ORIGINAL RESEARCH

The Correlation of Neutrophil–Lymphocyte Ratio and Eosinophil Count with SCORTEN in SJS/TEN

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Introduction: Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute severe cutaneous adverse reactions commonly caused by medication. Precise evaluation of disease severity in initial setting must be obtained to start appropriate treatment. Neutrophil and lymphocyte ratio (NLR) plays a role in displaying inflammatory reaction while eosinophils count (EC) influences immunological dysregulation including the proliferation of cytotoxic cells in early onset of SJS/TEN.
Objective: To evaluate whether NLR and EC serve as prognostic markers of disease severity in patients with SJS/TEN using SCORTEN.
Methods: A single center study with retrospective study included SJS/TEN patients at Dr. Moewardi General Hospital Surakarta in January 1st 2018–December 31st 2020. The required laboratory data was assessed at the beginning of the patient's admission through medical records. The significance analysis were performed using one-way ANOVA and Spearman while the receiver-operator curve were used to evaluate the prognostic value of variables for severity in SJS/TEN patients.
Results: The total sample in this study was 24 patients with majority female (58%) and range from 25 to >50 years (54%). The results demonstrated of significant difference and positively correlated between NLR and EC with severity of SJS/TEN ($p<0.01$; $r>0.05$). The specificity and sensitivity of 51%;61% and 70%;60%, respectively.
Conclusion: NLR and EC can be used as prognosticators of severity in SJS/TEN while further research on other inflammatory markers with increased number of samples and study centers are needed to provide more actual data.
Keywords: eosinophil, neutrophil–lymphocyte ratio, Stevens–Johnson syndrome, toxic epidermal necrolysis

Introduction

Epidermal necrolysis is a rare, severe, life threatening skin reaction caused by a reaction toward a medication.[1] Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are included into epidermal necrolysis marked by an extensive necrosis and epidermal and/or mucosa epithelial detachment which are distinguished based on the extent of skin detachment, the occurrence of typical and atypical macular target lesions and lesions.[2] SJS phenomenon is defined as severe drug reaction that involves less than 10%, SJS-TEN overlap involves 10–30% and TEN involves skin detachment of more than 30% of body surface area.[3,4]

Epidermal necrolysis due to medication reaction is a hypersensitivity reaction spectrum that turns into health problem inflicting life threatening anaphylaxis.[3] Global SJS/TEN incidences range from 1 up to 6 cases per 1,000,000 population.[5] SJS/TEN prevalence among women is higher compared to men with a comparison of 10:6 and it can occur to all ages, however the risk is increasing over the age of 65 and it rarely happens among children.[6,7] Comorbidity history such as Human Immunodeficiency Virus (HIV), vascular diseases, and cancer increase mortality risks.[8]

Disease course of SJS/TEN continues to be studied. Medications are discovered as the cause of the disease. Several high-risk medications are sulfonamide, aromatic antiepileptic drugs, allopurinol, oxicam nonsteroidal anti-inflammatory, lamotrigine, nevirapine. The risk is seemingly limited in the first 8 weeks of the treatment before the onset of the reaction.[8] The expanding keratinocyte apoptosis is triggered by the activation of cytotoxic reaction mediated by cells and

strengthened by cytokine, particularly granulysin which is a cytolytic protein.[8] Hypersensitivity reaction type IV is the pathomechanism for the occurrence of SJS/TEN. Major predilection of SJS/TEN are face, upper body, and proximal extremities.[9,10] It is varied in terms of severity degrees from the reddish mucosa, papules, erythematosus area with target lesions until characterized by the occurrence of vesicular and bullous, also the parts with extensive necrotic.[10]

Diagnosis establishment is made based on the clinical history and empirical risks of the medicines that may inflict SJS/TEN. Unspecific prodromal symptoms and signs such as sore throat, runny nose, cough, headache, fever, and malaise are discovered in 1 to 3 days of early onset.[11] Acute mucocutaneous reaction such as erythematosus area and Nikolsky sign or the dislodgement of epidermis due to lateral pressure found in an advanced onset of skin lesions.[12] Skin biopsy for histopathology and immunofluorescence examination is the gold standard in diagnosis establishment, especially if there is an alternative diagnosis to consider.[13,14] Laboratory supporting examination is conducted merely for the evaluation of severity, prognosis, and daily management for life threatening conditions in intensive care unit (ICU).[3,15] In an early phase of the disease, hematology abnormalities are discovered including neutrophile, lymphocyte, eosinophile, thrombocyte, and C-reactive protein (CRP) as well as interleukins (IL) and they are all related to the inflammation response toward a disease.[16–18] One of the ways to integrate the measurements of systemic immunity is by conducting systemic inflammation evaluation that can be obtained by performing a complete hematology measurement. The increasing ratio of neutrophile and lymphocyte as an inflammation marker has contributed as the prognosticator index in coronary heart disease, chronic kidney disease, heart failure, and advanced cancer.[2,3]

Mortality risk of SJS/TEN is relatively high that is around 10% for SJS, 30% for SJS overlap TEN and 50% for TEN.[19] Increased age, significant comorbidity, and extensive skin detachment are correlated with poor prognosis. Prognosticator index (SCORTEN) that contains seven points of scoring namely age, detached or compromised body surface, heart rate, cancer malignancy, serum urea, serum glucose, and serum bicarbonate, serve in the evaluation of severity degree and mortality risk among SJS/TEN patients.[20] This study aim to evaluate whether NLR and EC serve as prognostic markers of disease severity in patients with SJS/TEN using SCORTEN.

Methods
Study Design
The study was an observational analytic study with a retrospective cohort study approach. The study was conducted by observing medical record data of patients taken based on the diagnosis from the 10th revised edition of International Statistical Classification of Diseases and Related Health Problems (ICD-10) namely L.51 which is used to categorize Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Inclusion criteria included age ranges from 0 up to >70 years old, the therapy given and comorbid. Exclusion criteria included patients with incomplete medical record.

Neutrophil–lymphocyte ratio (NLR) and eosinophil count (EC) are the comparison of the number of neutrophil and lymphocyte also eosinophil used to determine the evaluation of systemic inflammatory response categorized as independent variable. The examinations of neutrophil, lymphocyte and eosinophil level were conducted in Clinical Pathology Laboratory of Dr. Moewardi Hospital Surakarta by using automate flow cytometry method with Mindray BC-1800® hematology analyzer. Severity degree of SJS/TEN was measured through SCORTEN (Score of Toxic Epidermal Necrolysis) prognosticator index which consisted of seven questions categorized as dependent variables (Table 1).

Study Population and Data Collection
The population of the study was all patients with SJS/TEN diagnosis in outpatient care and inpatient care units of all department of Dr. Moewardi Hospital Surakarta during the period of 1 January 2018 – 31 December 2020. The study had undergone analysis from ethics committee of Dr. Moewardi Hospital Surakarta and it was proven by an ethical clearance from Health Research Ethics Commission of Dr. Moewardi Hospital; Surakarta number 632/V/HREC/2021. The size of the sample was determined by the number of SJS/TEN patients who visited Dr. Moewardi Hospital Surakarta during the period of 1 January 2020 – 31 December 2020, who met the inclusion and exclusion criteria. In addition, we included

Table 1 SCORTEN[a] Prognosticator Index[8]

Prognosticator Index	Point
Age (>40years)	1
Heart Rate (>120x/minute)	1
Malignancy	1
Skin lesions (>10% of body surface area)	1
Serum Urea >28 mg/dl (10mmol/L)	1
Serum Bicarbonate >20 mEq/L	1
Serum Glucose >252 mg/dl (14mmol/L)	1

Abbreviation: [a]SCORTEN, SCORe of toxic epidermal necrolysis.

patients under 18 year olds whose parents allowed their children to join the study by signing the informed consent form. The minimal number of samples for each group was determined by the total consecutive sampling.

Statistical Analysis

Categorical variables were expressed as numbers and continuous variable were expressed as median. For the statistics data analysis, the study used Kolmogorov–Smirnov as a normality test. One-Way ANOVA (p) test and Spearman (r) correlation test was conducted to discover the association of each comparative and correlation between neutrophil–lymphocyte ratio and eosinophil count with SJS/TEN severity degree, measured by using SCORTEN. The study used SPSS version 22.0 (IBM Corp, Armonk, New York) for data analysis and it was considered significant if the value of $p<0.05$.

Ethical Issues

This study was approved by Health Research Ethical Committee of Dr. Moewardi General Hospital/Faculty of Medicine, Sebelas Maret University, Surakarta, Central Java Indonesia (632/V/HREC/2021). The study was conducted in accordance with the Declaration of Helsinki. Patient confidentiality was assured.

Results

The study was a single-center study conducted in August 2021 in Dr. Moewardi Hospital Surakarta. The study data were secondary data obtained from medical records of SJS/TEN patients in Dr. Moewardi Hospital Surakarta including both inpatients and outpatients during the period of 1 January 2018 – 31 December 2020 who met the inclusion and exclusion criteria of the study. The study subjects were selected by using non-probability sampling with a total sampling type. During the determined period of time, it obtained 24 study subjects who met the criteria, with the number of respondents was 10 men (42%) and 14 women (58%). The age ranged from 7–68 years, with the largest age group between 25 to >50, as many as 13 people (54%), and the smallest age group was <10 years as only 1 person (4%). It obtained data that the most treatment duration for SJS/TEN Dr. Moewardi Hospital Surakarta was < 10 days (50%) (Table 2).

The data of medications as the causative agents for SJS/TEN were obtained in 16 medical reports, whereas in the other 8 medical records the causative medication data mentioned were still dubious as the certain cause of drug-related skin eruption. The most frequent causative medications were the class of analgetic (30%; paracetamol and ibuprofen), antibiotic (12%; amoxicillin) and anticonvulsant (12%; phenytoin). The distributions of causative agent medications can be seen in detail in Table 3.

Patient's clinical manifestations and laboratory data including age, gender, heart rate, the level of bicarbonate, neutrophil, lymphocyte, eosinophil, urea nitrogen, and glucose collected were collected from inpatient medical records.

Table 2 Characteristic for Subject of the Study

Variable	Steven Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)			Percentage (%)
	SJS (n)	SJS overlap TEN (n)	TEN (n)	
Gender Categories				
Male	4	4	2	10 (42%)
Female	7	5	2	14 (58%)
Age				
<10 y.o.[a]	0	0	1	1 (4%)
10–25 y.o.	4	4	2	10 (42%)
25–50 y.o.	2	1	0	3 (12%)
>50 y.o.	6	3	1	10 (42%)
Treatment duration				
<10 days	7	5	0	12 (50%)
>10 days	3	3	1	7 (29%)
Deceased	1	1	3	5 (21%)
SCORTEN[b]				
SCORTEN <3	9	7	1	17 (71%)
SCORTEN >3	2	2	3	7 (29%)

Abbreviations: [a] y.o, year old; [b]SCORTEN, SCORe of toxic epidermal necrolysis.

The laboratory data was obtained in the beginning of hospital admission (Day 0) or within 24 hours after admitted into the ward (Day 1). Evaluations of NLR and EC were calculated based on each index whereas SCORTEN was calculated within 24 hours since the patients obtained the treatment in Dr. Moewardi Hospital (Table 2).

The distribution of inflammation characteristic signs among the study subjects were related to SCORTEN prognosticator index. The results of *One-Way ANOVA* comparative analysis and Spearman correlation analysis (Table 4) indicated that the average calculation of neutrophil–lymphocyte ratio (NLR) the value of $p < 0.01$ and $r > 0.05$ therefore it implied a strong statistics significance. Based on *One-Way ANOVA* and *Spearman* comparative analysis results it can be concluded that there is a significant average distinction of every inflammatory marker with SCORTEN among SJS/TEN patients in Dr. Moewardi Hospital Surakarta.

Based on the significant difference of inflammatory marker value from the result of numerical comparative test the researchers conducted sensitivity and specificity examinations over each inflammatory marker to determine severity degree among SJS/TEN patients. It used ROC (receiver operator characteristics) curve and AUC (area under the curve) to determine sensitivity and specificity of each inflammatory marker. ROC and AUC curves obtained the limit value of inflammatory markers used as SJS/TEN prognosticator.

Coordinates of ROC curve may determine the value of neutrophil–lymphocyte ratio which meant as SCORTEN threshold and it obtained NLR threshold value was 6.6 with a sensitivity value of 61% and a specificity value of 51%. In addition, coordinates of ROC curve also determined the value of eosinophil count as SCORTEN threshold and it obtained EC threshold value of 13.2 with a sensitivity value of 70% and a specificity value of 60% (Figure 1).

Discussion

Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are included in rare, severe, life threatening skin reactions caused by a reaction toward a medication.[1] There are several indicators on SCORTEN scoring that may

Table 3 The Medication Distribution as the Causative Agent Among Study Subjects

Group	Name of Drugs	Percentage
Non-Steroid Anti Inflammatory (NSAID)	Ibuprofen	2 (4%)
	Paracetamol	11 (26%)
Antibiotic *broad-spectrum*	Amoxicilin	5 (12%)
	Cefotaxime	1 (2%)
	Cefodroxil	3 (8%)
	Ciprofloxacin	1 (2%)
	Levofloxacin	2 (4%)
	Thiamphenicol	1 (2%)
Anticonvulsant	Phenobarbital	1 (2%)
	Phenytoin	5 (12%)
	Gabapentin	1 (2%)
	Amitripyline	1 (2%)
	Valproat Acid	1 (2%)
	Carbamazepin	1 (2%)
Others	Dapsone	2 (4%)
	Clorpheniramine	1 (2%)
	Candersartan	1 (2%)
	ISDN	1 (2%)
	Clonidine	1 (2%)
	Dexamethasone	1 (2%)
	Duviral	1 (2%)
	Nevirapine	1 (2%)

affect the prognosis of SJS/TEN patients. Clinical manifestations and distributions based on age and gender, as well as causative agent drugs are very varied and affected by population differences. The differences among the populations in terms of medication consumption habits and the scales of reaction from the medications they often use with the population's pharmacogenetic tendency will affect the frequency of SJS/TEN occurrence.[21]

In the study, the largest distribution based on age was among SJS/TEN group aged between 25 - >50 years as many as 13 people (54%). Concerning to research, age variable is categorized based on the guidelines of Health Department of the Republic of Indonesia year 2009 concerning ages namely child (<10 years), adolescence (10–25 years), adult (25–50 years) and elderly (>50 years). Age is one of the demography characteristics evaluated for the severity degree among SJS/TEN patients by using SCORTEN. The similar result is also obtained by Jelvehgari et al in Iran in 2010 in which SJS/TEN frequently occurs at the age range of 30–39 years.[22] The data discovered by Dubey et al in Pakistan in 2016 indicate the escalated incidence rates among age group above 40 years.[23] The increasing SJS/TEN incidences along with the increasing age is due to the increasing medications exposure and the decreasing clearance function among the age group. Among the elderlies the function shifting of liver and kidneys may decrease the ability to eliminate medications.

Table 4 Comperative and Correlation Test Using Statistical Analysis

Variable	Total (n=24) Mean ± SD	p-value[d]	r-value[e]
1.NLR[a]		0.00	0.36
1.1.SCORTEN[b] <3	n = 17 6.83 ± 2.60		
1.2.SCORTEN >3	n = 7 6.90 ± 3.86		
2.EC[c]		0.26	0.26
2.1.SCORTEN <3	n = 17 4.20 ± 3.78		
2.2.SCORTEN >3	n = 7 0.81 ± 3.06		

Abbreviations: [a]NLR, neutrophil-lymphocytes ratio; [b]SCORTEN, SCORe of toxic epidermal necrolysis; [c]EC, eosinophil count, [d]statistical significant one-way ANOVA with p<0.05; [e]statistical significant Spearman with r>0.05.

Distribution of the most study subjects was female study subjects with a comparison of 7:5. The study result is similar to a study by Hasan et al in Malang in 2016 in which the ratio of women and men is 1.14:1.[24] The study conducted by Mockenhaupt et al on epidemiology in China in 2019 indicates that female gender category has 10 times higher incidences than male.[8] The tendency of higher SJS/TEN incidences on women is presumably because the occurrence of several conditions among women that react toward medication pharmacokinetic. The conditions include menarche, pregnancy, lactation, and the fact that women are more likely to seek medications compared to men.[23,24]
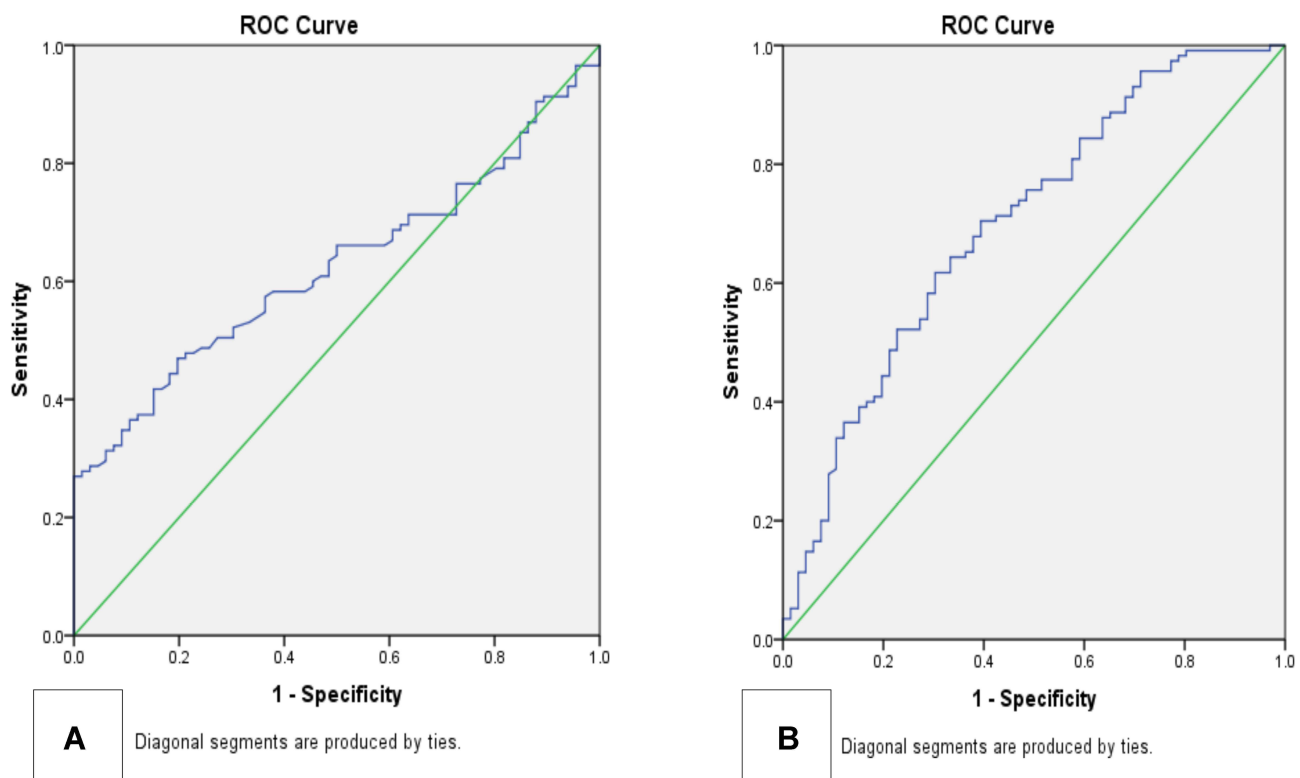

Figure 1 A. ROC[a] curve of Neutrophil-lymphocyte ratio (NLR) toward SCORTEN with AUC **B**. ROC curve of Eosinophil count (EC) toward SCORTEN with AUC[b]
Abbreviations: [a]ROC, Receiver Operator Characteristics; [b]AUC, Area Under Curve.

The study was still dubious to determine the medication type specificity of SJS/TEN causative agents. It is due to the patient's tendency to consume more than one type of medications. Identification can be performed by observing medication administration chronology and medication's ability to generate SSJ/TEN. Medication administration chronology inside the patient's body can be observed by calculating the time duration between the first intake and the onset of SJS/TEN occurred within the period of one up to four weeks. Non-Steroid anti inflammation medications (NSAID) were discovered as the most causative agent in the study. It presumably happened due to the genetic effect of each individual. If one has the tendency or potential allergy to NSAID or other medications, therefore even a small dosage of NSAID or other medications may lead to the allergy reaction to NSAID or other medications. In a study by Sasi and Taufiq in Surabaya in 2018, it is discovered that the most causative agents are from analgetic – antipyretic (mefenamic acid, paracetamol), antibiotic (cotrimoxazole) and anticonvulsant (carbamazepine).[25] In a study by Choon et al in Malaysia in 2012 it was discovered that antibiotic (cotrimoxazole) and anticonvulsant (phenytoin and carbamazepine) are the most causative medications for SJS/TEN among the population.[26] The causative medications differences occur because there are varieties of medication patterns in each population and the characteristic of the population. Analgetic class, namely paracetamol and ibuprofen, and antibiotic class, namely amoxicillin and cefadroxil, were drug regimen therapy frequently used in the study. In addition, phenytoin was also discovered as the type of anticonvulsant frequently used for epilepsy management and neuropathy in the population of the study.

Distribution of the most patient's treatment duration in the study was <10 days with an average of 6.5 days. Mortality risk in SJS/TEN is relatively high, which are 10% for SJS, 30% for SJS overlap TEN and 50% for TEN.[19] Mortality rate is mostly caused by sepsis. Mortality rate in the study was 21% with the cause of death was septic shock. The varied treatment duration might get affected by severity degree, comorbidity, and the complication arose. To date, SCORTEN turns out to be the scoring system used to evaluate the severity degree of SJS/TEN patients.

The study result indicated that NLR among SJS/TEN patients were significantly higher than the threshold 6.6 in SCORTEN >3 with the sensitivity of 61% and specificity of 51%. It is also discovered in a retrospective single-center study by Wang et al in China in 2015–2020 which indicated that NLR of patients with SCORTEN >3 is significantly higher than patients with SCORTEN <3. Patients with SCORTEN >3 are also significantly older and having higher procalcitonin level, that it can be concluded that the older age and procalcitonin sign are important prognostic factors in SJS/TEN. ROC analysis indicated that among the inflammatory markers such as neutrophil–lymphocyte ratio, platelet-lymphocyte ratio, CRP-albumin ratio and albumin-fibrinogen ratio, only NLR that has predictive value for mortality with limit value of 5.79 ($p<0.05$) and specificity of 63.6% also sensitivity of 85.7%. The result indicated that among the four signs, only NLR that was able not only to reflect the severity degree and SJS/TEN inflammation condition but also predict mortality risk. However, the inflammatory marker is not an independent risk factor, hence further study in the future is required to validate the observation.[27]

In recent years, there are additional inflammatory markers used as the prognosticator index such as neutrophil and lymphocyte ratio as well as eosinophil count. However, the studies on those indicators in drug eruption cases are still less noticed. Evaluation of neutrophil–lymphocyte ratio (NLR) combines information of two opposite immune paths therefore it reflects an inflammatory balance and turns to be a better prognosticator compared to single parameter. Several studies have indicated that NLR is related to disease activity in several autoimmune inflammation diseases and it is also a systemic inflammatory marker among patients with psoriasis.[28] As study by Takayoshi et al in Japan in 2017 reports that NLR in SJS/TEN is significantly higher than in other skin lesions such maculopapular exanthema and positively correlates with the chemokine level regulated by thymus (TARC) which is related to the early stage of a disease. It indicates that NLR can reflect the inflammation condition of SJS/TEN in the early onset that it can help the clinicians in establishing the diagnosis faster the predicting the potential severity.[29,30]

The result of the study indicated that eosinophil count among SJS/TEN patients was significantly higher than the threshold 13.2 in SCORTEN >3 with the sensitivity value of 70% and specificity value of 60%. It has a similarity with a study by Yang et al in China in 2013 that indicates the percentage of patients with eosinophil in drug eruption group is significantly higher than of those in control group.[30] In addition, a study by Kimberly et al in Massachusetts of 1983–2013 indicates that patients with a spectrum of drug eruption skin lesions such as multiform erythema have higher of eosinophil. Accumulation of eosinophile occurs in several diseases such as allergy, parasite infection, autoimmune

diseases, inflammatory disorder, and cancer as well as in consumption of medication.[29] The foundation of clinical attention is that eosinophilia is related to numerous severe hypersensitivity reactions including organ-specific reaction (such as nephritis which is mediated by immune complex, hepatitis, and pneumonitis) and severe skin reaction (SCAR; such as SJS, TEN and drug rashes with eosinophilia and systemic symptoms syndrome (DRESS).[17]

During drug eruption acute stage, eosinophil circulating to skin lesions or at apoptosis in bigger number than what bone marrow can re-produce therefore it contributes in the high level of circulating eosinophil. A study by Kimberly et al in Massachusetts during 1983–2013 discovers that patients with spectrum of drug eruption skin lesions such as multiform erythema, have high eosinophil.[17] The high level of circulating eosinophil among patients with multiform erythema may be generated by the previously-explained over production of IL-5, IL-3 and GM-GSF in the peripheral blood and lesions during drug eruptions. High level of cytokine may stimulate differentiation and proliferation of eosinophil in bone marrow and it increases eosinophil recruitment into peripheral blood and lesions. The number of eosinophils is positively correlated with poor liver function, long hospitalization, and the prolonged use of corticosteroid among patients with drug eruption. The number of eosinophil does not return to its normal without systemic corticosteroid which is the most effective agent to reduce eosinophil, therefore the tendency of poor liver function, long hospitalization, and the number of circulating eosinophil may become prognostic markers that drug eruption cases are not limited only in SJS/TEN.[30] The result of the study indicated that eosinophil count among SJS/TEN patients was significantly higher than the threshold of 13.2 in SCORTEN >3 with the sensitivity of 70% and specificity of 60%.

SCORTEN is based on seven clinical and laboratory variables which are easily measured and have been validated to be used during 24 and 72 hours of inpatient. Intensive care or burn care should be performed in SJS/TEN cases based on the extent of the detached skin and the occurrence of comorbid. Patients with limited detached skin and the SCORTEN score 0–1 also unprogressive disease can be immediately treated in general care unit, whereas patients with more severe disease and the SCORTEN score 2 should, if possible, be transferred into intensive care unit or burn unit.[6,8]

However, certain aspects remain to be explored in order to propose its utility in clinical setting. There are several limitations to our study. It discovered relatively low SJS/TEN cases which was presumably related to incomplete and less-structured diagnosis process. The medical record data which were not yet integrated also affected the reporting over the number of cases, particularly when skin eruption diagnosis is a secondary diagnosis in the medical record. Basically, a comprehensive anamnesis is a supporting factor in establishing SJS/TEN diagnosis. Further large-scale prospective cohort studies are needed in order to accurately assess the role of each predictive biomarker. Each of predictive biomarker should be sequentially measured throughout each dose and disease severity to reveal the most appropriate dose-dependent correspond to disease mortality. The use of several diagnosis criteria that have been developed may help determining the type of medications that cause skin eruption.

Conclusion

In the study complete blood test and SCORTEN evaluation is performed to establish the diagnosis and stratify mortality risk. The study subjects are 24 patients diagnosed with SJS/TEN. The majority study subjects are female (58%) with the distribution of the majority age ranges from 25 - >50 years (54%). The study discovers that NLR and EC are positively correlated with the disease's severity degree score and having efficacy to determine the mortality risk of SJS/TEN (SCORTEN). It is supported by several literature which indicate that NLR serves in reflecting inflammation reaction mediated by chemokine and regulated by thymus (TARC) in disease's early stage. Immunopathology study indicates the occurrence of cytotoxic cells including T killer and lymphocyte T CD8+ specifically in the early onset of the disease that generates increased proliferation and eosinophil differentiation in the bone marrow controlled by cytokine produced by T cell.

It can be concluded that neutrophil–lymphocyte ratio and eosinophil count are positively correlated with the severity degree of SSJ/TEN during 2018–2020 in Dr. Moewardi General Hospital Surakarta both for inpatients and outpatients during 2018–2020. Subsequently, the other studies can be conducted by using primary data to get accurate supporting data as well as to extend the study coverage such as evaluation of other inflammatory markers. A study with several study centers consisting of primary to tertiary hospitals may be conducted in order to get more samples, and able to present the more actual subject characteristics.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report that there are no conflicts of interest in the study.

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