PROFILE AND CLINICAL OUTCOMES OF DRUG THERAPY FOR SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS IN YOGYAKARTA HEALTH SERVICES

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ABSTRACT

Systemic Lupus Erythematosus (SLE) is an autoimmune disorder that causes chronic inflammation. The cause of SLE is healthy tissue being attacked by the body's immune system. Symptoms in SLE are diverse because they are based on the organs attacked by the body's autoantibodies. This study aims to determine the treatment profile and clinical outcomes in SLE patients. The type of research was descriptive observational, using retrospective data from medical records of outpatient and inpatient SLE patients at Panti Rapih Hospital Yogyakarta. Treatment profile data and clinical outcomes were analyzed descriptively using Statistical Package for Social Sciences (SPSS). There were 20 SLE patients, 18 female (90%) and two male (10%). Age 20-59 years 19 patients (95%), ≥ 60 years one patient (5%). Comorbidities were renal disorders in 10 patients (50%) and respiratory disorders in 8 (40%). SLE drug therapy received was corticosteroids for as many as 15 people (75%), immunosuppressants for 12 people (60%), NSAIDs for 10 people (50%), and antimalarials for five people (25%). Patients experienced a decrease in pain scale of seven people (35%), remission of symptoms and complaints 5 (25%), decreased pain and remission 4 (20%), and no clinical outcomes 4 (20%)

Keywords: SLE, treatment profile, clinical outcomes, corticosteroids, antimalarials

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INTRODUCING

Systemic Lupus Erythematosus (SLE) is a chronic multisystem autoimmune rheumatic disease affecting many organ systems (Shaikh, Maliha F et al.2017). SLE can trigger inflammation, affecting many body parts, including the skin, joints, blood cells, lungs, heart, and other organs. However, the etiology and pathogenesis of this autoimmune disease remain unknown (Vojdani, 2014).

Based on WHO records, the number of lupus diseases in the world is recorded at 5 million people, with 16,000 new cases each year. The incidence and prevalence of SLE in Asia-Pacific countries range from 0.9 to 3.1 and 4.3 to 45.3 per 100,000, respectively. In addition, the incidence of SLE in North America and Europe ranges from 3.7 to 49 and 1.5 and 7.4 per 100,000 person-years, respectively. (Fatoye, Francis et al. 2022). Prevalence data in Indonesia is unknown; based on a survey conducted in

Malang, it was reported that the incidence rate was 0.5% of the total population (Pusdatin, 2017). Based on data from the Indonesian Lupus Foundation (Yayasan Lupus Indonesia), in 2007, the prevalence of SLE was 4 cases per 100,000 population. Based on hospital reports in 2014, 1,169 cases of inpatients had lupus. In 2016, hospitalized patients with lupus almost doubled from 2014, namely 2,166. Lupus patients who died in 2015 were 110 patients. However, deaths increased in 2016 to 550. About 25% of hospitalized patients die, so special attention is needed (Perhimpunan rheumatologi Indonesia 2019).

Treatment of SLE patients aims to manage symptoms, induce remission, and maintain remission as long as possible while the disease progresses. The medicamentous treatment of SLE includes NSAIDs, antimalarials, corticosteroids, and immunosuppressants (Perhimpunan rheumatologi Indonesia, 2011). Clinical outcomes can be the result of treatment for each drug. In SLE, clinical outcomes can be seen through the patient's medical record every time a routine examination is done at the hospital, on complaints in medical records such as reduced pain, reduced skin rashes, complaints of weakness, and fatigue to improve pain scale data. Specific goals or therapeutic outcomes of SLE management include reducing disease activity, achieving long remission, reduced pain and organ function to achieve optimal quality of life (perhimpunan rheumatologi Indonesia, 2011). Seeing the difficulty of determining treatment for SLE disease and treatment outcomes, this research needs to be done to find related treatment profiles and clinical outcomes at Panti Rapih Yogyakarta Hospital in 2017-2022.

METHODS

The type of research in this study is observational descriptive. The data used was retrospectively from the medical records of SLE patients who underwent outpatient and inpatient care at Panti Rapih Hospital Yogyakarta in 2017-2022. Data on drug use and clinical outcomes (pain scores and patient complaints) were taken from the medical records of SLE patients. The data obtained was analyzed using descriptive or univariate statistical analysis using the Statistical Package for Social Sciences (SPSS) application.

Tools and Materials

The tools used in this study are medical record data collection forms at Panti Rapih Yogyakarta Hospital in 2017-2022. The material used in this study is the medical records of patients diagnosed with SLE outpatient and inpatient at Panti Rapih Yogyakarta Hospital for 2017-2022.

Population and Sample

The population in this study were patients diagnosed with SLE at Panti Rapih Yogyakarta Hospital for the period 2017-2022. The sample in this study is part of the population that fits the specified criteria.

The inclusion criteria were patients with a diagnosis of SLE with ICD M32.9, inpatients and outpatients receiving SLE drug therapy, and all ages, and the exclusion criteria were patients suffering from Steven Johnson Syndrome disease.

Research Stages

The study was conducted after obtaining ethical approval. The research data was collected in the medical records section by selecting patient medical records that fit the predetermined inclusion and exclusion criteria. These included patients diagnosed with SLE with ICD M32.9, all ages, outpatients and inpatients, complete medical records, and receiving drug therapy for SLE.

Data Analysis

Data on demographic characteristics, treatment profiles, and clinical outcomes were analyzed descriptively.

RESULTS AND DISCUSSION

This study was conducted after obtaining ethical approval from the Research Ethics Committee of Panti Rapih Yogyakarta Hospital, namely with No. 1/SKEPK-KKE/I/2023.

Patient Demographics and Clinical Characteristics

Demographic Data

Demographic data included age and gender—patient age classification based on WHO guidelines (2013), as listed in Table 1.

Table 1. Demographic data

Subject Characteristics	Total (n=20)	Percentage (%)
Age (years)		
Child (0-9)	0	0
Teenagers (10-19)	0	0
Adults (20-59)	19	95
Elderly (≥ 60)	1	5
Gender		
Men	2	10
Female	18	90

The results showed that the highest age in consecutive SLE patients was the adult age group (20-59 years), with as many as 19 (95%). This is to the statement of the Indonesian Rheumatology Association (2019), namely, the highest age range of SLE patients is productive age (21-30 years), and other studies report that 24 of 56 patients (42.85%) are aged 20-29 years (Nyoman et al. *et al.,* 2020). Telomere shortening is one of the causes of many SLE detections in the adult age range. Telomeres are DNA-protein complexes covering the ends of chromosomes that function as DNA protectors against damage and serve as a defense for chromosome stability at cell division. At this age, telomere shortening occurs significantly, reducing one or more nucleotides of lymphocyte DNA, causing lymphocytes to fail to recognize the body's own antigens. This will increase the risk of autoimmune diseases (Brinks *et al.,* 2016 Perhimpunan Reumatologi Indonesia, 2019).

In this study, women suffered more from SLE, namely 18 (90%). This is in line with other studies that reported that SLE patients were mostly suffered by women, namely 87% (Astini, S. P et al., 2021). A hypothesis states that the risk of SLE in women is higher than in men due to genetic factors. In women, gene expression through DNA methylation has a greater chance of failing in its termination. The X chromosome with inactive genes is demethylated, causing reactivation of methylation-sensitive genes and cell autoreactivity of lupus T cells, making women more likely to develop SLE than men. The hormone factor in SLE is more influential in the severity of estradiol. There is an increase in the amount of estrogen hormone production in women. In SLE, estrogen induces T lymphocyte activation through ER-α and ER-β and increases the expression of T cell activation markers such as CD154 and calcineurin (Lin et al., 2011; Rider et al., 2006). Estrogen has also been

shown to exacerbate lupus disease severity through ERα-independent mechanisms along with other immune effects that contribute to lupus pathogenesis, including modulation of the Toll-like receptor (TLR) pathway, dendritic cell development, or E2-TWEAK signaling (Scott et al., 2018).

COMORBIDITIES

SLE patients also experience comorbidities that are most likely a result of the SLE disease itself, as shown in Table 2.

Table 2. List of comorbidities

Comorbidities	Total	Percentage (%)
Kidney disorders	10	16,13
Respiratory distress	8	12,90
Anemia	7	11,29
Hypertension	5	8,07
Skin disease	5	8,07
Arthritis	4	6,45
Urinary tract disorders	4	6,45
Hyperthyroid	1	1,61
Diabetes	1	1,61
Dyspepsia	1	1,61
Miscellaneous	14	22,58
Without comorbidities	2	3,23

SLE can cause multiple organ and tissue damage. A large case-control study from the UK Clinical Practice Research Datalink reported that SLE patients had significantly increased incidence of comorbidities with adjusted relative rates (Rees, F. et al., 2016). In this study, renal impairment was most prevalent in SLE patients, as many as ten patients (10.16%), which is in line with other studies that report the manifestation of renal impairment in SLE patients is around 30-50%. Glomerular disorders are generally detected in the first year of diagnosis but are generally asymptomatic (Bertsias G. et al., 2012). Excess autoimmune activity in the kidney occurs when autoantibodies target intrinsic antigens in the glomerulus, such as annexin two and chromatin. These intraglomerular immune complexes activate complement factors and other alternative pro-inflammatory pathways in the intrarenal. Subsequently, interstitial plasma cells (B cells and T cells), recruited by pro-inflammatory cytokines (IFN-α and Toll-like receptors (TLRs)), support the formation of advanced immune complex deposits in the renal tubulointerstitial bed. (Giani & Septian, 2022).

Treatment Profile

SLE Medication

Table 3. SLE drug list

SLE Medication	Number (people)	Percentage (%)
Corticosteroids	15	75
Immunosuppressants	12	60
NSAIDS	10	50
Antimalarials	5	25

These results are in line with other studies that show that corticosteroids are most commonly used for (88.9%) immunosuppressants (71.1%) (Furaida et al., 2020). In general, treatment options are based on the extent and severity of the disease; the drugs given are NSAIDs, antimalarials, corticosteroids, and immunosuppressant drugs (Ramadheni, Putri et al., 2015). Corticosteroids reduce the production of cytokines that cause inflammation, thereby reducing tissue damage. In addition, it also reduces the immune system's ability to work by affecting how white blood cells work. In the case of lupus patients, corticosteroid drugs are needed because they have immunosuppression and anti-inflammatory effects that shorten the healing period and reduce mortality (Putri et al.; A. B., 2020). Immunosuppressants are needed in SLE patients because these drugs suppress the

immune system, so attacks on organs can be controlled. NSAIDs are given to treat musculoskeletal symptoms, cirrhosis, and headache. Then, antimalarials relieve symptoms such as joint swelling and skin rashes (Ramadheni, Putri et al., 2016).

The most commonly used corticosteroids were methyl prednisolone, clobetasol, dexamethasone, hydrocortisone, prednisone, dexamethasone, and triamcinolone. Many other studies also reported that methylprednisolone was the most widely used drug (90%) (Ramadheni, Putri, et al., 2015) and 82% (Suwandi et al. el al., 2022). The anti-inflammatory potential of methylprednisolone is greater than prednisone. Glucocorticoids are shorter-acting, such as prednisone and methylprednisolone. This is advantageous over long-acting steroids such as dexamethasone because the GK half-life is shorter, and it is easier to switch to alternate-day therapy (Ramadheni, Putri et al., 2015). According to a case report, there are side effects of long-term systemic corticosteroid use, namely steroid acne in the anterior and posterior thoracic regions and superior extremities dextra and sinistra, Cushing's syndrome (moon face, weight gain, and headache) and leukocytosis, which were subsequently reduced and improved. The decrease in corticosteroid consumption is carried out slowly (Putri et al.; A. B., 2020).

This study's most widely used immunosuppressant was mycophenolate mofetil (MMF), followed by cyclosporine, methotrexate, and azathioprine. Other studies also reported that mycophenolate mofetil was most commonly used (Islami et al., 2022). MMF is associated with fewer side effects, such as severe infections, alopecia, and amenorrhea, and is thus considered better than CYC. In addition, treatment with MMF results in a high complete remission rate, and the drug shows a good safety profile (Furuto, Yoshitaka et al., 2020). Methotrexate (MTX) serves as a steroid replacement therapy in mild to moderate SLE, especially in joint and skin manifestations of SLE (Bertsias, 2017).

Clinical manifestations of SLE patients vary from joint pain or mild skin disorders to severe internal organ disorders that are life-threatening (Aringer M. et al., 2016) by the Indonesian Rheumatology Association (2011) which states that the administration of NSAIDs is required for SLE patients. in this study, it was found that SLE patients received several types of NSAID drugs. Starting from the most used are metampiron, diclofenac potassium, diclofenac sodium, meloxicam and ibuprofen.

SLE patients also receive antimalarial drug therapy, namely chloroquine and hydroxychloroquine. Antimalarial drugs are used in SLE patients with mild to severe manifestations and should be taken regularly. Serum levels of hydroxychloroquine should be monitored to avoid any side effects, especially from chloroquine and hydroxychloroquine (Gatto, 2018). Treatment with chloroquine antimalarials is by the approval of the FDA (Food and Drug Administration) as a therapy for lupus nephritis, which has a mechanism to reduce inflammation (Lee, S.J et al., 2011). Chloroquine administration is also recommended by EULAR/ERA-EDTA in patients with lupus nephritis (Bertsias et al.,

2012). chloroquine and hydroxychloroquine because they can improve survival and remission, reduce disease activity and infection, have a good effect on lipid profiles, and prevent thrombosis and organ failure (Anonymous., 2019).

Clinical Outcomes

Table 4. Clinical outcomes of SLE patients

Clinical Outcomes	Total	Percentage (%)
Decrease in pain scale	7	35
Remission of symptoms or complaints	5	25
Decrease in pain scale and remission of symptoms or complaints	4	20
No clinical outcome or no improvement	4	20
Total	20	100

Outcomes are closely related to the goals of therapy. This is to the Indonesian Rheumatology Association's (2011) statement that the specific objectives of SLE treatment are achieving a long remission time, decreasing disease progression, reducing pain complaints, and maintaining organ function to continue working usually so that activities run well. An optimal quality of life is achieved (Indonesian Rheumatology Association, 2011).

Clinical outcomes in SLE patients in this study were seen from the assessment of disease activity Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) Score System. However, the medical record is written quite commonly in the form of pain scores and written statements that the patient feels the symptoms or complaints experienced are improving. In addition, the patient has laboratory test data that needs to be written or done at least once every three months. So the clinical outcomes in this study were written based on the score points contained in SLEDAI, including pain scales based on arthritis conditions, information such as improving cough and runny nose complaints based on pleurisy symptoms, skin problems in the form of new rashes, appetite based on hematological diagnoses, and dizziness based on lupus headache. (Saleh, A. M. et al., 2014).

Pain Scale

This study's most common clinical outcome was a decrease in pain scale, with as many as seven patients (35%). The pain scale was obtained from the patient's medical record data with the NPRS scale. The data is seen from each patient check-up or control every month, and the score determines whether there is a decrease in pain scale or not. If the examination reads numbers 1-10 and the subsequent examination becomes a pain scale of 0, then the patient has a decrease in pain scale. This study's pain scale clinical outcome statement is an NPRS (Numeric Pain Rating Scale) scale. The NPRS scale is a scale that functions to assess pain. The NPRS scale is easy to understand, simple, and sensitive (dose, gender, and ethnic differences). The NPRS scale is better at assessing acute pain than the Visual Analog Scale (VAS). The NPRS has an 11-point scale with a score of 0-10 (Yudiyanta, 2015).

The administration of NSAIDs addresses the management of these musculoskeletal manifestations, as they can relieve musculoskeletal pain, swelling, and soreness. These drugs have pain relieving, anti-inflammatory, and anticoagulant properties, which are beneficial in treating common lupus-related manifestations (Maidhof, William, et

al., 2012). In addition to NSAIDs, paracetamol was also used in this study in as many as five patients. Paracetamol was used because it is considered to have low gastrointestinal side effects. This drug has a non-selective system of action that restrains cyclooxygenase enzymes (cox-1 and cox-2). Inhibition of cox-2 will result in decreased prostaglandin production. Prostaglandins are mediators of pain, fever, and anti-inflammation. If paracetamol inhibits prostaglandins, the pain will decrease (Astini, S. P et al., 2021).

CONCLUSIONS

Based on the results of the study, it can be concluded that based on age, SLE is mostly suffered in adulthood (20-59 years), women are most at risk of suffering from SLE, the most widely used drugs are corticosteroids, and drug therapy in SLE provides clinical outcomes in the form of decreased pain scale and remission.

REFERENCE

Aringer, M., Dörner, T., Leuchten, N., & Johnson, S. R. (2016). Toward new criteria for systemic lupus erythematosus - A standpoint. *Lupus*, *25*(8), 805–811. https://doi.org/10.1177/0961203316644338

Astini, S. P., Udayani, N. N. W., & Meriyani, H. (2021). Studi Retrospektif Penggunaan Obat dan Potensi Interaksi Obat Pasien Systemic Lupus Erythematosus. *Jurnal Ilmiah Medicamento*, *7*(2), 77–83. https://doi.org/10.36733/medicamento.v7i2.2271

Bertsias, G., Cervera, R., & Boumpas, D. T. (2012). Learning objectives: Use the epidemiology and natural history of. In *EULAR Textbook on Rheumatic Diseases* (pp. 476–505).

Bertsias, G. K., Tektonidou, M., Amoura, Z., Aringer, M., Bajema, I., Berden, J. H. M., Boletis, J., Cervera, R., Dörner, T., Doria, A., Ferrario, F., Floege, J., Houssiau, F. A., Ioannidis, J. P. A., Isenberg, D. A., Kallenberg, C. G. M., Lightstone, L., Marks, S. D., Martini, A., … Boumpas, D. T. (2012). Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Annals of the Rheumatic Diseases*, *71*(11), 1771–1782. https://doi.org/10.1136/annrheumdis-2012-201940

Bertsias, G., & Sgantzos, M. (2017). Flares in systemic lupus erythematosus: diagnosis, risk factors and preventive strategies. *Mediterranean Journal of Rheumatology*, *28*(1), 223–226.

Brinks, R., Hoyer, A., Weber, S., Fischer-Betz, R., Sander, O., Richter, J. G., Chehab, G., & Schneider, M. (2016). Age-specific and sex-specific incidence of systemic lupus erythematosus: An estimate from cross-sectional claims data of 2.3 million people in the German statutory health insurance 2002. *Lupus Science and Medicine*, *3*(1),

10–12. https://doi.org/10.1136/lupus-2016-000181

Furuto, Y., Kawamura, M., Namikawa, A., Takahashi, H., & Shibuya, Y. (2020). Efficacy of High-Dose Mycophenolate Mofetil in Multitarget Therapy for Lupus Nephritis: Two Consecutive Case Reports. *Cureus*, *12*(1), 1–11. https://doi.org/10.7759/cureus.6834

Gatto, M., Zen, M., Iaccarino, L., & Doria, A. (2019). New Therapeutic Strategies in Systemic Lupus Erythematosus Management. *Nature Reviews Rheumatology*, *15*(1), 30–48. https://doi.org/10.1038/s41584-018-0133-2

Giani, M. T., & Septian, M. R., 2022, Diagnosis dan Tata Laksana Nefritis Lupus, Cermin Dunia Kedokteran, 49(2), 671–676

Islami, A. A., Jafar, F. I., & Kuncoro, H. 2021. Evaluasi Ketepatan Penggunaan Obat pada Pasien Lupus Eritematosus Sistemik (LES) di RSUD Kanujoso Djatiwibowo Kota Balikpapan Tahun 2020-2021. Proceeding of Mulawarman Pharmaceuticals Conferences, 15(April 2021), 135–138.

Lee, S. J., Silverman, E., & Bargman, J. M. (2011). The role of antimalarial agents in the treatment of SLE and lupus nephritis. *Nature Reviews Nephrology*, *7*(12), 718–729. https://doi.org/10.1038/nrneph.2011.150

Lin, H. L., Yen, J. H., Chiou, S. S., Tsai, W. C., Ou, T. T., Wu, C. C., & Liu, H. W. (2011). Estradiol upregulates calcineurin expression via overexpression of estrogen receptor alpha gene in systemic lupus erythematosus. *Kaohsiung Journal of Medical Sciences*, *27*(4), 125–131. https://doi.org/10.1016/j.kjms.2010.12.005

Maidhof, W., & Hilas, O. (2012). *Lupus: An Overview of the Disease And* Management *Options* (Vol. 37, Issue 4).

Nyoman Angga P. Darma, Tjokarda Istri Anom Saturti, & Pande Ketut Kurniari. (2020). Karakteristik Manifestasi Klinis Pasien Sistemik Lupus Eritematosus Di Poliklinik Rematologi Rsup Sanglah Periode Juni –September 2018. *Jurnal Medika Udayana*, *9*(5), 1–6. https://ojs.unud.ac.id/index.php/eum

Perhimpunan rheumatologi Indonesia, (2011). *Diagnosis dan Pengelolaan Lupus Eritematosus Sistemik*. Perhimpunan Reumatologi Indonesia.

Perhimpunan rheumatologi Indonesia, (2019). Diagnosis dan Pengelolaan Lupus Eritematosus Sistemik. In *Perhimpunan Rheumatologi Indonesia*. https://doi.org/10.2307/3460461

Pusdatin kemenkes RI. Infodatin "situasi lupus Indonesia." Published online 2017

Putri, J. G., & Wisan, A. B. (2020). Efek Samping Terapi Kortikosteroid Sistemik Jangka Panjang pada Pasien Lupus Erimatosus Sistemik dan Tatalaksana Dermatologi. *Cermin Dunia Kedokteran*, *47*(2), 127–129. http://103.13.36.125/index.php/CDK/article/view/356

Ramadheni, P., Raveinal, & Imamukhlisa, D.

(2016). Pola Penggunaan dan Analisa Drug Related Problem's Obat Kortikosteroid pada Pasien LES di Bangsal Penyakit Dalam RSUP Dr. M. Djamil Padang Tahun 2013. *Scientia : Jurnal Farmasi Dan Kesehatan*, *5*(1), 15. https://doi.org/10.36434/scientia.v5i1.62

Rees, F., Doherty, M., Grainge, M., Lanyon, P., Davenport, G., & Zhang, W. (2016). Burden of Comorbidity in Systemic Lupus Erythematosus in the UK, 1999-2012. *Arthritis Care and Research*, *68*(6), 819–827. https://doi.org/10.1002/acr.22751

Rider, V., Li, X., Peterson, G., Dawson, J., Kimler, B. F., & Abdou, N. I. (2006). Differential expression of estrogen receptors in women with systemic lupus erythematosus. *Journal of Rheumatology*, *33*(6), 1093–1101.

Saleh, A. M, Kurniati N, dan Syarif BH., 2014, Penilaian Aktivitas Penyakit Lupus Eritematosus Sistemik dengan Skor SLEDAI di Departemen Ilmu Kesehatan Anak RSCM. Sari Pediatri, 16(4), 291–297

Scott, J. L., Wirth, J. R., Eudaly, J., Ruiz, P., & Melissa, A. (2018). Complete knockout of estrogen receptor alpha is not directly protective in murine lupus. *Clin Immunol.*, *183*, 132–141. https://doi.org/10.1016/j.clim.2017.08.010.

Shaikh, M. F., Jordan, N., & D'cruz, D. P. (2017). Sytemic Lupus Erythematosus. In *CME RHEUMATOLOGY Clinical Medicine* (Vol. 17, Issue 1). https://doi.org/10.7861/clinmedicine.17-1-78

Suwandi, K. A., Yuliwulandari, R., Hasibuan, F. D., & Arsyad. (2022). Gambaran Efek Samping Penggunaan Kortikosteroid Jangka Panjang Pada Pasien Systemic Lupus Erythematosus (SLE) Di Rumah Sakit Umum Daerah Pasar Rebo Periode Juli 2017 – Juli 2019 Overview Of Long Term Corticosteroid Use Side Effect In Systemic Lupus Eryt. *Junior Medical Journal*, *1*(1), 1–8.

Vojdani, A. (2014). A potential link between environmental triggers and autoimmunity. Autoimmune *Diseases*, *2014*, 1–18. https://doi.org/10.1155/2014/798029

Yudiyanta, Khoirunnisa, N., & Novitasari, R. 2015. Assessment Nyeri. Yogyakarta: Departemen Neurologi, Fakultas Kedokteran Universitas Gadjah Mada.