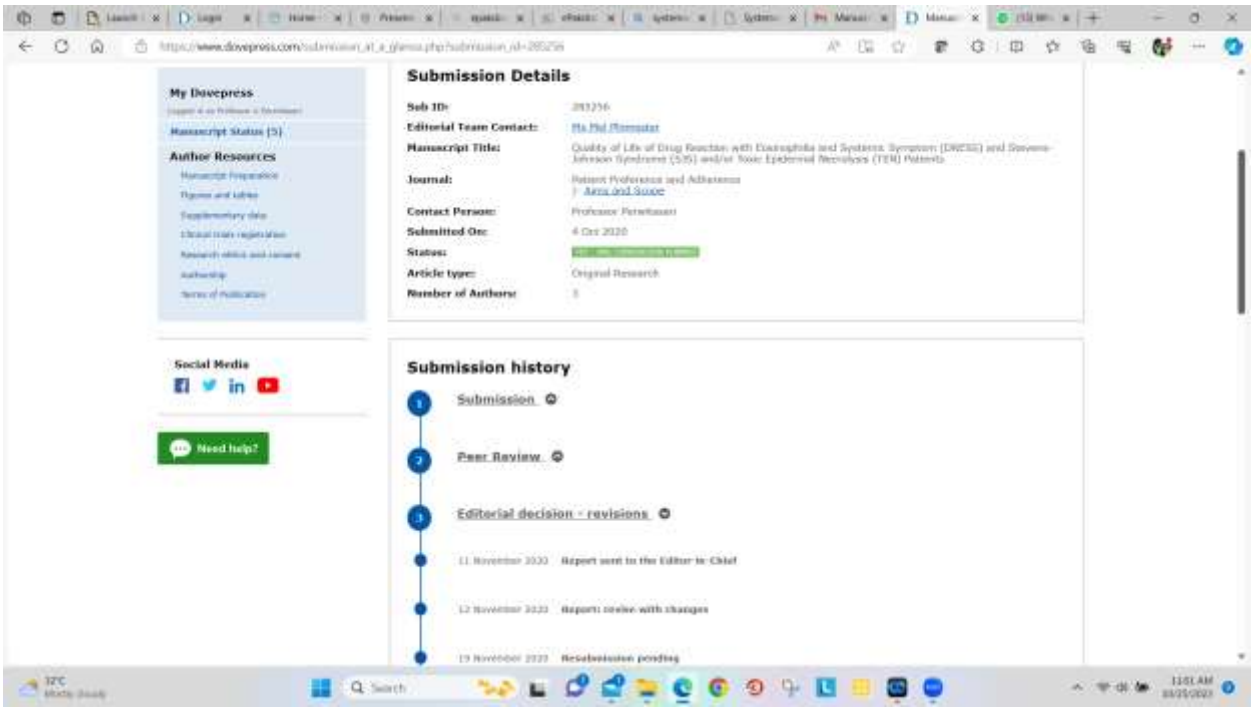
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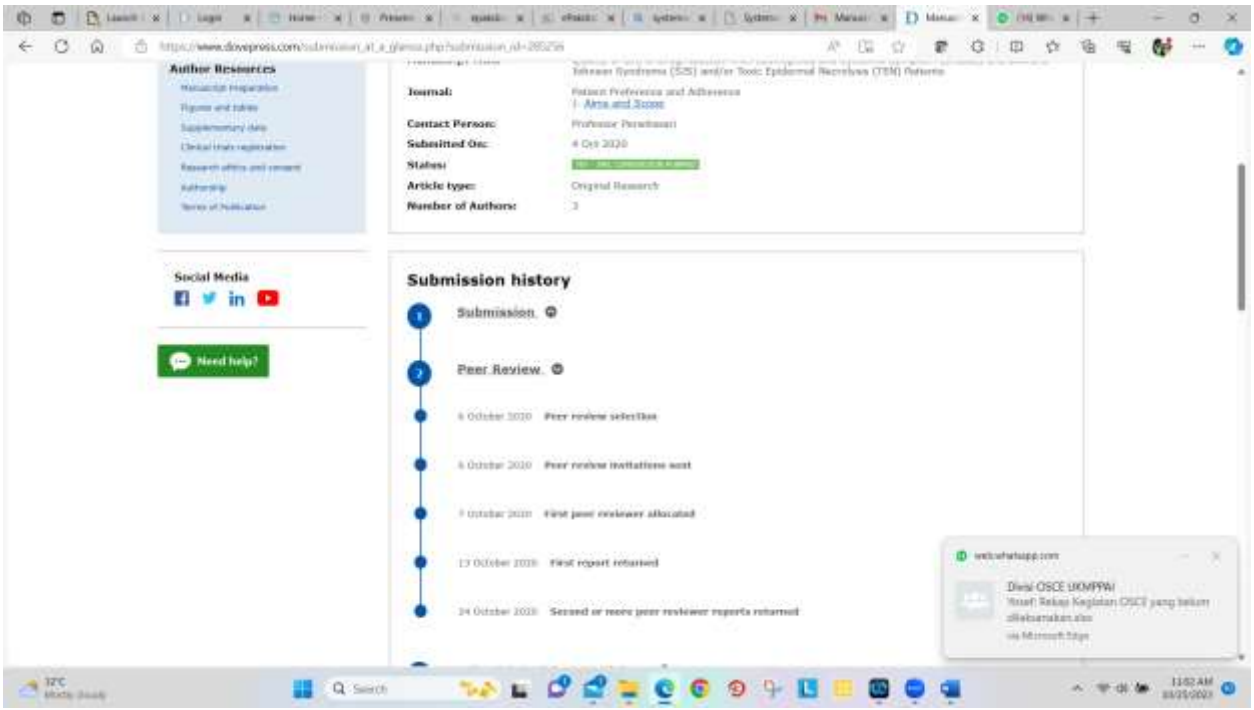
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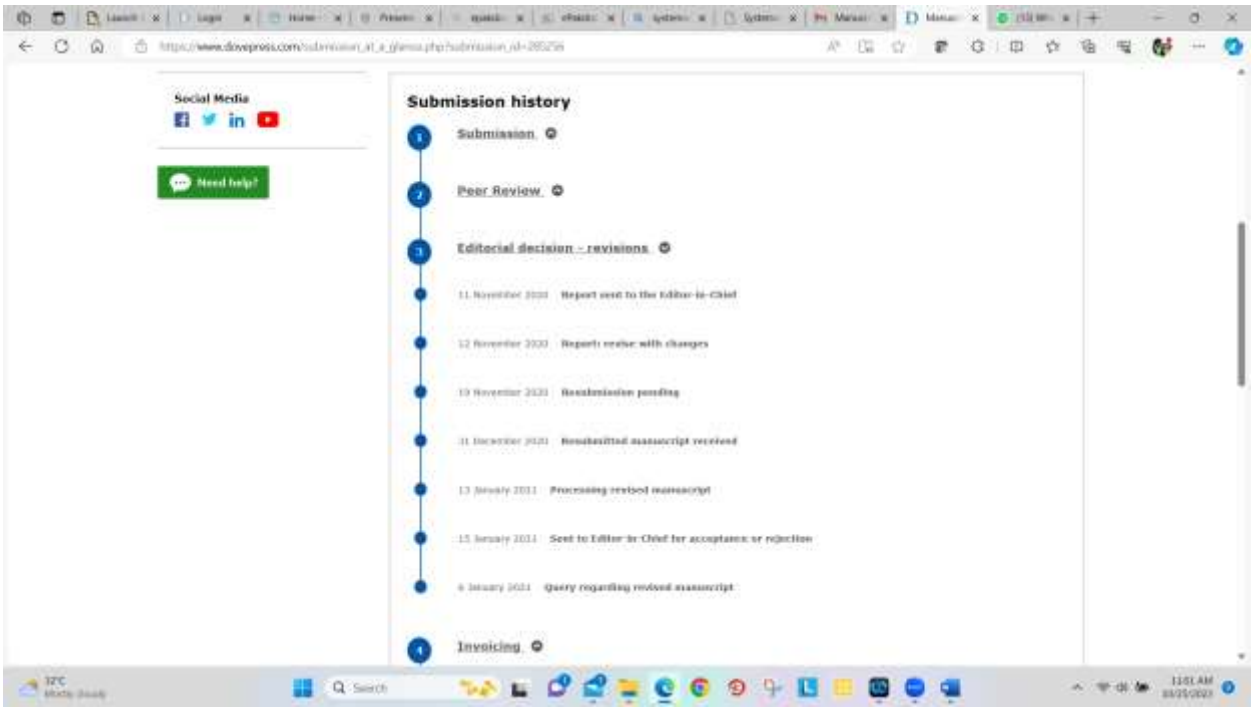
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ORIGINAL RESEARCH

Quality of Life of Drug Reaction With Eosinophilia and Systemic Symptom (DRESS) and Stevens Johnson Syndrome (SJS) and/or Toxic Epidermal Necrolysis (TEN) Patients

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Abstract:

Purpose: *Drug Reaction With Eosinophilia and Systemic Symptom* (DRESS), *Stevens Johnson Syndrome* (SJS), and *Toxic Epidermal Necrolysis* (TEN) are acute hypersensitivity reactions with the potential to reduce the life quality of exposed individuals. This study aims to determine the quality of life of patients suffering from DRESS, SJS, SJS/TEN.

Patients and methods: A cross sectional approach was used to get the quality of life data from DRESS, SJS, and/or TEN patients at Dr. Sardjito general hospital, Yogyakarta. The utility index and VAS score differences of EQ-5D-5L were analyzed based on the diagnosis.

Results: We recruited 58 patients. Most of the patients were female (63%). The mean value of utility index was 0.61, 0.08 and 0.03 for DRESS, SJS and SJS/TEN patients, respectively (*p value* <0.01). Furthermore, the mean of VAS score was 73.36, 57.93 and 50.00 for DRESS, SJS and SJS/TEN patients, respectively (*p value* <0.01).

Conclusions: In general, the quality of life of DRESS patients is better than the quality of life of SJS and/or TEN patients.

Keywords: DRESS, QoL, SJS, TEN, skin diseases

Introduction

Pharmaceutical services are essential health practices that aim to increase rational drug use, the safety, cost efficiency, and the life quality of patients.[1] According to previous research, problems related to drug quality and therapy failure cause greater costs for patients. [2] Advances in health science, especially pharmacy, have a great impact on drug use, which directly causes some side effects (adverse drug reaction). The drug side effects that occur on the skin are called adverse cutaneous drug reaction (ACDR),[3] while at an intense level, they are called severe cutaneous adverse reaction (SCAR).[4]

The SCAR incidence, such as drug reaction with eosinophilia and systemic symptom (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) rarely occured, however, they have the potential to cause disabilities or death with 10% mortality rate. [5,6] The DRESS is a collection of symptoms and idiosyncratic allergic reactions caused by drug administration in therapeutic doses. [7] At the advanced stages of DRESS, several organ dysfunctions arise in the liver, kidneys, lungs, and heart.[3,8] The most common complications in DRESS patients are found in the liver (50% - 87%) and kidneys (10% - 53%). [9]

The SJS and TEN are severe and life-threatening diseases involving the skin and mucous membranes, characterized by the release of epidermis, water-filled lesions, and peeling of the mucosa. They also occur due to reactions from drugs, although the occurrence is rare. [10] The difference between SJS and TEN is the percentage of affected body surface, SJS affects 10%, while TEN attacks 30%, and the occurrence of both SJS-TEN cause skin lesions of 10% - 30%. The incidences of SJS and TEN are 1 - 6 cases and 0.4 - 1.2 cases / million / year, respectively.[11] DRESS, SJS and TEN are not only health problems, they also cause psychological stress and fear following the life-threatening reactions. Most DRESS, SJS, and TEN patients are found to receive outpatient care after being hospitalized by primary doctors, such as internal medicine specialists, skin and genital specialists. The research conducted in Korea stated that SJS and TEN treatment costs are comparable to treating the five most expensive diseases nationally. [12,13] Meanwhile, in the DRESS case, some patients experienced relapse a few months after the first hospitalization, this caused additional costs. [14]

The research conducted by Nogueira (2003) stated that the assessment of SJS / TEN patients' quality of life using the Short Formulary-36 (SF-36) questionnaire shows some problems, such as psychological, social, and economic disorders for approximately 30 years. All these occur at productive age, causing high anxiety and depression. [15] In this study, the Euro Quality of Life-5 Dimensions (EQ-5D) questionnaire was used due to its easy and understandable features. The high mortality rate of these illnesses, the cost impact, and the patients' quality of life are important information for pharmacists, doctors, and policy makers during treatment periods. Therefore, this research was carried out based these attributes at Dr. Sardjito general hospital, Yogyakarta from 2014-2018. The purpose of this study was to determine the quality of life of DRESS, SJS, and TEN patients.

Materials and Methods

This study was an observational, with cross sectional approach, which is conducted prospectively. A total of 21 DRESS, 32 SJS, 5 SJS/TEN hospitalized patients was included in this study, with the code ICD-10 DRESS (L.27.0), SJS (L51.1), and TEN (L51.2). The ICD-10 code has been implemented since 2006. The diagnosis of DRESS, SJS/TEN and causality analysis

was defined by the physician. We collected the patients' characteristics and drugs used from the patients' medical record, from January to December 2019 and we did not use the sample size due to the limited number of patients.

Patients' quality of life data was collected using EQ-5D-5L questionnaire. The patients gave their consents prior to the commencement of this study and they filled in the questionnaire during the hospital discharge. The patients we also informed about the purpose of the study. This study was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Gadjah Mada University-Dr. Sardjito Yogyakarta, with ethical approval number KE / FK / 1111 / EC 19 October 2018 and conducted in accordance with the Declaration of Helsinki.

To calculate the patients' quality of life, the EQ-5D-5L (five level) questionnaire was used. The EQ-5D-5L instrument is a standardized system that collects quality of life information on five dimensions: mobility, self-care, daily activities, pain/discomfort, anxiety/depression. Each domain is scored from 1 to 5, with 1 having no problems, 2 slight problems, 3 moderate, 4 severe, and 5 being unable to undertake the activity described. This questionnaire is already available and validated in Bahasa Indonesia[16]. The five dimensions digit can be combined into a 5-digit number that describes the participant's quality of life. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problem with self-care, moderate problems with doing daily activities, severe pain or discomfort, and extreme anxiety or depression. [16]

To convert an individual EQ-5D-5L health state to a single EQ-5D-5L index score, standard values (weights) which are attributed to each of the levels in each dimension, were obtained from the Indonesian value set. The index was calculated by deducting from 1 the appropriate weights for the value for full health (i.e.state 12345). The EQ-5D-5L instrument also describes self-reported overall health status on a visual analogue scale (EQ-VAS), which has a score between 0 ("worst imaginable health status") and 100 ("best imaginable health state"). Both the EQ-5D-5L utility index and VAS score were used as dependent variables in the statistical analysis. [16]

A comparison was made by assessing the utility index and VAS score of DRESS, SJS, and TEN patients using One-Way Anova test.

Results

We recruited 21,32 and 5 patients of DRESS, SJS and SJS/TEN, respectively. The patients demographic data and clinical characteristics such as gender, age, duration of hospitalization, causative agent, and therapy during the treatment is shown in Table 1. The frequency of DRESS (62%), SJS (65%), and SJS/TEN (60%) in female are greater compared to male patients, with the highest mean age is 38.8 years old. The mean hospitalization duration for DRESS, SJS and SJS/TEN patients are 10.5, 11.6 and 12 days, respectively.

The main drugs causing DRESS are antibiotics (67%) followed by non-steroidal anti-inflammation drugs (NSAIDs) (24%), oral anti-tuberculosis (14%), and anti-convulsants (14%). Meanwhile, the main cause of SJS is antibiotics (56%), followed by anti-convulsants (44%), and NSAIDs (18%), while TEN was antibiotics (80%), followed by NSAIDs (20%), anti-retrovirals (ARVs) (20%), and anti-convulsants (14%).

An overview of the patient's treatment is shown in Table 2. All the DRESS, SJS, and TEN patients received fluid and electrolyte therapy (100%). The specific therapy given to DRESS patients is corticosteroid injection (90%), while for those with SJS are corticosteroid injection (96%), oral corticosteroids (90%), and cyclosporin-corticosteroid (3%). Lastly, for TEN patient there are corticosteroids injection (100%) and oral corticosteroids (60%).

Table 3 presents the utility and VAS differences between DRESS, SJS and SJS/TEN patients. The utility value of DRESS patients is higher than the utility value of SJS and SJS/TEN patients (0.62 vs 0.08 and 0.03). The VAS score of DRESS patients is also higher than the VAS score of SJS and SJS/TEN patients (73.36 vs 57.93 and 50.00). The differences of utility and VAS score among the groups are significant (p value <0.05). There are significant differences of utility index and VAS scores among the groups. However, there are no significant differences of utility index and VAS scores between SJS and SJS/TEN groups.

Table 4 presents the health profiles of DRESS, SJS and SJS/TEN patients based on EQ-5D-5L. In the mobility, self-care, usual activities and anxiety/depression, the proportion of DRESS patients with ‘no problem’ and ‘severe problem’ is higher than SJS and SJS/TEN patients. However, in the pain/discomfort dimension, patients in all diagnosis, experience more severe

problems. In general, The DRESS patients has better health profiles in all dimensions than other diagnosis. This situation is also presented by Table 5, whereas only DRESS and SJS patients state the best health, based on the VAS score. Furthermore, the proportion of patients with the best health is higher in DRESS diagnosis than SJS. Patients with SJS and SJS/TEN have the worst health

Discussion

Our study shows that in general, DRESS patients had better quality of life than SJS/TEN patients. The female patients have a higher incidence of DRESS, SJS, and SJS/TEN compared to men. This result is in accordance with that of Velasco-Tirado et al (2018), which stated that SJS / TEN were more common in women than men, with a male to female ratio of 0.6.[17] The mean age of DRESS, SJS, and TEN patients in this study is not significantly different. Meanwhile, other studies had reported that the incidence rate and age increase were equal. Therefore, the higher the age, the greater the risk of experiencing skin disorders, such as SJS and TEN, due to high rate of drug consumption at older age and their interactions.[18,19]

The mean of hospitalization duration for DRESS, SJS, and TEN patients were less than the mean of hospitalization of study conducted by Yang et al [13] in Korea. The study showed that hospitalization duration of SJS patients had no significant difference from those with TEN. The average hospitalization duration for SJS and TEN patients were 20 (8-60 days) and 21.5 (20-292 days), respectively. Meanwhile, the duration for DRESS patients were shorter than that of SJS and TEN, which was 14 (3-218) days. [13]

The drug class that most often caused DRESS, SJS, and SJS/TEN in this study is antibiotics. Those causing DRESS are cefadroxil, ceftazidim, cefuroxim, cefixime, ceftriaxone, dapsone, cefotaxim, cotrimoxazole, and ciprofloxacin. These results are in accordance with previous studies which showed that, antibiotics caused the highest and most common cases of DRESS. [20-22] The drugs that caused the greatest incidence of SJS and TEN are also antibiotics . This result is consistent with previous research, which stated that the largest drug class causing SJS / TEN was antibiotics (40%), namely penicillin, cotrimoxazole, cephalosporins, quinolones,

carbapenems, clindamycin, tetracyclines, and macrolides. [23] The research conducted in India stated that the largest group of agents causing SJS / TEN were antibiotics (35.55%), followed by anticonvulsants (28.89%), and antipyretics (17.78%). The reported antibiotics were fluoroquinolone (ofloxacin, norfloxacin, and levofloxacin), and sulfonamides (sulfametizol and sulfasalazin). [24] Another previous study stated that sulfadoxine exposure is one of the risk factors of ocular and mucocutaneous sequelae in SJS/TEN survivors. [25]

The management of DRESS, SJS, and TEN patients in acute phase included discontinuation of drugs causing skin reactions, providing support and therapy.[26] In this study, fluids and electrolytes are used by all the patients. The fluid and electrolyte requirements is an essential element of SJS / TEN therapy. Therefore, appropriate fluid replacement therapy is needed in conditions of hyponatremia, hypokalemia, or hypophosphatemia. [26] The previous research at Dr. Soetomo hospital, found that the improvement in the balance of electrolytes and protein in SJS and TEN patients was 100% and 88.8%, respectively. [18]

According to this study, the most widely used therapies for SJS and TEN patients is corticosteroid, both injectable and orally administered. The systemic corticosteroids used at Sardjito general hospital are 5 mg / ml injection of dexamethasone, 125 mg of methyl prednisolone, 16 mg of methyl prednisolone, 8 mg of methyl prednisolone, and 5 mg of prednisone tablets. In the study conducted in india, all patients received systemic corticosteroids, such as dexamethasone (64.44%), prednisolone (31.11%), and dexamethasone and prednisolone pulse therapy (8.88%).[24] The study conducted by Chantaphakul et al (2015) stated that steroid was more used for the patients that survived from SJS and TEN compared to the non-survivors, while the use of corticosteroids prevented eye complications. [27]

The DRESS patients has better quality of life in all domains compared to those with SJS and/or TEN. According to Zavala et al, (2018) study, patients with SJS / TEN were characterized by necrosis and extensive epidermal shedding (epidermolysis). These symptoms made SJS/TEN patients had a higher level of difficulty in carrying out their daily activities. [28] The research conducted by Nishikaku et al, (2016) showed that the survivors of SJS/TEN experienced severe emotional and physical complications, as well as health-related life quality problems that required

long-term medical treatment. [29] Severe physical complications, which are experienced by SJS/TEN survivors may affect patients' health and lives. These complications can be not sufficiently treated by the physician due to the under recognized symptoms. [30] Even though DRESS patients often find multi-organ involvement, such as liver, lung, kidney, and blood disorders, they are still able to carry out their normal activities. However, the mean VAS score and utility of normal population in Indonesia was higher than our findings. The VAS score of normal population was 79,38 (SD: 14,01) and the utility value as 0.91 (SD: 0.11). [16] The SJS/TEN patients who have long-term complications might also experience psychological complications and decreased of quality of life. Thus, the psychological support during and after the hospitalization must be considered to increase their quality of life. [31]

The small sample size and the generic questionnaire re the study limitation for our study. Due to the importance of the finding, it is suggested to do the future studies with the bigger sample size and using the specific questionnaire for skin disease.

Conclusions

The quality of life of DRESS patients is better than the quality of life of SJS and SJS/TEN patients. The differences of quality of life could be influenced by the symptoms of the disease

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Disclosure

The authors have no conflicts of interest in this study.

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Table 1. Clinical and Demographic Characteristics of DRESS, SJS, and SJS/TEN Patients

Characteristic	DRESS (%) N = 21	SJS (%) N = 32	SJS/TEN (%) N = 5
Gender			
Male	8 (38)	17 (53)	2 (40)
Female	13 (62)	21 (65)	3 (60)
Age (Mean±SD)	38,8 ± 10,97	33,3 ±17,20	34 ±13
IQR, *p value*: 0.521	16.00	27.00	28.50
Hospitalization Duration	10,5 ± 6,70	11,6 ± 5,60	12 ± 2,90
IQR, *p value*: 0.749	13.50	12.75	5.50
7			
Causative Agent (ATC Classification)			
Antibiotic (J01CA04)	14 (67)	18 (56)	4 (80)
NSAIDs (M01A)	5 (24)	6 (18)	1 (20)
OAT (J04A)	3 (14)	2 (6)	0 (0)
ARV (J05A)	1 (5)	4 (12.5)	1 (20)
Anti-convulsant (N03AA)	3 (14)	14 (44)	1 (20)
Other	0 (0)	16 (50)	3 (60)

Description: NSAIDs (non-steroidal anti-inflammatory drugs), OAT (anti-tuberculosis drug), ARVs (antivirals), other drugs, such as allopurinol, paracetamol, domperidone, ambroxol, tramadol, diazepam, and bromhexine

322 Table 2. Overview of Inpatient Treatment of DRESS, SJS, and SJS/TEN

Drug Therapy	The number of Patient (%) DRESS (N = 21)	SJS (N = 32)	SJS/TEN (N = 5)
Supportive Therapy (ATC classification)			
Acid-related disorder drugs (A02)		20 (63)	5 (100)
Antihistamines (R06)		22 (69)	4 (80)
Analgesic (N02)		21 (66)	4 (80)
Fluid and electrolyte therapy (B05XA)	21 (100)	32 (100)	5 (100)
Antithrombotic agents (B01)		5 (16)	2 (7)
Antibiotic (J01CA04)		16 (50)	5 (100)
Specific Therapy			
Corticosteroid injection (H02)	19 (90)	31 (96)	5 (100)
Corticosteroid oral (H02))	19 (90)	29 (90)	3 (60)
Cyclosporine + corticosteroid (L40D01+ H02)		1 (3)	0 (0)
Topical Therapy			
Eye Medications (corticosteroids D07)	5 (24)	8 (25)	0 (0)
Eye Medications (Antibiotics D06A)		20 (63)	3 (60)
Eye Medications (Eomlien and protectives D03A)		25 (78)	4 (80)
Skin Medications (corticosteroids D07)		3 (9)	1 (20)
Skin Medications (Antibiotics D06A)		26 (81)	4 (80)
Skin Medications (Emollients D02A)	14 (67)	15 (47)	3 (60)
Skin Medications (Antiseptic /silver sulfadiazine D08AL)		20 (63)	3 (60)
Mouthwash (Antiseptic D08AG)		8 (25)	1 (20)

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Table 3. The mean score of utility and VAS in DRESS, SJS and SJS/TEN patients

Patients	n	Utility mean, IQR	SD	*p value*
DRESS	21	0.61, 0.44	0.23	0.001*
SJS	32	0.08, 0.65	0.42	
SJS/TEN	5	0.03, 1.08	0.01	
		VAS mean, IQR	SD	*p value*
DRESS	21	73.36, 26.25	14.48	0.008*
SJS	32	57.93, 32.50	26.37	
SJS/TEN	5	50.00, 55.00	24.35	

*: significant difference (normally distributed data, One way Anova test

1. Table 4. Health profiles of DRESS, SJS and SJS/TEN patients based on EQ-5D-5L

Dimensions		DRESS (%)	SJS (%)	SJS/TEN (%)
Mobility	No problem	36.4	10.3	20.0
	Slight problem	31.8	34.5	40.0
	Moderate problem	31.8	31.0	0
	Severe problem	0	13.8	20.0
	Unable to do	0	10.3	20.0
Self care	No problem	40.9	3.4	0
	Slight problem	27.3	44.8	0
	Moderate problem	31.8	17.2	20.0
	Severe problem	0	17.2	40.0
	Unable to do	0	17.2	40.0
Usual Activities	No problem	50.0	0	20.0
	Slight problem	31.8	31.0	0
	Moderate problem	18.2	34.5	20.0
	Severe problem	0	20.7	20.0
	Unable to do	0	13.8	40.0
Pain/Discomfort	No problem	9.1	3.4	0
	Slight problem	40.9	13.8	0
	Moderate problem	45.5	24.1	40.0
	Severe problem	4.5	44.8	40.0
	Unable to do	0	13.8	20.0
Anxiety/Depression	No problem	40.9	6.9	40.0
	Slight problem	18.2	10.3	0
	Moderate problem	40.9	31.0	20.0
	Severe problem	0	44.8	40.0
	Unable to do	0	6.9	0

348 Table 5. VAS profile of DRESS, SJS and SJS/TEN patients based on EQ-5D-5L

VAS score	DRESS (%)	SJS (%)	SJS/TEN (%)
The best health	9.1	3.4	0
The worst health	0	10.3	0

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ORIGINAL RESEARCH

Quality of Life of Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) and Stevens-Johnson Syndrome (SJS) and/or Toxic Epidermal Necrolysis (TEN) Patients

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Purpose: Drug Reaction With Eosinophilia and Systemic Symptom (DRESS), Stevens-Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN) are acute hypersensitivity reactions with the potential to reduce the life quality of exposed individuals. This study aims to determine the quality of life of patients suffering from DRESS, SJS, SJS/TEN.

Patients and Methods: A cross-sectional approach was used to get the quality of life data from DRESS, SJS, and/or TEN patients at Dr. Sardjito general hospital, Yogyakarta. The utility index and VAS score differences of EQ-5D-5L were analyzed based on the diagnosis.

Results: We recruited 58 patients. Most of the patients were female (63%). The mean value of utility index was 0.61, 0.08 and 0.03 for DRESS, SJS and SJS/TEN patients, respectively (p value <0.01). Furthermore, the mean of VAS score was 73.36, 57.93 and 50.00 for DRESS, SJS and SJS/TEN patients, respectively (p *value* <0.01).

Conclusion: In general, the quality of life of DRESS patients is better than the quality of life of SJS and/or TEN patients.

Keywords: DRESS, QoL, SJS, TEN, skin diseases

Introduction

Pharmaceutical services are essential health practices that aim to increase rational drug use, the safety, cost efficiency, and the life quality of patients.[1] According to previous research, problems related to drug quality and therapy failure cause greater costs for patients.[2] Advances in health science, especially pharmacy, have a great impact on drug use, which directly causes some side effects (adverse drug reaction). The drug side effects that occur on the skin are called adverse cutaneous drug reaction (ACDR),[3] while at an intense level, they are called severe cutaneous adverse reaction (SCAR).[4]

The SCAR incidence, such as drug reaction with eosinophilia and systemic symptom (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) rarely occurred, however, they have the potential to cause disabilities or death with 10% mortality rate.[5,6] The DRESS is a collection of symptoms and idiosyncratic allergic reactions caused by drug administration in therapeutic doses.[7] At the advanced stages of DRESS, several organ dysfunctions arise in the liver, kidneys, lungs, and heart.[3,8] The most common complications in DRESS patients are found in the liver (50–87%) and kidneys (10–53%).[9]

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The SJS and TEN are severe and life-threatening diseases involving the skin and mucous membranes, characterized by the release of epidermis, water-filled lesions, and peeling of the mucosa. They also occur due to reactions from drugs, although the occurrence is rare.[10] The difference between SJS and TEN is the percentage of affected body surface, SJS affects 10%, while TEN attacks 30%, and the occurrence of both SJS-TEN cause skin lesions of 10%–30%. The incidences of SJS and TEN are 1–6 cases and 0.4–1.2 cases/million/year, respectively.[11]

DRESS, SJS and TEN are not only health problems, they also cause psychological stress and fear following the life-threatening reactions. Most DRESS, SJS, and TEN patients are found to receive outpatient care after being hospitalized by primary doctors, such as internal medicine specialists, skin and genital specialists. The research conducted in Korea stated that SJS and TEN treatment costs are comparable to treating the five most expensive diseases nationally.[12,13] Meanwhile, in the DRESS case, some patients experienced relapse a few months after the first hospitalization, this caused additional costs.[14]

The research conducted by Nogueira (2003) stated that the assessment of SJS/TEN patients' quality of life using the Short Formulary-36 (SF-36) questionnaire shows some problems, such as psychological, social, and economic disorders for approximately 30 years. All these occur at productive age, causing high anxiety and depression.[15] In this study, the Euro Quality of Life-5 Dimensions (EQ-5D) questionnaire was used due to its easy and understandable features. The high mortality rate of these illnesses, the cost impact, and the patients' quality of life are important information for pharmacists, doctors, and policy makers during treatment periods. Therefore, this research was carried out based these attributes at Dr. Sardjito general hospital, Yogyakarta from 2014 to 2018. The purpose of this study was to determine the quality of life of DRESS, SJS, and TEN patients.

Patients and Methods

This study was an observational, with cross-sectional approach, which is conducted prospectively. A total of 21 DRESS, 32 SJS, 5 SJS/TEN hospitalized patients were included in this study, with the code ICD-10 DRESS (L.27.0), SJS (L51.1), and TEN (L51.2). The ICD-10 code has been implemented since 2006. The diagnosis of DRESS, SJS/TEN and causality analysis was defined by the physician. We collected the patients' characteristics and drugs used from the patients' medical record, from January to December 2019 and we did not use the sample size due to the limited number of patients.

Patients' quality of life data was collected using EQ-5D-5L questionnaire. The patients gave their consents prior to the commencement of this study and they filled in the questionnaire during the hospital discharge. The patients we also informed about the purpose of the study. This study was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Gadjah Mada University-Dr. Sardjito Yogyakarta, with ethical approval number KE/FK/1111/EC 19 October 2018 and conducted in accordance with the Declaration of Helsinki.

To calculate the patients' quality of life, the EQ-5D-5L (five level) questionnaire was used. The EQ-5D-5L instrument is a standardized system that collects quality of life information on five dimensions: mobility, self-care, daily activities, pain/discomfort, anxiety/depression. Each domain is scored from 1 to 5, with 1 having no problems, 2 slight problems, 3 moderate, 4 severe, and 5 being unable to undertake the activity described. This questionnaire is already available and validated in Bahasa Indonesia.[16] The five dimensions digit can be combined into a 5-digit number that describes the participant's quality of life. For example, state 11,111 indicates no problems on any of the 5 dimensions, while state 12,345 indicates no problems with mobility, slight problem with self-care, moderate problems with doing daily activities, severe pain or discomfort, and extreme anxiety or depression.[16]

To convert an individual EQ-5D-5L health state to a single EQ-5D-5L index score, standard values (weights) which are attributed to each of the levels in each dimension, were obtained from the Indonesian value set. The index was calculated by deducting from 1 the appropriate weights for the value for full health (i.e.state 12,345). The EQ-5D-5L instrument also describes self-reported overall health status on a visual analogue scale (EQ-VAS), which has a score between 0 ("worst imaginable health status") and 100 ("best imaginable health state"). Both the EQ-5D-5L utility index and VAS score were used as dependent variables in the statistical analysis.[16]

A comparison was made by assessing the utility index and VAS score of DRESS, SJS, and TEN patients using One-Way Anova test.

Results

We recruited 21.32 and 5 patients of DRESS, SJS and SJS/TEN, respectively. The patients demographic data and

AQ6 **Table 1** Clinical and Demographic Characteristics of DRESS, SJS, and SJS/TEN Patients

Characteristics	DRESS (%) N = 21	SJS (%) N = 32	SJS/TEN (%) N = 5
Gender			
Male	8 (38)	17 (53)	2 (40)
Female	13 (62)	21 (65)	3 (60)
Age (Mean±SD)	38,8 ± 10.97	33,3 ±17,20	34 ±13
IQR, *p* value: 0.521	16.00	27.00	28.50
Hospitalization duration	10,5 ± 6.70	11,6 ± 5.60	12 ± 2.90
IQR, *p* value: 0.749	13.50	12.75	5.50
7			
Causative Agent (ATC Classification)			
Antibiotic (J01CA04)	14 (67)	18 (56)	4 (80)
NSAIDs (M01A)	5 (24)	6 (18)	1 (20)
OAT (J04A)	3 (14)	2 (6)	0 (0)
ARV (J05A)	1 (5)	4 (12.5)	1 (20)
Anti-convulsant (N03AA)	3 (14)	14 (44)	1 (20)
Other	0 (0)	16 (50)	3 (60)

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; OAT, anti-tuberculosis drug; ARVs, antivirals; other drugs, such as allopurinol, paracetamol, domperidone, ambroxol, tramadol, diazepam, and bromhexine.

clinical characteristics such as gender, age, duration of hospitalization, causative agent, and therapy during the treatment is shown in Table 1. The frequency of DRESS (62%), SJS (65%), and SJS/TEN (60%) in female are greater compared to male patients, with the highest mean age is 38.8 years old. The mean hospitalization duration for DRESS, SJS and SJS/TEN patients are 10.5, 11.6 and 12 days, respectively.

The main drugs causing DRESS are antibiotics (67%) followed by non-steroidal anti-inflammation drugs (NSAIDs) (24%), oral anti-tuberculosis (14%), and anti-convulsants (14%). Meanwhile, the main cause of SJS is antibiotics (56%), followed by anti-convulsants (44%), and NSAIDs (18%), while TEN was antibiotics (80%), followed by NSAIDs (20%), anti-retrovirals (ARVs) (20%), and anti-convulsants (14%).

An overview of the patient's treatment is shown in Table 2. All the DRESS, SJS, and TEN patients received fluid and electrolyte therapy (100%). The specific therapy given to DRESS patients is corticosteroid injection (90%), while for those with SJS are corticosteroid injection (96%), oral corticosteroids (90%), and cyclosporin-corticosteroid (3%). Lastly, for TEN patient there are corticosteroids injection (100%) and oral corticosteroids (60%).

Table 3 presents the utility and VAS differences between DRESS, SJS and SJS/TEN patients. The utility value of DRESS patients is higher than the utility value of SJS and SJS/TEN patients (0.62 vs 0.08 and 0.03). The VAS score of DRESS patients is also higher than the VAS score of SJS and SJS/TEN patients (73.36 vs 57.93 and 50.00). The differences of utility and VAS score among the groups are significant (p value <0.05). There are significant differences of utility index and VAS scores among the groups. However, there are no significant differences of utility index and VAS scores between SJS and SJS/TEN groups.

Table 4 presents the health profiles of DRESS, SJS and SJS/TEN patients based on EQ-5D-5L. In the mobility, self-care, usual activities and anxiety/depression, the proportion of DRESS patients with "no problem" and "severe problem" is higher than SJS and SJS/TEN patients. However, in the pain/discomfort dimension, patients in all diagnosis, experience more severe problems. In general, The DRESS patients have better health profiles in all dimensions than other diagnosis. This situation is also presented by Table 5, whereas only DRESS and SJS patients state the best health, based on the VAS score. Furthermore, the proportion of patients with the best health is higher in DRESS diagnosis than SJS. Patients with SJS and SJS/TEN have the worst health.

Discussion

Our study shows that in general, DRESS patients had better quality of life than SJS/TEN patients. The female patients have a higher incidence of DRESS, SJS, and SJS/TEN compared to men. This result is in accordance with that of Velasco-Tirado et al (2018), which stated that SJS/

Table 2 Overview of Inpatient Treatment of DRESS, SJS, and SJS/TEN

Drug Therapy	The Number of Patient (%)		
	DRESS (N = 21)	SJS (N = 32)	SJS/TEN (N = 5)
Supportive Therapy (ATC Classification)			
Acid-related disorder drugs (A02)		20 (63)	5 (100)
Antihistamines (R06)		22 (69)	4 (80)
Analgesic (N02)		21 (66)	4 (80)
Fluid and electrolyte therapy (B05XA)		32 (100)	5 (100)
Antithrombotic agents (B01)	21 (100)	5 (16)	2 (7)
Antibiotic (J01CA04)		16 (50)	5 (100)
Specific Therapy			
Corticosteroid injection (H02)	19 (90)	31 (96)	5 (100)
Corticosteroid oral (H02))	19 (90)	29 (90)	3 (60)
Cyclosporine + corticosteroid (L40D01+ H02)		1 (3)	0 (0)
Topical Therapy			
Eye medications (corticosteroids D07)	5 (24)	8 (25)	0 (0)
Eye medications (Antibiotics D06A)		20 (63)	3 (60)
Eye medications (Eomlien and protectives D03A)	14 (67)	25 (78)	4 (80)
Skin medications (corticosteroids D07)		3 (9)	1 (20)
Skin medications (antibiotics D06A)		26 (81)	4 (80)
Skin medications (emollients D02A)		15 (47)	3 (60)
Skin medications (antiseptic/silver sulfadiazine D08AL)		20 (63)	3 (60)
Mouthwash (antiseptic D08AG)		8 (25)	1 (20)

TEN were more common in women than men, with a male to female ratio of 0.6.[17] The mean age of DRESS, SJS, and TEN patients in this study is not significantly different. Meanwhile, other studies had reported that the incidence rate and age increase were equal. Therefore, the higher the age, the greater the risk of experiencing skin disorders, such as SJS and TEN, due to high rate of drug consumption at older age and their interactions.[18,19]

The mean of hospitalization duration for DRESS, SJS, and TEN patients were less than the mean of hospitalization of study conducted by Yang et al,[13] in Korea. The study showed that hospitalization duration of SJS patients had no significant difference from those with TEN. The average hospitalization duration for SJS and TEN patients were 20 (8–60 days) and 21.5 (20–292 days), respectively. Meanwhile, the duration for DRESS patients were shorter than that of SJS and TEN, which was 14 (3–218) days.[13]

The drug class that most often caused DRESS, SJS, and SJS/TEN in this study is antibiotics. Those causing DRESS are cefadroxil, ceftazidime, cefuroxime, cefixime, ceftriaxone, dapsone, cefotaxime, cotrimoxazole, and ciprofloxacin. These results are in accordance with previous studies which showed that, antibiotics caused the highest and most common cases of DRESS.[20–22] The drugs that caused the greatest incidence of SJS and TEN are also antibiotics. This result is consistent with previous research, which stated that the largest drug class causing SJS/TEN was antibiotics (40%), namely penicillin, cotrimoxazole, cephalosporins, quinolones, carbapenems, clindamycin, tetracyclines, and macrolides.[23] The research conducted in India stated that the largest group of agents causing SJS/TEN were antibiotics (35.55%), followed by anticonvulsants (28.89%), and antipyretics (17.78%). The reported antibiotics were fluoroquinolone (ofloxacin, norfloxacin, and levofloxacin), and sulfonamides (sulfametizol and sulfasalazine).[24] Another

Table 3 The Mean Score of Utility and VAS in DRESS, SJS and SJS/TEN Patients

Patients	n	Utility Mean, IQR	SD	p value
DRESS	21	0.61, 0.44	0.23	0.001*
SJS	32	0.08, 0.65	0.42	
SJS/TEN	5	0.03, 1.08	0.01	
		VAS Mean, IQR	**SD**	***p* value**
DRESS	21	73.36, 26.25	14.48	0.008*
SJS	32	57.93, 32.50	26.37	
SJS/TEN	5	50.00, 55.00	24.35	

Note: *Significant difference (normally distributed data), One way Anova test.

Table 4 Health Profiles of DRESS, SJS and SJS/TEN Patients Based on EQ-5D-5L

Dimensions		DRESS (%)	SJS (%)	SJS/TEN (%)
Mobility	No problem	36.4	10.3	20.0
	Slight problem	31.8	34.5	40.0
	Moderate problem	31.8	31.0	0
	Severe problem	0	13.8	20.0
	Unable to do	0	10.3	20.0
Self care	No problem	40.9	3.4	0
	Slight problem	27.3	44.8	0
	Moderate problem	31.8	17.2	20.0
	Severe problem	0	17.2	40.0
	Unable to do	0	17.2	40.0
Usual activities	No problem	50.0	0	20.0
	Slight problem	31.8	31.0	0
	Moderate problem	18.2	34.5	20.0
	Severe problem	0	20.7	20.0
	Unable to do	0	13.8	40.0
Pain/ Discomfort	No problem	9.1	3.4	0
	Slight problem	40.9	13.8	0
	Moderate problem	45.5	24.1	40.0
	Severe problem	4.5	44.8	40.0
	Unable to do	0	13.8	20.0
Anxiety/ Depression	No problem	40.9	6.9	40.0
	Slight problem	18.2	10.3	0
	Moderate problem	40.9	31.0	20.0
	Severe problem	0	44.8	40.0
	Unable to do	0	6.9	0

Table 5 VAS Profile of DRESS, SJS and SJS/TEN Patients Based on EQ-5D-5L

VAS Score	DRESS (%)	SJS (%)	SJS/TEN (%)
The best health	9.1	3.4	0
The worst health	0	10.3	0

previous study stated that sulfadoxine exposure is one of the risk factors of ocular and mucocutaneous sequelae in SJS/TEN survivors.[25]

The management of DRESS, SJS, and TEN patients in acute phase included discontinuation of drugs causing skin reactions, providing support and therapy.[26] In this study, fluids and electrolytes are used by all the patients. The fluid and electrolyte requirements is an essential element of SJS/TEN therapy. Therefore, appropriate fluid replacement therapy is needed in conditions of hyponatremia, hypokalemia, or hypophosphatemia.[26] The previous research at Dr. Soetomo hospital, found that the improvement in the balance of electrolytes and protein in SJS and TEN patients was 100% and 88.8%, respectively.[18]

According to this study, the most widely used therapies for SJS and TEN patients is corticosteroid, both injectable and orally administered. The systemic corticosteroids used at Sardjito general hospital are 5 mg/mL injection of dexamethasone, 125 mg of methyl prednisolone, 16 mg of methyl prednisolone, 8 mg of methyl prednisolone, and 5 mg of prednisone tablets. In the study conducted in india, all patients received systemic corticosteroids, such as dexamethasone (64.44%), prednisolone (31.11%), and dexamethasone and prednisolone pulse therapy (8.88%).[24] The study conducted by Chantaphakul et al (2015) stated that steroid was more used for the patients that survived from SJS and TEN compared to the non-survivors, while the use of corticosteroids prevented eye complications.[27]

The DRESS patients have better quality of life in all domains compared to those with SJS and/or TEN. According to Zavala et al, (2018) study, patients with SJS/TEN were characterized by necrosis and extensive epidermal shedding (epidermolysis). These symptoms made SJS/TEN patients had a higher level of difficulty in carrying out their daily activities.[28] The research conducted by Nishikaku et al, (2016) showed that the survivors of SJS/TEN experienced severe emotional and physical complications, as well as health-related life quality problems that required long-term medical treatment.[29] Severe physical complications, which are experienced by SJS/TEN survivors may affect patients' health and lives. These complications can be not sufficiently treated by the physician due to the under recognized symptoms.[30] Even though DRESS patients often find multi-organ involvement, such as liver, lung, kidney, and blood disorders, they are still able to carry out their normal activities. However, the mean VAS score and utility of normal population in Indonesia was higher than our findings. The VAS score of normal population was 79.38 (SD: 14.01) and the utility value as 0.91 (SD: 0.11).[16] The SJS/TEN patients who have long-term complications might also experience psychological complications and decreased of quality of life. Thus, the psychological support during and after the hospitalization must be considered to increase their quality of life.[31]

The small sample size and the generic questionnaire are the study limitation for our study. Due to the importance of the finding, it is suggested to do the future studies with the bigger sample size and using the specific questionnaire for skin disease.

Conclusions

The quality of life of DRESS patients is better than the quality of life of SJS and SJS/TEN patients. The differences of quality of life could be influenced by the symptoms of the disease.

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Disclosure

The authors have no conflicts of interest in this work.

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ORIGINAL RESEARCH

Quality of Life of Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) and Stevens-Johnson Syndrome (SJS) and/or Toxic Epidermal Necrolysis (TEN) Patients

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Purpose: Drug Reaction With Eosinophilia and Systemic Symptom (DRESS), Stevens-Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN) are acute hypersensitivity reactions with the potential to reduce the life quality of exposed individuals. This study aims to determine the quality of life of patients suffering from DRESS, SJS, SJS/TEN.

Patients and Methods: A cross-sectional approach was used to get the quality of life data from DRESS, SJS, and/or TEN patients at Dr. Sardjito general hospital, Yogyakarta. The utility index and VAS score differences of EQ-5D-5L were analyzed based on the diagnosis.

Results: We recruited 58 patients. Most of the patients were female (63%). The mean value of utility index was 0.61, 0.08 and 0.03 for DRESS, SJS and SJS/TEN patients, respectively (p value <0.01). Furthermore, the mean of VAS score was 73.36, 57.93 and 50.00 for DRESS, SJS and SJS/TEN patients, respectively (p *value* <0.01).

Conclusion: In general, the quality of life of DRESS patients is better than the quality of life of SJS and/or TEN patients.

Keywords: DRESS, QoL, SJS, TEN, skin diseases

Introduction

Pharmaceutical services are essential health practices that aim to increase rational drug use, the safety, cost efficiency, and the life quality of patients.[1] According to previous research, problems related to drug quality and therapy failure cause greater costs for patients.[2] Advances in health science, especially pharmacy, have a great impact on drug use, which directly causes some side effects (adverse drug reaction). The drug side effects that occur on the skin are called adverse cutaneous drug reaction (ACDR),[3] while at an intense level, they are called severe cutaneous adverse reaction (SCAR).[4]

The SCAR incidence, such as drug reaction with eosinophilia and systemic symptom (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) rarely occurred, however, they have the potential to cause disabilities or death with 10% mortality rate.[5,6] The DRESS is a collection of symptoms and idiosyncratic allergic reactions caused by drug administration in therapeutic doses.[7] At the advanced stages of DRESS, several organ dysfunctions arise in the liver, kidneys, lungs, and heart.[3,8] The most common complications in DRESS patients are found in the liver (50–87%) and kidneys (10–53%).[9]

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The SJS and TEN are severe and life-threatening diseases involving the skin and mucous membranes, characterized by the release of epidermis, water-filled lesions, and peeling of the mucosa. They also occur due to reactions from drugs, although the occurrence is rare.[10] The difference between SJS and TEN is the percentage of affected body surface, SJS affects 10%, while TEN attacks 30%, and the occurrence of both SJS-TEN cause skin lesions of 10%–30%. The incidences of SJS and TEN are 1–6 cases and 0.4–1.2 cases/million/year, respectively.[11]

DRESS, SJS and TEN are not only health problems, they also cause psychological stress and fear following the life-threatening reactions. Most DRESS, SJS, and TEN patients are found to receive outpatient care after being hospitalized by primary doctors, such as internal medicine specialists, skin and genital specialists. The research conducted in Korea stated that SJS and TEN treatment costs are comparable to treating the five most expensive diseases nationally.[12,13] Meanwhile, in the DRESS case, some patients experienced relapse a few months after the first hospitalization, this caused additional costs.[14]

The research conducted by Nogueira (2003) stated that the assessment of SJS/TEN patients' quality of life using the Short Formulary-36 (SF-36) questionnaire shows some problems, such as psychological, social, and economic disorders for approximately 30 years. All these occur at productive age, causing high anxiety and depression.[15] In this study, the Euro Quality of Life-5 Dimensions (EQ-5D) questionnaire was used due to its easy and understandable features. The high mortality rate of these illnesses, the cost impact, and the patients' quality of life are important information for pharmacists, doctors, and policy makers during treatment periods. Therefore, this research was carried out based these attributes at Dr. Sardjito general hospital, Yogyakarta from 2014 to 2018. The purpose of this study was to determine the quality of life of DRESS, SJS, and TEN patients.

Patients and Methods

This study was an observational, with cross-sectional approach, which is conducted prospectively. A total of 21 DRESS, 32 SJS, 5 SJS/TEN hospitalized patients were included in this study, with the code ICD-10 DRESS (L.27.0), SJS (L51.1), and TEN (L51.2). The ICD-10 code has been implemented since 2006. The diagnosis of DRESS, SJS/TEN and causality analysis was defined by the physician. We collected the patients' characteristics and drugs used from the patients' medical record, from January to December 2019 and we did not use the sample size due to the limited number of patients.

Patients' quality of life data was collected using EQ-5D-5L questionnaire. The patients gave their consents prior to the commencement of this study and they filled in the questionnaire during the hospital discharge. The patients also informed about the purpose of the study. This study was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Gadjah Mada University-Dr. Sardjito Yogyakarta, with ethical approval number KE/FK/1111/EC 19 October 2018 and conducted in accordance with the Declaration of Helsinki.

To calculate the patients' quality of life, the EQ-5D-5L (five level) questionnaire was used. The EQ-5D-5L instrument is a standardized system that collects quality of life information on five dimensions: mobility, self-care, daily activities, pain/discomfort, anxiety/depression. Each domain is scored from 1 to 5, with 1 having no problems, 2 slight problems, 3 moderate, 4 severe, and 5 being unable to undertake the activity described. This questionnaire is already available and validated in Bahasa Indonesia.[16] The five dimensions digit can be combined into a 5-digit number that describes the participant's quality of life. For example, state 11,111 indicates no problems on any of the 5 dimensions, while state 12,345 indicates no problems with mobility, slight problem with self-care, moderate problems with doing daily activities, severe pain or discomfort, and extreme anxiety or depression.[16]

To convert an individual EQ-5D-5L health state to a single EQ-5D-5L index score, standard values (weights) which are attributed to each of the levels in each dimension, were obtained from the Indonesian value set. The index was calculated by deducting from 1 the appropriate weights for the value for full health (i.e.state 12,345). The EQ-5D-5L instrument also describes self-reported overall health status on a visual analogue scale (EQ-VAS), which has a score between 0 ("worst imaginable health status") and 100 ("best imaginable health state"). Both the EQ-5D-5L utility index and VAS score were used as dependent variables in the statistical analysis.[16]

A comparison was made by assessing the utility index and VAS score of DRESS, SJS, and TEN patients using One-Way Anova test.

Results

We recruited 21.32 and 5 patients of DRESS, SJS and SJS/TEN, respectively. The patients demographic data and

Table 1 Clinical and Demographic Characteristics of DRESS, SJS, and SJS/TEN Patients

Characteristics	DRESS (%) N = 21	SJS (%) N = 32	SJS/TEN (%) N = 5
Gender			
Male	8 (38)	17 (53)	2 (40)
Female	13 (62)	21 (65)	3 (60)
Age (Mean±SD)	38,8 ± 10.97	33,3 ±17,20	34 ±13
IQR, *p* value: 0.521	16.00	27.00	28.50
Hospitalization duration	10,5 ± 6.70	11,6 ± 5.60	12 ± 2.90
IQR, *p* value: 0.749	13.50	12.75	5.50
7			
Causative Agent (ATC Classification)			
Antibiotic (J01CA04)	14 (67)	18 (56)	4 (80)
NSAIDs (M01A)	5 (24)	6 (18)	1 (20)
OAT (J04A)	3 (14)	2 (6)	0 (0)
ARV (J05A)	1 (5)	4 (12.5)	1 (20)
Anti-convulsant (N03AA)	3 (14)	14 (44)	1 (20)
Other	0 (0)	16 (50)	3 (60)

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; OAT, anti-tuberculosis drug; ARVs, antivirals; other drugs, such as allopurinol, paracetamol, domperidone, ambroxol, tramadol, diazepam, and bromhexine.

clinical characteristics such as gender, age, duration of hospitalization, causative agent, and therapy during the treatment is shown in Table 1. The frequency of DRESS (62%), SJS (65%), and SJS/TEN (60%) in female are greater compared to male patients, with the highest mean age is 38.8 years old. The mean hospitalization duration for DRESS, SJS and SJS/TEN patients are 10.5, 11.6 and 12 days, respectively.

The main drugs causing DRESS are antibiotics (67%) followed by non-steroidal anti-inflammation drugs (NSAIDs) (24%), oral anti-tuberculosis (14%), and anti-convulsants (14%). Meanwhile, the main cause of SJS is antibiotics (56%), followed by anti-convulsants (44%), and NSAIDs (18%), while TEN was antibiotics (80%), followed by NSAIDs (20%), anti-retrovirals (ARVs) (20%), and anti-convulsants (14%).

An overview of the patient's treatment is shown in Table 2. All the DRESS, SJS, and TEN patients received fluid and electrolyte therapy (100%). The specific therapy given to DRESS patients is corticosteroid injection (90%), while for those with SJS are corticosteroid injection (96%), oral corticosteroids (90%), and cyclosporin-corticosteroid (3%). Lastly, for TEN patient there are corticosteroids injection (100%) and oral corticosteroids (60%).

Table 3 presents the utility and VAS differences between DRESS, SJS and SJS/TEN patients. The utility value of DRESS patients is higher than the utility value of SJS and SJS/TEN patients (0.62 vs 0.08 and 0.03). The VAS score of DRESS patients is also higher than the VAS score of SJS and SJS/TEN patients (73.36 vs 57.93 and 50.00). The differences of utility and VAS score among the groups are significant (p value <0.05). There are significant differences of utility index and VAS scores among the groups. However, there are no significant differences of utility index and VAS scores between SJS and SJS/TEN groups.

Table 4 presents the health profiles of DRESS, SJS and SJS/TEN patients based on EQ-5D-5L. In the mobility, self-care, usual activities and anxiety/depression, the proportion of DRESS patients with "no problem" and "severe problem" is higher than SJS and SJS/TEN patients. However, in the pain/discomfort dimension, patients in all diagnosis, experience more severe problems. In general, The DRESS patients have better health profiles in all dimensions than other diagnosis. This situation is also presented by Table 5, whereas only DRESS and SJS patients state the best health, based on the VAS score. Furthermore, the proportion of patients with the best health is higher in DRESS diagnosis than SJS. Patients with SJS and SJS/TEN have the worst health.

Discussion

Our study shows that in general, DRESS patients had better quality of life than SJS/TEN patients. The female patients have a higher incidence of DRESS, SJS, and SJS/TEN compared to men. This result is in accordance with that of Velasco-Tirado et al (2018), which stated that SJS/

Table 2 Overview of Inpatient Treatment of DRESS, SJS, and SJS/TEN

Drug Therapy	The Number of Patient (%)		
	DRESS (N = 21)	SJS (N = 32)	SJS/TEN (N = 5)
Supportive Therapy (ATC Classification)			
Acid-related disorder drugs (A02)		20 (63)	5 (100)
Antihistamines (R06)		22 (69)	4 (80)
Analgesic (N02)		21 (66)	4 (80)
Fluid and electrolyte therapy (B05XA)		32 (100)	5 (100)
Antithrombotic agents (B01)	21 (100)	5 (16)	2 (7)
Antibiotic (J01CA04)		16 (50)	5 (100)
Specific Therapy			
Corticosteroid injection (H02)	19 (90)	31 (96)	5 (100)
Corticosteroid oral (H02))	19 (90)	29 (90)	3 (60)
Cyclosporine + corticosteroid (L40D01+ H02)		1 (3)	0 (0)
Topical Therapy			
Eye medications (corticosteroids D07)	5 (24)	8 (25)	0 (0)
Eye medications (Antibiotics D06A)		20 (63)	3 (60)
Eye medications (Eomlien and protectives D03A)	14 (67)	25 (78)	4 (80)
Skin medications (corticosteroids D07)		3 (9)	1 (20)
Skin medications (antibiotics D06A)		26 (81)	4 (80)
Skin medications (emollients D02A)		15 (47)	3 (60)
Skin medications (antiseptic/silver sulfadiazine D08AL)		20 (63)	3 (60)
Mouthwash (antiseptic D08AG)		8 (25)	1 (20)

TEN were more common in women than men, with a male to female ratio of 0.6.[17] The mean age of DRESS, SJS, and TEN patients in this study is not significantly different. Meanwhile, other studies had reported that the incidence rate and age increase were equal. Therefore, the higher the age, the greater the risk of experiencing skin disorders, such as SJS and TEN, due to high rate of drug consumption at older age and their interactions.[18,19]

The mean of hospitalization duration for DRESS, SJS, and TEN patients were less than the mean of hospitalization of study conducted by Yang et al,[13] in Korea. The study showed that hospitalization duration of SJS patients had no significant difference from those with TEN. The average hospitalization duration for SJS and TEN patients were 20 (8–60 days) and 21.5 (20–292 days), respectively. Meanwhile, the duration for DRESS patients were shorter than that of SJS and TEN, which was 14 (3–218) days.[13]

The drug class that most often caused DRESS, SJS, and SJS/TEN in this study is antibiotics. Those causing DRESS are cefadroxil, ceftazidime, cefuroxime, cefixime, ceftriaxone, dapsone, cefotaxime, cotrimoxazole, and ciprofloxacin. These results are in accordance with previous studies which showed that, antibiotics caused the highest and most common cases of DRESS.[20–22] The drugs that caused the greatest incidence of SJS and TEN are also antibiotics. This result is consistent with previous research, which stated that the largest drug class causing SJS/TEN was antibiotics (40%), namely penicillin, cotrimoxazole, cephalosporins, quinolones, carbapenems, clindamycin, tetracyclines, and macrolides.[23] The research conducted in India stated that the largest group of agents causing SJS/TEN were antibiotics (35.55%), followed by anticonvulsants (28.89%), and antipyretics (17.78%). The reported antibiotics were fluoroquinolone (ofloxacin, norfloxacin, and levofloxacin), and sulfonamides (sulfametizol and sulfasalazine).[24] Another

Table 3 The Mean Score of Utility and VAS in DRESS, SJS and SJS/TEN Patients

Patients	n	Utility Mean, IQR	SD	p value
DRESS	21	0.61, 0.44	0.23	0.001*
SJS	32	0.08, 0.65	0.42	
SJS/TEN	5	0.03, 1.08	0.01	
		VAS Mean, IQR	**SD**	***p* value**
DRESS	21	73.36, 26.25	14.48	0.008*
SJS	32	57.93, 32.50	26.37	
SJS/TEN	5	50.00, 55.00	24.35	

Note: *Significant difference (normally distributed data), One way Anova test.

Table 4 Health Profiles of DRESS, SJS and SJS/TEN Patients Based on EQ-5D-5L

Dimensions		DRESS (%)	SJS (%)	SJS/TEN (%)
Mobility	No problem	36.4	10.3	20.0
	Slight problem	31.8	34.5	40.0
	Moderate problem	31.8	31.0	0
	Severe problem	0	13.8	20.0
	Unable to do	0	10.3	20.0
Self care	No problem	40.9	3.4	0
	Slight problem	27.3	44.8	0
	Moderate problem	31.8	17.2	20.0
	Severe problem	0	17.2	40.0
	Unable to do	0	17.2	40.0
Usual activities	No problem	50.0	0	20.0
	Slight problem	31.8	31.0	0
	Moderate problem	18.2	34.5	20.0
	Severe problem	0	20.7	20.0
	Unable to do	0	13.8	40.0
Pain/ Discomfort	No problem	9.1	3.4	0
	Slight problem	40.9	13.8	0
	Moderate problem	45.5	24.1	40.0
	Severe problem	4.5	44.8	40.0
	Unable to do	0	13.8	20.0
Anxiety/ Depression	No problem	40.9	6.9	40.0
	Slight problem	18.2	10.3	0
	Moderate problem	40.9	31.0	20.0
	Severe problem	0	44.8	40.0
	Unable to do	0	6.9	0

Table 5 VAS Profile of DRESS, SJS and SJS/TEN Patients Based on EQ-5D-5L

VAS Score	DRESS (%)	SJS (%)	SJS/TEN (%)
The best health	9.1	3.4	0
The worst health	0	10.3	0

previous study stated that sulfadoxine exposure is one of the risk factors of ocular and mucocutaneous sequelae in SJS/TEN survivors.[25]

The management of DRESS, SJS, and TEN patients in acute phase included discontinuation of drugs causing skin reactions, providing support and therapy.[26] In this study, fluids and electrolytes are used by all the patients. The fluid and electrolyte requirements is an essential element of SJS/TEN therapy. Therefore, appropriate fluid replacement therapy is needed in conditions of hyponatremia, hypokalemia, or hypophosphatemia.[26] The previous research at Dr. Soetomo hospital, found that the improvement in the balance of electrolytes and protein in SJS and TEN patients was 100% and 88.8%, respectively.[18]

According to this study, the most widely used therapies for SJS and TEN patients is corticosteroid, both injectable and orally administered. The systemic corticosteroids used at Sardjito general hospital are 5 mg/mL injection of dexamethasone, 125 mg of methyl prednisolone, 16 mg of methyl prednisolone, 8 mg of methyl prednisolone, and [illegible] of prednisone tablets. In the study conducted in India, all patients received systemic corticosteroids, such as dexamethasone (64.44%), prednisolone (31.11%), and dexamethasone and prednisolone pulse therapy (8.88%).[24] The study conducted by Chantaphakul et al (2015) stated that steroid was more used for the patients that survived from SJS and TEN compared to the non-survivors, while the use of corticosteroids prevented eye complications.[27]

The DRESS patients have better quality of life in all domains compared to those with SJS and/or TEN. According to Zavala et al, (2018) study, patients with SJS/TEN were characterized by necrosis and extensive epidermal shedding (epidermolysis). These symptoms made SJS/TEN patients had a higher level of difficulty in carrying out their daily activities.[28] The research conducted by Nishikaku et al, (2016) showed that the survivors of SJS/TEN experienced severe emotional and physical complications, as well as health-related life quality problems that required long-term medical treatment.[29] Severe physical complications, which are experienced by SJS/TEN survivors may affect patients' health and lives. These complications can be not sufficiently treated by the physician due to the under recognized symptoms.[30] Even though DRESS patients often find multi-organ involvement, such as liver, lung, kidney, and blood disorders, they are still able to carry out their normal activities. However, the mean VAS score and utility of normal population in Indonesia was higher than our findings. The VAS score of normal population was 79.38 (SD: 14.01) and the utility value as 0.91 (SD: 0.11).[16] The SJS/TEN patients who have long-term complications might also experience psychological complications and decreased of quality of life. Thus, the psychological support during and after the hospitalization must be considered to increase their quality of life.[31]

The small sample size and the generic questionnaire are the study limitation for our study. Due to the importance of the finding, it is suggested to do the future studies with the bigger sample size and using the specific questionnaire for skin disease.

Conclusions

The quality of life of DRESS patients is better than the quality of life of SJS and SJS/TEN patients. The differences of quality of life could be influenced by the symptoms of the disease.

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Disclosure

The authors have no conflicts of interest in this work.

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