Risk Factors for Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) in Dr. Soetomo General Hospital Surabaya

Josephine Queena Maureen Wijanto[1], Damayanti[2], Mohammad Fathul Qorib[3], Sylvia Anggraeni[2], Cita Rosita Sigit Prakoeswa[2]

[1]Undergraduate of Medicine Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Dermatology and Venereology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia - Dr. Soetomo General Hospital Surabaya, Indonesia
[3]Department of Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
*Corresponding author: damayanti@fk.unair.ac.id

Abstract

Introduction: Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are rare cases but can be life-threatening if not immediately treated. Basic knowledge about SJS and TEN is crucial for doctors so the incidence can be prevented, however the study about SJS and TEN in Indonesia is still minimal. Thus, we aim to analyze the risk factors for SJS and TEN in Dr. Soetomo General Hospital Surabaya period of 2017-2020. **Methods:** This was a retrospective analytical observational study with case control design using total sampling from medical records data in 2017-2020. Risk factors for sex, age, infection, and comorbidities were analyzed with bivariate and multivariate analysis. **Results:** From a total 28 sample cases, most sex was man (53.57%), but there was no significant effect against SJS/TEN (p=1.000). Most ages were 26-45 & 46-65 years (39.29%). There was no significant effect between age and SJS/TEN (p=0.789). Infection that was reported only pneumonia (21.43%) and apparently there was significant correlation against SJS/TEN (p=0.023). Highest comorbidity was conjunctivitis (25%). Highest number of drugs suspected to cause SJS/TEN was carbamazepine (20%), paracetamol (20%), and phenytoin (15.56%). **Conclusion:** Sex, age, infection, and comorbidities are risk factors for SJS and TEN, however in this study, factor that influence the occurrence of SJS/TEN is infection by Mycoplasma pneumoniae.

Keywords: Stevens Johnson syndrome, toxic epidermal necrolysis, risk factors

1. Introduction

Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe hypersensitivity reactions characterized by bullae in the skin and mucous membrane erosion. Those are classified as the same disease but distinguished based on the extent of the epidermal damage (<10% for SJS, 10-30% for overlap SJS-TEN, >30% for TEN). Etiology is unclear but the main factor is reaction to medication such as anticonvulsants, allopurinol, antibiotics, & NSAIDs [1]. According to UK-based Clinical Practice Research Datalink, from 551 validated SJS/TEN cases in the period 1995-2013, the incidence of SJS/TEN is 5.76 cases per million person per year with most cases occurring in patients aged 1-10 years and ≥80 years [2]. Another research showed that the incidence rate of SJS is 5 cases per million person per year and TEN is 2 cases per million person per year [3]. A similar study conducted in Indonesia reported that there are 35 SJS cases and 3 TEN cases in Dr. Mohammad Hoesin Central General Hospital Palembang from 2006-2008 and 22 SJS cases in Dr. M. Djamil Central General Hospital Padang from 2010-2011 [4,5]. SJS and TEN are rare cases, but the

mortality rate is high, ranging from 25-70% and found higher in older age (>50 years) due to several factors such as comorbidity. Although the mortality rate in children was lower, the long term complication was more often. Complications that frequently occur are sepsis, pneumonia, kidney failure, and complication of the eye. The incidence risk of SJS/TEN is found higher in women than in men with ratio 3:2 and the risk can increase in autoimmune/HIV sufferers [6,7]. If the risk factor is greater, the possibility and severity of SJS/TEN is bigger. Until now, especially in Indonesia, only few studies identified these risk factors because of the rare cases. Thus, we conducted this study to take precautionary steps in susceptible patients.

2. Methods

This study had been approved by Dr. Soetomo General Hospital Surabaya through ethical clearance. This study was a retrospective analytical observational study with a case control design that was conducted in Dr. Soetomo General Hospital Surabaya from October 2020 until March 2021. Data were collected secondary from medical records using total sampling. The population of this study was patients that were being treated in Dr. Soetomo General Hospital Surabaya period January 2017-December 2020. The inclusion criteria for sample of case were all hospitalized patients with diagnosis of SJS (L51.1)/TEN (L51.2)/Overlap SJS-TEN (L51.3) according to International Classification of Disease 10 (ICD-10), while for the sample of control were all hospitalized patients with diagnosis besides SJS/TEN/Overlap SJS-TEN and had a medication history similar to the sample of case. Subjects were excluded if the medical record data is incomplete. We recorded all data on sex, age, medication history, history of infection, and comorbidity as the risk factors then data were processed using IBM SPSS Statistics ver. 23. The risk factors analyzed in bivariate analysis using chi-square test and multivariate analysis. P value of <0.05 considered as significant.

3. Results

In 2017-2020, 29 SJS patients (82.86%) and 3 TEN patients (17.14%) were hospitalized in Dermatology and Venereology Inpatient Installation Dr. Soetomo General Hospital Surabaya and there was no patient of overlap SJS-TEN (Table 1). From a total of 35 cases, there were 7 incomplete medical records so the sample of cases that will be analyzed in this study were 28 cases that met the inclusion criteria. Thus, the number of control samples was adjusted with the case samples with ratio 1:1, so the total sample is 56 cases.

Table 1. The number of SJS and TEN cases

Diagnosis	Number of cases (n)	Percentage (%)
SJS	29	82.86
TEN	6	17.14
Overlap SJS-TEN	0	0
Total	35	100

Characteristics of the subject are shown in Table 2. There was male predominance in both groups, with 15 men & 13 women in the case group and 16 men & 12 women in the control group. Most ages in case group were 26-45 & 46-65 years, while in control group was 46-65 years.

Table 2. Characteristics of the subject

Characteristics	Case		Control	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
Sex				
Men	15	53.57	16	57.14
Women	13	46.43	12	42.86
Age (years)				
0-5	0	0	1	3.57
6-11	0	0	3	10.71
12-25	6	21.43	9	32.14
26-45	11	39.29	4	14.29
46-65	11	39.29	10	35.71
>65	0	0	1	3.57

Although the male prevalence was higher in both groups, there was no statistically significant correlation. It was analyzed using chi-square test and the result can be seen on Table 3.

Table 3. Correlation between sex and SJS/TEN

Sex	Case, n (%)	Control, n (%)	p-value
Men	15 (53.57)	16 (57.14)	1.000
Women	13 (46.43)	12 (42.86)	

As mentioned before, children and elderly can increase the severity risk, therefore the age variable was analyzed using chi-square test as shown in Table 4. However, there was no statistically significant difference.

Table 4. Correlation between age and SJS/TEN

Age	Case, n (%)	Control, n (%)	p-value
<10 or >40 years	13 (46.43)	15 (53.57)	0.789
10-40 years	15 (53.57)	13 (46.43)	

Infection by Mycoplasma pneumoniae, bacteria causing pneumonia, was also the risk factor for SJS/TEN. As seen on Table 5, this study found there were 7 (25%) SJS/TEN patients that suffered pneumonia, but there was only 1 (3.57%) non-SJS/TEN patients that suffered pneumonia. A significant difference was found when the binary logistic regression test was performed although the result was weak with OR 0.111 (95% CI 0.013-0.975, p=0.047).

Table 5. Correlation between infection and SJS/TEN

Infection	Case, n (%)	Control, n (%)	OR	95% CI		p-value
				Lower	Upper	
Pneumonia	7 (25)	1 (3.57)	0.111	0.013	0.975	0.047

The most common comorbidities observed in this study were hypertension, diabetes mellitus, epilepsy, conjunctivitis, stroke, kidney failure, and also brain tumor as elaborated in Table 6. Each patient can have more than one comorbid. Generally, prevalence of hypertension, diabetes mellitus, epilepsy, and stroke were higher in the case group than in the control group, but when the binary logistic regression test was performed, there was no significant difference. There were 7 patients (25%) of SJS/TEN and 1 patient (3.57%) of non-SJS/TEN which had conjunctivitis. A statistically significant difference was found in these groups (p=0.047), however the conjunctivitis patients' risk of experiencing SJS/TEN was low with OR 0.111 (95% CI 0.013-0.975). Meanwhile, kidney failure and brain tumor patients' risk of experiencing SJS/TEN was high with OR 1.000, but the result was statistically insignificant (p=1.000), maybe due to the few samples and equal prevalence between case and control.

Table 6. Correlation between comorbidity and SJS/TEN

Comorbid	Case, n (%)	Control, n (%)	OR	95% CI		p-value
				Lower	Upper	
Hypertension	6 (21.43)	2 (7.14)	0.282	0.052	1.541	0.144
Diabetes mellitus	5 (17.86)	1 (3.57)	0.170	0.019	1.565	0.118
Epilepsy	5 (17.86)	2 (7.14)	0.354	0.063	2.002	0.240
Conjunctivitis	7 (25)	1 (3.57)	0.111	0.013	0.975	0.047
Stroke	5 (17.86)	0 (0)	0.000	0.000	-	0.999
Kidney failure	2 (7.14)	2 (7.14)	1.000	0.131	7.644	1.000
Brain tumor	2 (7.14)	2 (7.14)	1.000	0.131	7.644	1.000

A total of 45 suspected drugs causing SJS/TEN were obtained because each patient might be prescribed more than one drug. Number of cases with assumption of one suspected drug were 12 (34.29%), with assumption of several drugs were 16 (45.71%), while there were 7 (20%) cases where the medication history was unclear/unknown. Table 7 showed that the suspected drugs were anticonvulsants (n=20; 44.44%), NSAIDs (n=16; 35.56%), antibiotics (n=8; 17.78%), and antigout (n=1; 2.22%). Most common drug from anticonvulsants were carbamazepine (n=9; 20%) and phenytoin (n=7; 15.56%), from NSAIDs were paracetamol (n=9; 20%) and mefenamic acid (n=5; 11.11%), and from antibiotics were ciprofloxacin (n=3; 8.89%)

Table 7. Suspected drugs causing SJS/TEN

Drug classes	Frequency (n)	Percentage (%)
Anticonvulsants	20	44.44

Carbamazepine	9	20
Phenytoin	7	15.56
Valproic acid	2	4.44
Clobazam	1	2.22
Gabapentin	1	2.22
NSAIDs	16	35.56
Paracetamol	9	20
Mefenamic acid	5	11.11
Ibuprofen	2	4.44
Antibiotics	8	17.78
Ciprofloxacin	4	8.89
Cefadroxil	2	4.44
Cefixime	1	2.22
Erythromycin	1	2.22
Antigout	1	2.22
Allopurinol	1	2.22
Total	45	100

4. Discussion

This study involved 29 (82.86%) SJS patients, 6 (17.14%) TEN patients, and no overlap SJS-TEN patients. Most of the research studying this disease also showed a similar case proportion [7,8]. Previous study by Yang et al. reported the highest case was SJS with 938 patients (80.38%) then followed by TEN with 229 patients (19.62%) [9].

In line with several studies, although men population was higher than women [3,10], there was no correlation between male sex and SJS/TEN [11]. Otherwise, a study by Velasco Tirado et al. stated that there was correlation between male sex and SJS/TEN [12]. Actually most research found that the higher population was women [13,14,15]. A research in Egypt reported that women were 2x more susceptible to have SJS/TEN and it was associated with estrogen deficiency. This is supported by the fact that SJS most frequently occurs in the perimenopause period in women and an experiment using mice with normal levels of estrogen showed a suppression of the development of SJS, while mice with less than normal levels of estrogen by given the act of ovariectomy showed a condition that mimicked SJS [16]. Another study also found women predominance but there was no correlation to SJS/TEN [17]. Distribution of sex was highly varied in SJS/TEN cases. In contrast to those studies, Tan & Tay reported the same ratio between men and women [18], so there was no correlation between sex and SJS/TEN [19].

This study found the youngest age of SJS/TEN patients was 16 years and the oldest was 65 years. Distribution of age with highest proportion was 26-45 & 46-65 years, similar to the previous studies that most distribution was 25-44 years in Dr. Soetomo General Hospital Surabaya & 20-49 years in UK [15,2]. Although the risk factor was young and old age [6,7], our study found a dominance in the middle age (10-40 years). However, there was no correlation to SJS/TEN which is relevant to a study in Kenya [17]. This result was possible because SJS/TEN could happen in all ages [9].

Infection by Mycoplasma pneumoniae showed a correlation with SJS/TEN. A study in Japan reported from a total of 257 SJS/TEN patients, 47.5% of them had infection and the 3.3% was pneumonia. Infection, especially pneumonia, can increase the incidence and mortality of SJS/TEN but the pathophysiology was still unclear so further research should be conducted [20,21]. There was an assumption that it involved the role of T cell. CD4 T cell could prevent the life-threatening skin damage, while CD8 T cell could trigger the secretion of granulysin and FasL that could induce keratinocyte apoptosis. Infection could affect the balance of CD4 & CD8 T cells so it can result in unintended immune response. Hence, infection could worsen the development of SJS/TEN [20,22]. Infection by viruses commonly found as well, particularly HIV. Rzany et al. reported that patients with AIDS were 1000x more at risk of experiencing severe skin eruption [23]. The suspected mechanism was multifactorial, such as polypharmacy in HIV/AIDS management, immune dysregulation, and metabolism of certain drugs [24]. Unfortunately there were no results for HIV testing in this study because the test was not routinely performed, so we could not identify its correlation with SJS/TEN.

Most common comorbids were conjunctivitis, hypertension, diabetes mellitus, and epilepsy, but only conjunctivitis that correlated with SJS/TEN. Similar results stated by Sousa-Pinto et al. that most common comorbids were hypertension followed by diabetes mellitus and both were not correlated with SJS/TEN [8]. Recent study in India reported there were 81.48% SJS/TEN patients that experienced conjunctivitis [25]. The mechanism involved the role of granulysin, the cytotoxic granules produced by CD8 T cell and NK cell. There was plenty of granulysin in SJS/TEN patients. An increase in granulysin concentration was triggered by the activation of CD8 T cell or acute viral infection, which could lead to keratinocyte apoptosis or other tissue damage that generate a unique clinical presentation in SJS/TEN such as conjunctivitis [26]. In fact, conjunctivitis was one of the ophthalmic manifestations of SJS/TEN, not a comorbid. But, according to the data explanation on the medical records, conjunctivitis in those patients categorized as a secondary diagnosis, not as a diagnosis of complication so conjunctivitis was categorized as comorbid in this study. This could happen due to the possibility of misclassification bias during the process of data input.

The suspected drugs in this case were anticonvulsants, NSAIDs, antibiotics, antigout, and most other studies reported the same [13,14,27]. Drugs were the most common causative factor for the incidence of SJS/TEN and at least 200 drugs had been reported to be related to the disease onset [7,28]. This highlighted the importance of giving prescriptions carefully.

Our study has several limitations. First, the samples were relatively small because of the rare cases of SJS/TEN itself. Second, this study was conducted only in Dr. Soetomo General Hospital Surabaya so it can not widely describe the SJS/TEN cases.

5. Conclusion

This study concluded that sex and age are not significantly correlated to the incidence of SJS and TEN. However, this study found that infection, especially by Mycoplasma pneumoniae, is significantly correlated to the occurrence of SJS and TEN. Further research with greater sample size and more detailed discussion on each variable should be conducted to give a better description of the risk factors for SJS and TEN.

6. Conflict of Interest

The authors declare there is no conflict of interest.

References

[1]   Oakley AM, Krishnamurthy K. Stevens Johnson Syndrome (Toxic Epidermal Necrolysis). StatPearls: Treasure Island (FL): StatPearls Publishing. 2020 Jan.

[2]   Frey N, Jossi J, Bodmer M, Bircher A, Jick SS, Meier CR, Spoendlin J. The epidemiology of Stevens-Johnson syndrome and toxic epidermal necrolysis in the UK. Journal of Investigative Dermatology. 2017 Jun 1;137(6):1240-7.

[3]   Suwarsa O, Yuwita W, Dharmadji HP, Sutedja E. Stevens-Johnson syndrome and toxic epidermal necrolysis in Dr. Hasan Sadikin General Hospital Bandung, Indonesia from 2009-2013. Asia Pacific Allergy. 2016 Jan 1;6(1):43-7.

[4]   Thaha MA. Sindrom stevens-johnson dan nekrolisis epidermal toksis di RSUP MH Palembang periode 2006-2008. Media Medika Indonesia. 2009;43(5):234-9.

[5]   Rahayu A, Gustia R, Rahmatini R. Profil Sindrom Stevens Johnson pada Pasien Rawat Inap di RSUP Dr. M. Djamil Padang Periode Januari 2010 sampai Desember 2011. Jurnal Kesehatan Andalas. 2014 May 1;3(2).

[6]   Weinand C, Xu W, Perbix W, Lefering R, Maegele M, Rathert M, Spilker G. 27 years of a single burn centre experience with Stevens–Johnson syndrome and toxic epidermal necrolysis: Analysis of mortality risk for causative agents. Burns. 2013 Nov 1;39(7):1449-55.

[7]   Diphoorn J, Cazzaniga S, Gamba C, Schroeder J, Citterio A, Rivolta AL, Vighi GD, Naldi L, REACT-Lombardia study group. Incidence, causative factors and mortality rates of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in northern Italy: data from the REACT registry. Pharmacoepidemiology and drug safety. 2016 Feb;25(2):196-203.

[8]   Sousa-Pinto B, Araújo L, Freitas A, Correia O, Delgado L. Stevens–Johnson syndrome/toxic epidermal necrolysis and erythema multiforme drug-related hospitalisations in a national administrative database. Clinical and translational allergy. 2018 Dec;8(1):1-0.

[9]   Yang MS, Lee JY, Kim J, Kim GW, Kim BK, Kim JY, Park HW, Cho SH, Min KU, Kang HR. Incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis: a nationwide population-based study using national health insurance database in Korea. PloS one. 2016 Nov 11;11(11):e0165933.

[10]   Barvaliya M, Sanmukhani J, Patel T, Paliwal N, Shah H, Tripathi C. Drug-induced Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS-TEN overlap: a multicentric retrospective study. Journal of postgraduate medicine. 2011 Apr 1;57(2):115.

[11]   Barlianto W. Faktor-faktor yang mempengaruhi derajat keparahan erupsi obat pada anak. Jurnal Kedokteran Brawijaya. 2013 Mar 11;26(1):53-6.

[12]   Velasco-Tirado V, Alonso-Sardón M, Cosano-Quero A, Romero-Alegría Á, Sánchez-los Arcos L, López-Bernus A, Pardo-Lledías J, Belhassen-García M. Life-threatening dermatoses: Stevens-Johnson Syndrome and toxic epidermal necrolysis. Impact on the Spanish public health system (2010-2015). PLoS One. 2018 Jun 18;13(6):e0198582.

[13]   Abdulah R, Suwandiman TF, Handayani N, Destiani DP, Suwantika AA, Barliana MI, Lestari K. incidence, causative drugs, and economic consequences of drug-induced sJs, Ten, and sJs–Ten overlap and potential drug–drug interactions during treatment: a retrospective analysis at an indonesian referral hospital. Therapeutics and clinical risk management. 2017;13:919.

[14]   Mokhtari F, Nikyar Z, Naeini BA, Esfahani AA, Rahmani S. Adverse cutaneous drug reactions: Eight year assessment in hospitalized patients. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2014 Aug;19(8):720.

[15]   Rahmawati YW, Indramaya DM. A Retrospective Study: Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Berkala Ilmu Kesehatan Kulit dan Kelamin. 2016 Oct 31;28(2):146-54.

[16]   El-Hamd MA, El-Dawla RE, Elmagid WA. A clinicoetiological analysis of patients with Stevens–Johnson syndrome and toxic epidermal necrolysis treated at Sohag University Hospital, Egypt. Journal of the Egyptian Women's Dermatologic Society. 2017 Jan 1;14(1):37-44.

[17]   Irungu K, Nyamu D, Opanga S. Characterization of Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis Among Patients Admitted to Kenyatta National Hospital: A Retrospective Cross-Sectional Study. Drugs-real world outcomes. 2017 Jun;4(2):79-85.

[18]   Tan SK, Tay YK. Profile and pattern of Stevens-Johnson syndrome and toxic epidermal necrolysis in a general hospital in Singapore: treatment outcomes. Acta dermato-venereologica. 2012 Jan 1;92(1):62-6.

[19]   Sharma VK, Sethuraman G, Minz A. Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and SJS-TEN overlap: A retrospective study of causative drugs and clinical outcome. Indian J Dermatol Venereol Leprol. 2008 May 1;74(8):238-40.

[20]   Okamoto-Uchida Y, Nakamura R, Sai K, Imatoh T, Matsunaga K, Aihara M, Saito Y. Effect of Infectious Diseases on the Pathogenesis of Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis. Biological and Pharmaceutical Bulletin. 2017 Sep 1;40(9):1576-80.

[21]   Kim HI, Kim SW, Park GY, Kwon EG, Kim HH, Jeong JY, Chang HH, Lee JM, Kim NS. Causes and treatment outcomes of Stevens-Johnson syndrome and toxic epidermal necrolysis in 82 adult patients. The Korean journal of internal medicine. 2012 Jun;27(2):203.

[22]   Lee T, Bae YJ, Park SK, Park HJ, Kim SH, Cho YS, Moon HB, Lee SO, Kim TB. Severe pneumonia caused by combined infection with Pneumocystis carinii, parainfluenza virus type 3, cytomegalovirus and Aspergillus fumigatus in a patient with stevens-johnson syndrome/toxic epidermal necrolysis. Acta dermato-venereologica. 2010 Nov 1;90(6):625-9.

[23] Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bavinck JN, Sidoroff A, Schneck J, Roujeau JC, Flahault A. Stevens–Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. Journal of Investigative Dermatology. 2008 Jan 1;128(1):35-44.

[24] Chateau AV, Dlova NC, Dawood H, Aldous C. Outcomes of Stevens–Johnson syndrome and toxic epidermal necrolysis in HIV-infected patients when using systemic steroids and/or intravenous immunoglobulins in Pietermaritzburg, South Africa. Southern African journal of HIV medicine. 2019 Jan 1;20(1):1-8.

[25] Abrol A, Gulanikar A, Thakre S, Patel A. Study of ocular manifestations of Stevens-Johnson syndrome/toxic epidermal necrolysis. Indian Dermatology Online Journal. 2020 Jul;11(4):570.

[26] Chung WH, Hung SI, Yang JY, Su SC, Huang SP, Wei CY, Chin SW, Chiou CC, Chu SC, Ho HC, Yang CH. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. Nature medicine. 2008 Dec;14(12):1343-50.

[27] Halevy S, Ghislain PD, Mockenhaupt M, Fagot JP, Bavinck JN, Sidoroff A, Naldi L, Dunant A, Viboud C, Roujeau JC, EuroSCAR Study Group. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. Journal of the American Academy of Dermatology. 2008 Jan 1;58(1):25-32.

[28] Cheng L. Current pharmacogenetic perspective on Stevens-Johnson syndrome and toxic epidermal necrolysis. Frontiers in Pharmacology. 2021;12:195.