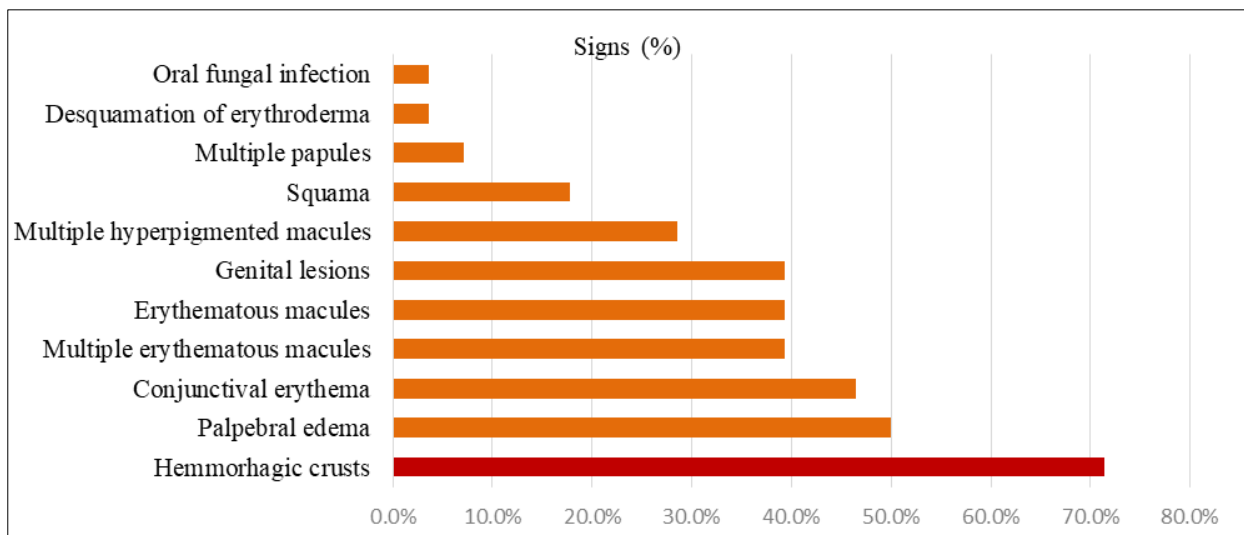
It was found that 100% of SJS-TEN patients received systemic corticosteroid therapy, 100% of patients (all) were observed for causative factors, 100% of patients (all) received NaCl therapy, 100% of patients (all) received burn wound care, 85.7% of patients were on a high-calorie high-protein (TKTP) diet management, 60.7% of patients received topical medication therapy, 57.1% of patients received antihistamine therapy, 50% of patients received antibiotic therapy, 50% of patients received eye medication, 28.6% of patients received analgesic therapy, 17.8% of patients received dextrose fluid therapy, 7.1% of patients were on a high-energy high-protein (TETP) diet management, 3.6% of patients were on a BSTIK (Fruit-Milk-Egg-Fish-Legumes) diet management and 3.6% of patients were on a high-calorie, adequate-protein, low-salt (TKCPRG) diet management.



**Figure 13** Distribution of research subjects based on therapy and management

### 3.10. Distribution of research subjects based on signs & symptoms of SJS-TEN patients

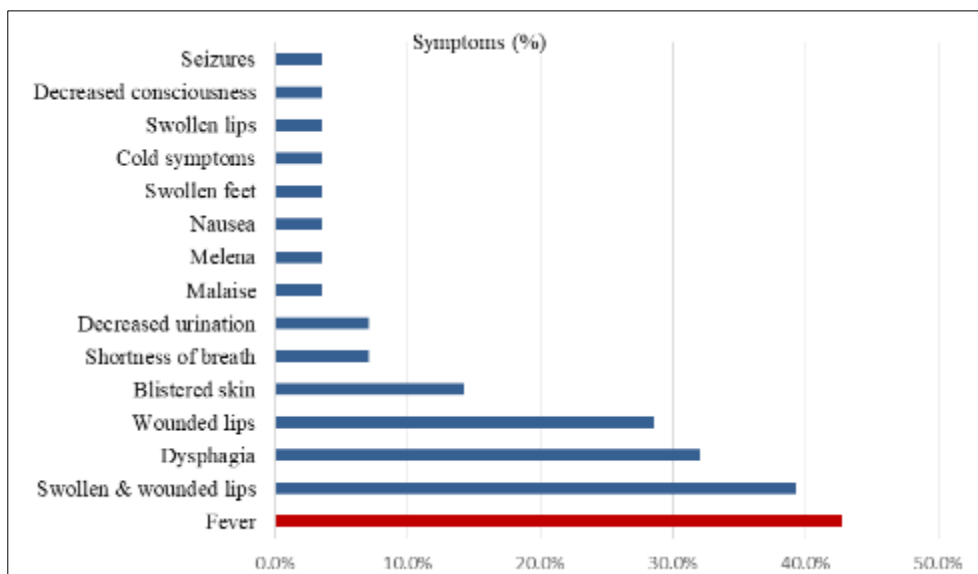
The research results showed : 71.4% of patients had hemorrhagic crusts, 50% of patients had palpebral edema, 46.4% of patients had conjunctival erythema, 39.3% of patients had multiple erythematous macules, 39.3% of patients had erythematous macules, 39.3% of patients had genital lesions, 28.6% of patients had multiple hyperpigmented macules, 17.8% of patients had squama, 7.1% of patients had multiple papules, 3.6% of patients had desquamation of erythroderma, 3.6% of patients had oral fungal infection.



**Figure 14** Distribution of research subjects based on signs

The research results showed : 42.8% of patients had fever, 39.3% of patients had swollen and wounded lips, 32.1% of patients had dysphagia, 28.6% of patients had wounded lips, 14.3% of patients had blistered skin, 7.1% of patients had shortness of breath, 7.1% of patients had decreased urination, 3.6% of patients had malaise, 3.6% of patients had melena, 3.6% of patients had nausea, 3.6% of patients had swollen feet, 3.6% of patients had cold symptoms, 3.6% of patients had swollen lips, 3.6% of patients had decreased consciousness, 3.6% of patients had seizures.





**Figure 15** Distribution of research subjects based on symptoms

## 4. Discussion

### 4.1. Prevalence of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Patients Based on Sex

In this study, it was found that the number of SJS-TEN patients who were male was higher than the number of SJS-TEN patients who were female. Similar results were also found in a study by Rahayu et al [14] at RSUP Dr. M. Djamil Padang, where the epidemiological distribution of SJS according to gender was predominantly male with 16 cases (72.73%), while females accounted for 6 cases (27.27%). The study by Shanmarkan et al [10] in India showed that males dominated the SJS group with a ratio of 1.63:1, while females dominated the TEN group with a ratio of 1:2.57. There was a male dominance in SJS or overlapping SJS-TEN (male-to-female ratio 1.77:1) and TEN (male-to-female ratio 1.35:1) [11]. This observation contradicts what was found in Egypt and differs from previous studies that showed equal influence on males and females [12, 13].

This finding contrasts with other studies that discovered that Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) more frequently affect females, with a ratio of 1.5:1 [14]. A retrospective study conducted at a general hospital in the Federal District of Brazil from 1999 to 2014 found that the majority of patients were female [15]. Based on these varying research outcomes, it is evident that the epidemiological distribution of SJS is not sex dependent. SJS occurs when the causative antigen enters the body of any individual, regardless of their sex, triggering a hypersensitivity reaction [16]. Böttiger et al. also asserted that SJS/TEN can occur in individuals of all sex [17].

### 4.2. Prevalence of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Patients Based on Age Group

In this study, it was found that 35.7% of the subjects were aged 19-44 years, categorized as adults, 21.4% were aged 45-59 years, categorized as pre-elderly, 17.9% were aged 10-18 years, categorized as teenagers, 17.9% were aged 60 years and above, categorized as elderly, and 7.1% were aged 6-10 years, categorized as children.

The study by Shanmarkan et al [10] in India showed similar results where the highest number of SJS-TEN cases were in the age group 11-30 years. The most affected age group in the study in Brazil was 0 to 10 years. The average age of patients was 23 years old, with a range from 47 days to 72 years [15]. A study with similar results from Yuli & Diah [18], at IRNA Kemuning in the years 2011-2014 also showed the age range of SJS and TEN patients with the highest distribution was the age group of 25-44 years with a total of 14 SJS patients and 4 TEN patients, where this age group is the range of adult age group.

Carba et al [19] found that the incidence increased between the ages of 11 and 20 years. Stella et al [20] reported that the incidence rate was proportional to the increase in age, the higher the age, the higher the risk of experiencing such skin disorders. This is related to the fact that as people get older, they use more drugs, and more drug interactions occur [20]. The increasing incidence of SJS/TEN with increasing age is likely due to more frequent drug prescriptions and comorbidities that alter drug effects [21]. However, Böttiger et al also stated that SJS/TEN can occur at all ages [17].

#### **4.3. Prevalence of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Patients Based of SJS/TEN Classification**

Total Body Surface Area (TBSA), or the total surface area of the body, is differentiated from detached skin lesions, including <10%, 10-30%, and >30% representing Stevens-Johnson Syndrome (SJS), SJS/TEN overlapping (SJS-TEN), and Toxic Epidermal Necrolysis (TEN), respectively [16]. The results of this study show that the majority of patients were classified as SJS, as much as 85.7%, followed by 7.1% classified as TEN, and 7.1% classified as SJS/TEN.

The prevalence rates of SJS and TEN can vary geographically. Certain populations may be genetically more inclined to one condition than the other, causing differences in prevalence in certain regions. A previous global population - based study also reported similar findings where the incidence of SJS was estimated at 1.0 to 6.0 per million and TEN was estimated at 0.4 to 1.2 per million [22]. A US-based study that analyzed national hospitalization records from 2009 to 2012 calculated incidences per million population of 8.61-9.69 for SJS, 1.46-1.84 for SJS/TEN overlapping, and 1.58-2.26 for TEN [23]. About 800-1,000 cases of SJS and 500-700 cases of TEN are reported each year in Japan [24].

Stevens-Johnson Syndrome typically presents with less skin detachment (less than 10% of body surface area), while Toxic Epidermal Necrolysis involves more extensive skin detachment (usually more than 30% of body surface area). As SJS is a less severe form, it is possibly more frequently diagnosed or recognized, thus leading to a potentially higher reported prevalence. The difficulty in obtaining a definitive diagnosis of SJS and TEN also poses a challenge in estimating accurate incidence. The diagnosis of Major Erythema Multiforme (MEM) was often confused with SJS and TEN until an expert consensus group suggested a consensus clinical classification [24].

#### **4.4. Prevalence of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Patients Based on Drug Usage**

Several factors are known to trigger SJS and TEN, including drugs, infections, malignancies, and idiopathic causes, but the most common cause is drugs, accounting for 60% of cases [14, 25, 26]. Therefore, drug exposure and the resulting hypersensitivity reactions are the cause of most SJS/TEN cases. Based on the results of this study, it was found that 71.4% were multiple drug users (use of more than one drug such as NSAIDs and antibiotics, NSAIDs and anticonvulsants, antibiotics and anticonvulsants, etc.) 10.7% were NSAID users, and 10.7% were anticonvulsant users, and 7.1% were antibiotics users.

Similar results were also obtained in the study by Sharma et al [27], where out of 26 patients, multiple drugs were involved in 21 cases, while a single drug was responsible in nine cases. The study by Sanmarkan et al [10] in India showed that nonsteroidal anti-inflammatory drugs (NSAIDs) were the most common group of drugs among the SJS group in 21/25 patients (23.8%). Antibiotics were the most common group of drugs causing TEN in 11/25 patients (44%). In the pediatric population, a proportional meta-analysis by Suasti et al [28] with 20 studies involving 303 children with Stevens-Johnson Syndrome (SJS) and/or Toxic Epidermal Necrolysis (TEN) reported antiepileptics as the largest contributing cause of drug with a proportion of 0.44 (95% CI : 0.37 , 0.51), followed by antibiotics, multiple drugs, NSAIDs (Nonsteroidal Anti-inflammatory Drugs), unclassified drugs, and acetaminophen (Paracetamol). A study by Rahmawati and Indramaya [18], also conducted at Dr. Soetomo Hospital, Surabaya, found that the drugs often reported as the cause of SJS and TEN were analgesics (32.86%), antibiotics (20.14%), and antiepileptics (15.9%). Another study in Singapore showed that the most common causes were antiepileptic drugs (35.7%), antibiotics (28.5%), and analgesics (14.3%) [29]. Meanwhile, a study by Sher et al in Europe found that the most common drugs causing the condition were antibiotics (42%), analgesics (23%), antigout (15%), and antiepileptics (15%) [30].

Multiple drugs such as NSAIDs, Paracetamol, and antibiotics are the most common drugs causing SJS and TEN in the study at Dr. Soetomo Hospital, Surabaya. This condition likely occurs because these drugs are easily available in the market without requiring a doctor's prescription. Patients with common complaints such as fever, muscle pain, or difficulty swallowing (dysphagia) can purchase these drugs without needing a doctor's prescription. The ease of obtaining drugs in Indonesia, including antibiotics and analgesics, without a doctor's prescription indirectly impacts the high incidence of SJS and TEN in Indonesia [18]. Some differences in causative drugs obtained from various other studies in different regions indicate that drugs classified as high risk in one area may not necessarily be high risk for other areas [31]. This syndrome can be induced by several drugs and usually occurs 1-4 weeks after the start of therapy. Granulysin has been found in lesions of patients with SJS/TEN and plays a significant pathogenic role in the condition, but the overall mechanism linking drugs, granulysin, and disease manifestation is still unclear [32]. Secretory granulysin is a cationic protein produced by cytotoxic T lymphocytes and natural killer cells. This protein has recently been identified as the main cytolytic molecule responsible for extensive keratinocyte necrosis in SJS/TEN. However, it is still unclear how many drugs from different classes cause granulysin secretion in SJS/TEN, and how cytotoxic T lymphocytes and natural killer cells regulate granulysin secretion in SJS/TEN [32].

The use of multiple drugs in combination with antiepileptic drugs was also found in this study. Generally, some drugs such as carbamazepine (CBZ) and phenytoin have a high incidence of causing Stevens-Johnson Syndrome (SJS) [33]. Recent studies show a strong association between HLA-B502 and drug induced SJS in Chinese/Asian ethnicity patients [34]. There is almost a 100% association of HLA-B502 with CBZ-induced SJS/TEN, implying that HLA-B\*502 is not just a genetic marker but also participates in the pathogenesis of SJS [35]. Although the cascade of immune mechanisms underlying SJS is still unclear, cytotoxic responses mediated by CD8+ T cells appear to be a major event causing SJS/TEN [35].

#### **4.5. Prevalence of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Patients Based on Comorbidities**

Based on the research results, it was found that 71.4% had multiple comorbidities (such as pneumonia, epilepsy, tumor, hypertension, and others), 10.7% had no comorbidities, 7.1% had Community-Acquired Pneumonia (CAP) as a comorbidity, 3.6% had hypertension as a comorbidity, 3.6% had bronchial asthma as a comorbidity, and 3.6% had reactive hepatitis as a comorbidity.

The most common comorbidity in patients with SJS and TEN in this study was multiple comorbidities. This is related to the most common use of multiple drugs. Comorbidity refers to the presence of two or more medical conditions in a person at the same time. These conditions might be unrelated or interrelated and may require different treatments or management strategies. Comorbidities are common in many medical conditions and can complicate a person's overall health. Having multiple comorbidities can lead to a more complex medical profile, as each condition may require specific medication and care. This can result in an increased number of prescribed drugs to address various health issues. While some drugs may be necessary to control symptoms, reduce complications, or improve quality of life, the use of multiple drugs also increases the risk of drug interactions, side effects, and adverse reactions [36].

Polypharmacy, or the use of multiple drugs, can cause drug interactions and result in unwanted side effects. One of the comorbidities in this study is epilepsy. The interaction of more than one type of antiepileptic drug can increase the risk of drug allergic reactions. The aromatic ring of anticonvulsants can become toxic metabolites that play a role in the pathogenesis of drug allergic reactions. In some individuals, the chemical metabolites become non-toxic because they are detoxified by the enzyme epoxide hydroxylase, but in some individuals these metabolite substances cannot be fully detoxified, thus acting as haptens and initiating an immune response, resulting in direct cell necrosis [30, 36, 37].

#### **4.6. Prevalence of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Patients Based on SCORTEN**

This study indicates that 39.3% of patients with a SCORTEN score of 1, 32% with a SCORTEN score of 0, 17.9% with a SCORTEN score of 3, and 10.7% with a SCORTEN score of 2. It is crucial to determine the prognosis of patients with SJS and TEN. Prognostic assessment using SCORTEN should ideally be performed within the first 24 hours of patient admission. By understanding the prognosis of SJS and TEN patients from the outset, clinicians will be aware of the mortality rate percentage, enabling a more holistic approach to patient care for SJS and TEN. The higher the SCORTEN, the higher the patient's risk of mortality [38].

To evaluate the prognosis of patients affected by SJS and TEN, there is a severity-of-illness score (SCORTEN) that should be applied within the first 48 hours of disease onset. SCORTEN consists of seven parameters: age >40 years; presence of malignancy; tachycardia (>120 bpm); epidermal detachment >10%; serum urea >10 mmol/l; serum glucose >14 mmol/l (approximately 252 mg/dl); and serum bicarbonate  $\leq$ 20 mmol/l. For each of these items, one point is given if the item is present or zero points if it is not. When a patient's score is three or more, they should be managed in an intensive care unit. A score  $\geq$ 5 predicts a mortality rate of approximately 90% [39]. The risk of death is higher in elderly patients and those with more extensive body surface involvement [40].

Age is a well-known risk factor for mortality in SJS and TEN, as reflected in the TEN Score (SCORTEN) [41]. Mortality from SJS and TEN in cases aged 40 and older is significantly higher than those under 40 years of age in a study in Korea [42]. The SCORTEN scoring system has been used to determine disease severity and predict mortality for over a decade. Bastuji-Garin's study results revealed a lower number of death cases than predicted by the SCORTEN score [41]. There was no significant difference in SCORTEN scores between the survival and non-survival groups. These findings underscore the limitations of SCORTEN as previously mentioned in certain review articles [43, 44, 45].

#### **4.7. Prevalence of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Patients Based on Complications**

Based on the results of this study, there are 71.4% of patients with multiple complications (such as keratoconjunctivitis with shortness of breath, and so on), 14.3% with keratoconjunctivitis complications, 7.1% with blepharitis complications, 3.6% with hepatosplenomegaly complications, and 3.6% without complications.

More than 50% of patients who survive TEN suffer from long-term residual symptoms (sequelae) of this disease. This includes symblepharon, conjunctival synechiae, entropion, inward-growing eyelashes, skin scar tissue, irregular pigmentation, eruptive nevi, and continuous erosion on mucous membrane, phimosis, vaginal synechiae, nail dystrophy, and diffuse hair loss [46]. A study in Brazil showed, the most common complications were lesion infections, sepsis and severe ocular lesions. No complications were found in 21% of cases [15].

The majority of complications found in this study were secondary complications, namely eye disorders (keratoconjunctivitis, blepharitis). Primary complications such as hypopigmentation and hyperpigmentation spots were found in the multiple complications section. Tertiary complications were also found in the form of liver abnormalities, namely hepatosplenomegaly. These results are similar to the complications that arose in studied in Thailand, India, Singapore, but in a different order [29, 47, 48].

Eye disorders are the most common residual symptoms requiring long-term medical care. In previous studies [49, 50, 51], the frequency of long-term ocular residual symptoms was about 20-50%. In the study by Yang et al [42] in Korea, it was found that among the complications associated with SJS or TEN, ocular residual symptoms were the most common (43.1% and 43.4% of SJS and TEN patients respectively) Well-known long-term complications include residual eye and skin symptoms [52, 53, 54]. In the study by Yang et al [55], dry eye syndrome and chronic conjunctivitis occurred in 32.4% and 21.6% of patients respectively.

In the cohort study, three patients without eye involvement during the acute stage experienced chronic residual symptoms after recovering from SJS/TEN. The manifestations of chronic residual symptoms included concurrent chronic conjunctivitis and nasolacrimal duct obstruction in one patient, chronic conjunctivitis in another patient, and dry eye syndrome in the third patient. A previous study on ocular complications had no eye involvement during the acute stage [54]. This indicates that SJS/TEN patients should be carefully followed up even without eye involvement at the acute stage [55].

#### **4.8. Prevalence of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Patients Based on Final Condition**

Based on the results of this study, it was found that 57.1% of patients improved and were discharged, 28.6% of patients died, 7.1% of patients were discharged against medical advice, and 7.1% of patients recovered.

SJS and TEN are considered severe and life-threatening diseases. The average reported mortality rate for SJS is 1-5%, and for TEN it is 25-35%; it can even be higher in elderly patients and those with a large extent of epidermal ablation [16]. Mortality rates for SJS and TEN have been reported to vary from 1-13% and 30-50%, respectively, and deaths have been reported to occur in a significant number even after discharge from the hospital [56, 57, 58, 59]. According to the survival analysis conducted by the RegiSCAR study group, the 6-week mortality rates for SJS, SJS/TEN overlap, and TEN were 12%, 29%, and 46% respectively [59]. The study by Yang et al [42] showed in-hospital mortality rates of 8.9% in the SJS group and 30.3% in the overlapping TEN group. The impact of disease severity on mortality was not as significant after discharge. Among those who died after discharge, the deaths were not closely related to SJS/TEN residual symptoms [42]. Based on a 2011 cohort analysis, in-hospital mortality was 5.7% and 15.1% for SJS and TEN respectively. Mortality increased with age, especially after the age of 40 [42].

#### **4.9. Prevalence of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Patients Based on Therapy and Management**

The results of this study for the therapy and management of SJS and TEN patients are shown that 100% of patients (all) were observed of causative factors, 100% of patients (all) were given systemic corticosteroid therapy, 100% of patients (all) received NaCl therapy, 100% of patients (all) received burn wound management, 85.7% of patients were given High Calories-High Protein (TKTP) diet management, 60.7% of patients were given topical drug, 57.1% of patients were given antihistamine, 50% of patients were given antibiotic, 50% of patients received eye medication, 28.6% of patients were given analgesic, 17.8% of patients were given dextrose fluid therapy, 7.1% of patients were given High Energy-High Protein (TETP) diet management, 3.6% of patients were given Fruit-Milk-Egg-Fish-Legumes (BSTIK) diet management, 3.6% of patients were given High Calorie, Adequate Protein, Low Salt (TKCPRG) diet management.

The management of SJS and TEN patients at Dr. Soetomo Hospital Surabaya found in this study resembles the management recommended by the literature. SJS and TEN therapy consists of discontinuing the drug as early as possible, supportive therapy, and specific therapy. Discontinuing the suspected drug (eliminating the drug) as soon as possible will reduce the mortality rate from 26% to 5%. Supportive therapy for patients with Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) includes care in special facilities such as burn units or intensive care rooms with room temperatures maintained above 30 °C to prevent hypothermia. In addition, patients are also given sufficient infusion fluids and nutrition. The use of dressings and other supportive therapies includes eye drops, mouthwash, and the use of antacids [14]. Treatment is based on symptoms and supportive fluid and electrolyte replacement. Dermal coverage to prevent secondary infection and fluid loss is also a crucial aspect of treatment. Several immunomodulatory therapies have been suggested to treat SJS and/or TEN, especially glucocorticoids and immunoglobulins [41]. To reduce mortality rates, the immediate withdrawal of any potential causative drugs and early transfer to a burn unit or other specialized units have been recommended [60, 61].

The use of corticosteroids remains controversial. Systemic steroids were the standard treatment until the early 1990s, although no proven benefit was shown in controlled trials. In the absence of strong evidence of efficacy, and due to the confusion resulting from the many reported steroid treatment regimens (short-duration treatment versus long-duration, various dosage regimens), their use has become increasingly debated. The use of short-term corticosteroids is key to preventing and minimizing damage from SJS and TEN [62]. In a study conducted by Rahmawati and Indramaya in 2016 [18], 37 patients suffering from Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) underwent corticosteroid therapy with doses of 0.15-0.2 mg/KgBW/day.

The results showed that all patients experienced recovery. The administration of corticosteroids was done with a gradual dose reduction (tapering off) based on the improvement of the patient's condition. The use of corticosteroids in SJS and TEN cases is based on the pathogenesis of these conditions, which are type four allergic reactions (delayed-type immune reactions) [18]. In addition, a recent retrospective monocenter study suggested that a short "pulse" of high-dose corticosteroids (dexamethasone) may be beneficial [63]. On the other hand, a recent retrospective case-control study in France and Germany concluded that corticosteroids did not show a significant effect on mortality compared to supportive care alone [63]. Another option for therapy is the use of intravenous immunoglobulins (IVIG). However, due to the very high cost of purchasing IVIG and inconsistent results from studies, this option is rarely used, especially in Indonesia [64].

#### **4.10. Prevalence of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Patients Based on Signs & Symptoms**

Based on the results of this study, it was found that 71.4% of SJS-TEN patients had hemorrhagic crusts as clinical sign, 50% had palpebral edema, 46.4% had conjunctival erythema, 39.3% had multiple erythematous macules, 39.3% had erythematous macules, 39.3% had genital lesions, 28.6% had multiple hyperpigmented macules, 17.8% had squama, 7.1% had multiple papules, 3.6% had desquamation of erythroderma, 3.6% had oral fungal infection. Meanwhile as its clinical symptoms, it was found that 42.8% SJS-TEN patients had fever, 39.3% had swollen and wounded lips, 32.1% had dysphagia, 28.6% had wounded lips, 14.3% had blistered skin, 7.1% had shortness of breath, 7.1% had decreased urination, 3.6% had malaise, 3.6% had melena, 3.6% had nausea, 3.6% had swollen feet, 3.6% had cold symptoms, 3.6% had swollen lips, 3.6% had decreased consciousness, 3.6% had seizures.

This disease begins with nonspecific symptoms such as fever and malaise, upper respiratory tract symptoms such as cough, rhinitis, eye pain, and myalgia. Over the next three to four days, blistering rashes and erosions appear on the face, body, limbs, and mucosal surfaces. Erythematous macules, targetoid, annular, or purpuric, flaccid bullae, large painful erosions, Nikolsky-positive (lateral pressure on the skin causes peeling of the epidermis). Initially, toxic epidermal necrolysis shows erythroderma and extensive erosions (with or without targetoid rash), while Stevens Johnson syndrome is more characterized by a targetoid rash, with fewer areas of denudation. Ulceration and mucosal erosions can involve the lips, mouth, pharynx, esophagus and digestive tract, eyes, genitals, upper respiratory tract. About half of patients have involvement of three mucosal sites. Patients are very ill, anxious, and in pain. The liver, kidneys, lungs, bone marrow, and joints can be affected by Stevens-Johnson syndrome/toxic epidermal necrolysis. Common symptoms include: Fever, malaise, headache, anorexia, pharyngitis. Symptoms due to acute dysfunction of the eye, lung, cardiovascular, gastrointestinal, kidney, and hematologic systems [65].

In the study by Chantaphakul et al [66], mucosal membrane involvement was observed in the oral cavity in 97.7% of cases and eye involvement was observed in 88.4% of the study population. It is important to recognize the clinical characteristics of mucocutaneous eruptions at an early stage due to the high mortality rate, ranging between 16 to 25% [58, 67]. In the course of the researcher's journey to conduct this study, both in terms of the process and its

implementation, there are several limitations and difficulties that need to be considered. These can serve as lessons for conducting future research, especially for studies with the same focus.

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## 5. Conclusion

- Out of 28 research subjects, the number of male SJS-TEN patients (15) was higher than the number of female SJS-TEN patients (13).
- The majority of the research subjects were adults (35.7%), followed by pre-elders (21.4%), and with the same distribution (17.9%) for adolescents and elders.
- The majority of patients (85.7%) has classified in SJS, followed by 7.1% classified in TEN as similar as patients who are in SJS/TEN.
- There were 71.4% patients who used multiple drugs at the same time, 10.7% of patients used NSAID as similar as anticonvulsant, and 7.1% of patients used antibiotic.
- The majority (71.4%) of patients had multiple comorbidities, followed by 10.7% without comorbidities, and 7.1% with CAP (Community Acquired Pneumonia) comorbidity.
- There were 39.3% with a SCORTEN of 1, 32.1% with a SCORTEN of 0, 17.9% with a SCORTEN of 3, and 10.7% with a SCORTEN of 2.
- Most of SJS-TEN patients (71.4%) had multiple complications, 14.3% had keratoconjunctivitis, 7.1% had blepharitis, 3.6% had hepatosplenomegaly as similar as patients that had none complication.
- All SJS-TEN patients (100%) in this study were observed for causative factors, given systemic corticosteroid therapy, received NaCl fluid therapy, and given burn wound management. 85.7% of patients were given High Calory-High Protein (TKTP) diet management, and followed by 60.7% of patients were given topical medication.
- From this study, the most shown SJS-TEN signs from the patients are hemorrhagic crusts (71.4%), palpebral edema (50%), and conjunctival erythema (46.4%). As its symptoms, 42.8% of patients had fever, 39.3% of patients had swollen and wounded lips, 32.1% of patients had dysphagia.

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## Compliance with ethical standards

### *Disclosure of conflict of interest*

The authors declare no competing interests.

### *Statement of ethical approval*

Letter of Exemption (Ref. No. : 1170/LOE/301.4.2/XII/2022)

### *Statement of informed consent*

In this study obtaining informed consent from the individuals whose records are being used may not be necessary. Informed consent is not required for descriptive research that uses medical records as the subject of the study. However, it's important to note that the specific requirements can vary depending on the ethical guidelines and regulations in place.

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