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**Research Article**

# *ABCB1* rs1045642 Genotypes and Clinical Response in Indonesian Patients with Systemic Lupus Erythematosus

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**Abstract**

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease often managed with immunosuppressants such as methylprednisolone (MP) and azathioprine (AZA), although therapeutic responses vary among individuals. Genetic variation, including polymorphisms in the ATP-Binding Cassette Subfamily B Member 1 (*ABCB1*) gene encoding the P-glycoprotein drug transporter, may influence treatment outcomes. The rs1045642 polymorphism has been linked to variable responses in SLE, but data in Indonesian populations are scarce. This study aimed to describe the distribution of the *ABCB1* rs1045642 polymorphism in SLE patients from Bandung, Indonesia, and to explore its potential association with therapy outcomes using MP and/or AZA. We conducted a cross-sectional study of 84 SLE patients, collecting clinical data from medical records. Treatment outcome was defined as achievement of lupus low disease activity state (LLDAS). Genomic DNA was extracted and sequenced to determine rs1045642 genotypes. A total of 84 SLE patients were included, predominantly aged 26–35 years (34%). Almost half had a disease duration of 6–10 years (49%). The majority achieved LLDAS (69%), and all patients were receiving methylprednisolone, with 78.6% also receiving azathioprine. The genotype distribution of *ABCB1* rs1045642 was AA 10.71%, AG 61.91%, and TT 27.38%, which deviated from Hardy–Weinberg equilibrium ($p < 0.05$). However, genetic variations were observed among patients with SLE. Further studies on other possible polymorphisms related to the outcome of SLE therapy are needed.

**Keywords:** *ABCB1*, rs1045642, single-nucleotide polymorphism, systemic lupus erythematosus

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**Abstrak**

Lupus eritematosus sistemik (LES) merupakan penyakit autoimun kronis yang umumnya ditangani dengan imunosupresan seperti metilprednisolon (MP) dan azatioprin (AZA), meskipun respons terapi bervariasi antar individu. Variasi genetik, termasuk polimorfisme pada gen ATP-Binding Cassette Subfamily B Member 1 (*ABCB1*) yang mengkode protein transpor obat P-glikoprotein, dapat memengaruhi hasil terapi. Polimorfisme rs1045642 pada gen ini telah dikaitkan dengan perbedaan respons pada pasien LES, namun data pada populasi Indonesia masih terbatas. Penelitian ini bertujuan untuk menggambarkan distribusi polimorfisme *ABCB1* rs1045642 pada pasien LES di Bandung serta menilai potensi hubungannya dengan luaran terapi menggunakan MP dan/atau AZA. Penelitian dilakukan dengan desain potong lintang pada 84 pasien LES, dengan data klinis diperoleh dari rekam medis. Luaran terapi ditentukan berdasarkan tercapainya kondisi *lupus low disease activity state* (LLDAS). DNA genom diekstraksi dan dianalisis untuk menentukan genotipe rs1045642. Sebanyak 84 pasien SLE diikutsertakan, dengan kelompok usia terbanyak 26–35 tahun (34%). Hampir setengah pasien memiliki durasi penyakit 6–10 tahun (49%). Sebagian besar mencapai LLDAS (69%), dan seluruh pasien mendapatkan terapi metilprednisolon, dengan 78,6% juga menerima azathioprine. Distribusi genotipe *ABCB1* rs1045642 adalah AA 10,71%, AG 61,91%, dan TT 27,38%, yang menyimpang dari keseimbangan Hardy–Weinberg ($p < 0,05$). Meski demikian, variasi genetik tetap teramati pada pasien SLE. Diperlukan studi lanjutan mengenai kemungkinan polimorfisme lain yang berhubungan dengan hasil terapi SLE.

**Kata kunci:** *ABCB1*, lupus eritematosus sistemik, rs1045642, *single-nucleotide polymorphism*

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## Introduction

Systemic lupus erythematosus (SLE), commonly referred to as lupus, is a chronic autoimmune disease characterized by inflammation and involvement of multiple organ systems.[1–3] Although the precise cause of SLE is not known for certain, autoimmune disease is the best hypothesis. Moreover, the interaction between various genetic and environmental factors may contribute to disease susceptibility.[2,4]

SLE presents many challenges, especially in terms of managing the chronic condition of this disease and its treatment regimen. Interestingly, the majority of patients with SLE have a reasonable quality of life, with the exception of ache, fatigue, and dependence on others.[5] SLE is treated using immunosuppressants such as methylprednisolone (MP) and/or azathioprine (AZA). The pharmacokinetics of immunosuppressants is complex owing to the various drug targets involved and the different signaling pathways and molecules. Variations in the effectiveness of therapy that occur are related to the development and severity of SLE disease and genetics.[6,7]

The present treatments for SLE cannot cure the disease; they mainly suppress disease activity and prevent flare-ups.[8,9] The desired therapeutic target is the condition with a lupus low disease activity state (LLDAS). The LLDAS has been designed to reflect a low SLE disease activity rather than changes in lupus activity and is considered a more clinically relevant outcome in studies of SLE. 10 Before the LLDAS, physicians used the SLE Disease Activity Index (SLEDAI)-2K or Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI. LLDAS can be used as a treatment response measurement that offers healthcare professionals an achievable target for patients with SLE that is significantly correlated with reduced levels of organ damage. Therefore, LLDAS is a good treatment target to reduce the risk of future SLE complications.[11,12]

Pharmacogenomics is an example of precision medicine, which aims to tailor clinical treatment to an individual or a specific group of people. Pharmacogenomic approaches explore how the DNA of patients affects their response to therapy. In some cases, their DNA can determine whether they have an inadequate response to a drug or whether a drug helps them or has no impact. Pharmacogenomics can enhance public health by enabling recognition of whether or not a drug is likely to benefit a patient and be safe for them to take. Knowledge of this information can assist medical doctors in identifying therapies that result in the best treatment.[13]

ATP-Binding Cassette Subfamily B Member 1 (*ABCB1*) or Multidrug Resistance Protein 1 (*MDR1*) is a gene that encodes P-glycoprotein (P-gp), forms a membrane, and functions as a transmembrane efflux pump. P-gp transports several drugs, including immunosuppressants used in the treatment of SLE. Notably, inter-ethnic differences in the distribution of ABCB1 variants are possible, which leads to inter-ethnic differences in P-gp pharmacokinetics.[14–16]

A systematic review article showed that the *ABCB1* gene polymorphism rs1045642 was included in the group of the best predictor genes for determining the effectiveness of SLE therapy with immunosuppressants.[6] The single nucleotide polymorphism (SNP) from C to T can increase sensitivity to AZA and cyclosporine drugs, 6 as well as decrease the clearance of and increase the sensitivity to methotrexate.[17] Other study about *ABCB1* gene polymorphism rs1045642 resulted in the risk of toxicity; These findings indicate that the rs1045642 SNP of *ABCB1* may contribute to the risk of steroid-induced ONFH, suggesting its potential value as

a biomarker for identifying individuals at higher risk prior to steroid therapy.[18] Linear with the study on 2022 that the findings indicate that the G2677T/A polymorphism (G > T/A) of ABCB1 and the TAT/TTT haplotype may exert a protective effect in HIMP treatment of AQP4-IgG+ NMOSD-ON, but not in MS-ON.[19]

Currently, there are no data on the *ABCB1* rs1045642 variation in Indonesia. Therefore, this study aimed to determine the distribution of the *ABCB1* rs1045642 polymorphism in patients with SLE in Bandung City, West Java, Indonesia, and to analyze the association between the rs1045642 polymorphism and the efficacy of SLE therapy using MP and/or AZA.

## Methods

This was an analytic observational cross-sectional study. The subjects included in this study were 84 female patients with SLE in Hasan Sadikin Hospital, Bandung City, Indonesia between 18 and 65 years of age, inclusive, who had taken MP and/or AZA for at least 1 year. Patients for whom treatment data were lacking were excluded. The clinical data of patients were retrieved from their medical records. The duration of SLE disease was designated as the length of time the patient had SLE. The treatment outcome was determined as the achievement of LLDAS.

The definition of LLDAS was fulfilled when all the following criteria were met: SLEDAI-2 K ≤4, SELENA-SLEDAI medical doctor worldwide assessment ≤1 without an interest in primary organ systems, no hemolytic anemia or gastrointestinal activity, no new capabilities of lupus disease activity as compared to the preceding assessment, ongoing prednisolone (or equivalent) dose of ≤7.5 mg daily, and well-tolerated preferred maintenance doses of immunosuppressive drugs and permitted biologic agents, excluding investigational drugs.[20] When the patient met those LLDAS criteria, the patient was considered as "Yes"; if the patient did not meet those criteria, the patient was considered as "No". Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), a validated instrument that measures global disease activity across multiple organ systems. In this scoring system, a score of ≤4 is commonly used to indicate low disease activity. The Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) modification of SLEDAI is a slightly adapted version applied in clinical trials and cohort studies, maintaining consistency with SLEDAI-2K while refining definitions for certain items. In this study, achievement of LLDAS was defined according to the validated criteria, which include a SLEDAI-2K score ≤4 with no major organ activity, no new disease activity, and stable therapy.[21,22]

The patients who agreed to participate in this study signed the informed consent before any study-related activity was conducted. Peripheral blood leukocytes from eligible patients with SLE were collected for DNA isolation. This study protocol was approved by the Health Research Ethics Committee Universitas Padjadjaran (No. 128/UN6.KEP/EC/2020).

### *DNA isolation and single-nucleotide polymorphism analysis*

DNA samples were isolated from EDTA-anticoagulated blood (Geneaid™, New Taipei City, Taiwan) and stored at −20°C until further use. The DNA was then amplified in a total volume of 50 µL of polymerase chain reaction (PCR) reaction mixture, containing 2 µL of DNA template, 1 µL of each primer forward and reverse, 25 µL of PCR Master Mix (Promega GoTaq® Green PCR Master

**Table 1. Characteristic of the *ABCB1* rs1045642 Polymorphism**

| Chromosome Position | Nucleotide Change | Wildtype Allele | Variant Allele | Gene Location |
|---|---|---|---|---|
| GRCh38.p13 Chr7: 87509329 | A > G | A | G | Exon 26 |

Mix, Promega, Fitchburg, Wisconsin), and 21 µL of nuclease-free water.

The following two primer sets were used in this study: forward 5′-AGGGTGTGATTTGGTTGCTA-3′ and reverse 5′-GGAGCCCATCCTGTTTGACT-3′ (Sigma Aldrich, Singapore). The amplification process was performed in a thermal cycler (Bio-Rad T100™, California, USA). The PCR reaction was initiated by denaturation at 95°C for 3 minutes, followed by 35 cycles of denaturation at 95°C for 30 s, annealing at 60°C for 30 s, and extension at 72ºC for 1 minute. The final extension step was performed at 72°C for 5 minutes. The expected amplicon size was 256 bp. Furthermore, the *ABCB1* rs1045642 polymorphism was determined using the Sanger sequencing method.

The results of the DNA sequencing were then aligned with the reference sequence of the *ABCB1* gene originating from Homo sapiens (https://www.ncbi.nlm.nih.gov/snp/rs1045642). The polymorphism in rs1045642 occurs if there is a change from A to G (Table 1). The alignment of the reference sequence and the resulting sequence was performed using the BioEdit 7.2 software.

### *Statistical analysis*

Using Lemeshow's formula for proportion with finite population correction, the required sample was 75 (95% confidence, 9% margin of error, p = 0.398 based on East

**Table 2. The Characteristics of Systemic Lupus Erythematosus Patients**

| Variable | n | % |
|---|---|---|
| **Age** | | |
| 17–25 years old | 19 | 22 |
| 26–35 years old | 29 | 34 |
| 36–45 years old | 22 | 27 |
| 46–55 years old | 11 | 13 |
| 56–65 years old | 3 | 4 |
| **Diagnosed disease duration** | | |
| 6–10 years | 41 | 49 |
| 11–15 years | 15 | 18 |
| 16–20 years | 6 | 7 |
| 21–25 years | 3 | 4 |
| **LLDAS** | | |
| Yes | 56 | 69 |
| No | 28 | 31 |
| **Medication** | | |
| Methylprednisolone (any use) | 84 | 100 |
| Azathioprine (any use) | 66 | 78.6 |
| Methylprednisolone only | 18 | 21.4 |
| Methylprednisolone + azathioprine | 66 | 78.6 |

**Table 3. Distribution of Polymorphism of *ABCB1* rs1045642 in Systemic Lupus Erythematosus Patients**

| Allele or Genotype | n | % |
|---|---|---|
| **Allele** | | |
| A | 122 | 48.85 |
| G | 150 | 51.15 |
| **Genotype** | | |
| AA | 9 | 10.71 |
| AG | 52 | 61.91 |
| GG | 23 | 27.38 |

Asian allele frequency from Ensembl23 , population size = 213 24). Allowing 10% for missing data, the final sample size was 83. The genotypic distribution data were then analyzed using the Hardy–Weinberg equilibrium (HWE) equation (HWE, df = 1). The association between the *ABCB1* rs1045642 polymorphism and lupus therapy outcome was planned to be analyzed using logistic regression to estimate odds ratios (OR) with 95% confidence intervals was analyzed using SPSS software.

## Results

In total, 84 female patients were examined for the *ABCB1* rs1045642 polymorphism. In this study, 22% were between 17–25 years of age and 34% were between 25–36 years of age (Table 2). The frequency of the AA, AG, and GG genotypes was 10.71%, 61.91%, and 27.38%, respectively (Table 3). The genotype distribution of *ABCB1* rs1045642 was AA 10.71%, AG 61.91%, and TT 27.38%, which deviated significantly from Hardy–Weinberg equilibrium (p = 0.012) (table 4). As a result, association analysis with therapeutic outcome (LLDAS) was not performed. Instead, we focused on describing the genotype profile and discussing, based on literature, the potential role of *ABCB1* in SLE pathogenesis and treatment response, as well as clinical characteristics influencing outcomes in this study.

**Table 4. Hardy-Weinberg equilibrium of *ABCB1* rs1045642**

| ABCB1 rs1045642 Genotype | Observation (O) | Expectation (E) | Proportion | Allele Frequency | Hardy-Weinberg Equilibrium | |
|---|---|---|---|---|---|---|
| Wild Type (AA) | 9 | 14,583 | 0,107 | 0,417 | $p^2$ | 0,174 |
| Heterozygote (AG) | 52 | 40,833 | 0,619 | | $2pq$ | 0,483 |
| Homozygote (GG) | 23 | 25,583 | 0,274 | 0,583 | $q2$ | 0,340 |
| Variation of allele frequency | 0,583 | | | | | |
| $\chi 2$ value | 6,282 | | | | | |
| p-value | 0,012 | | | | | |

## Discussion

Pharmacogenomics examines how genetic variation affects drug response and underpins the development of personalized medicine strategies. Among the key pharmacogenes, *ABCB1* encodes P-glycoprotein, a membrane transporter that regulates drug absorption and disposition, including immunosuppressants frequently used in systemic lupus erythematosus (SLE). The rs1045642 polymorphism in *ABCB1* has been investigated in relation to variable treatment outcomes, though findings across populations remain inconsistent.[25] The *ABCB1* rs1045642 polymorphism is a synonymous polymorphism, which changes the nitrogen base arrangement but does not cause a change in the amino acid for protein synthesis. Different authors have reported that subjects carrying the mutated SNP genotype exhibited lower P-gp expression in different tissues.[26]

The study included 84 female patients; its linear with the results of a study showing that 90% of patients with SLE are female. [27] Disease onset usually occurs between 15 and 44 years of age, which are included in the productive age.[28,29] In our study, all patients received methylprednisolone, and the majority also received azathioprine. It is important to note that MP is an *ABCB1* substrate, whereas AZA undergoes metabolism mainly via TPMT and NUDT15, with little evidence for *ABCB1* involvement. Thus, while *ABCB1* may influence MP pharmacokinetics and potentially treatment outcomes, concomitant use of AZA could affect LLDAS through mechanisms independent of ABCB1. This overlap limits our ability to isolate the pharmacogenetic impact of *ABCB1* on glucocorticoid response and represents a limitation of the present study.

The *ABCB1* rs1045642 G > A variant, also known as 3435C > T and Ile1145Ile, is the most common variant in *ABCB1*. Many studies have focused on position 3435, which is located in the middle of exon 26, and results in the conversion of cytosine to thymine. It is an unstable mutation that can then result in conversion to isoleucine, a hydrophobic amino acid residue. This isoleucine is well protected in many animals, from humans to primates, mice, and pigs. It is present in the second ATP-binding domain, which lies between the Q loop and the second characteristic motif in the ATP-binding cassette (ABC). The three SNPs are frequent and strongly correlated, creating a common haplotype at positions 1236C > T (G412G/rs1128503), 2677G > T (A893S/rs2032582), and 3435C > T (I1145I/rs1045642).[30]

The 3435C > T transition does not alter the amino acid encoded (Ile) at position 114522; the TT variant has been significantly associated with decreased mRNA expression and protein stability and may result in reduced drug transport capacity.[31] The effect of synonymous polymorphisms on proteins is not fully understood. However, it is assumed that they can affect the post-transcriptional processing of mRNA by interfering with the intron removal process or influencing the alternative transcript splicing process. Moreover, silent polymorphisms can have significant effects on the folding process of proteins and lead to abnormal shapes. In addition, the substitution resulting from silent polymorphisms frequently used in codon translation into rare codons can affect the folding rate of the protein and thereby alter its function or substrate specificity.[32] Alternatively, synonymous polymorphisms can change the structure and function of a protein by combining into a non-synonymous polymorphism that directly changes the amino acid sequence.[33] The synonymous variant *ABCB1* rs1045642 (C3435T) does not act in isolation but is commonly inherited together with rs1128503 (C1236T) and rs2032582

(G2677T/A), forming a haploblock across exon 12–26 of the *ABCB1* gene. These three loci are often in strong linkage disequilibrium, and haplotype combinations (e.g., 1236T–2677T–3435T) have been reported to alter P-glycoprotein expression, folding, and drug efflux activity more consistently than any single SNP. This genetic context may partly explain the variability in associations observed across studies: while some cohorts report a link between rs1045642 and treatment outcomes or disease susceptibility, others do not. Considering the haplotypic structure of *ABCB1*, future studies should integrate multi-locus analyses rather than focusing on rs1045642 alone to better capture the functional impact of *ABCB1* variation in SLE.[34,35] However, in this study, the absence of a relationship could result from our analysis of only one *ABCB1* mutation point, rs1045642.

Pharmacogenetic research is strongly influenced by ethnicity and population size. The effect of *ABCB1* variation on P-gp expression (at the mRNA and protein level) and activity in various tissues (such as the liver, gut, and heart) appears to be small. Although *ABCB1* polymorphisms and haplotypes have been associated with altered drug disposition and drug response, including the adverse effects of various *ABCB1* substrates in different ethnic populations, the results are highly conflicting, with limited clinical relevance.[36] In a Brazilian study, an association with prednisone dose was found in the recessive gene.[37] A study in a Caucasian population of kidney transplant recipients showed that the rs1045642 polymorphism was associated with high blood pressure in patients taking immunosuppressants one year after transplantation.[38] In a Japanese study, the AA genotype was associated with a reduced risk of osteonecrosis with methylprednisolone and prednisolone treatment in kidney transplant recipients compared with the AG + GG genotype.[39]

A study in China showed that *ABCB1* rs1045642 was significantly associated with P-gp expression in patients with refractory lupus nephritis in a population of Han Chinese patients with SLE.[40] *MDR1* polymorphism was associated with patient response to glucocorticoids and predisposition to Crohn's disease in a Chinese population.[41] Meanwhile, a meta-analysis by Chen et al. did not identify a relationship between polymorphisms and glucocorticoids. In contrast to previous studies, this relationship may be related to differences in the characteristics of unexpressed proteins, such as codon bias, expression efficiency, and differences in mRNA characteristics.[42]

Other infections could also affect the clinical care plan of SLE. Outcome assessment of long-term therapy of SLE also have not been well established. Although LLDAS could represent a degree of treatment reaction that provides clinicians an achievable target for patients with SLE that is essentially related to decreased levels of organ harm. LLDAS may be an excellent treatment target as a "surrogate" to prevent the hazard of future complications of SLE.[20,43]

In this study, association analysis was not performed because the genotype distribution of *ABCB1* rs1045642 deviated significantly from Hardy–Weinberg equilibrium. Several factors may account for this deviation, including the relatively small sample size, technical genotyping errors, population stratification, selection bias due to recruiting only SLE cases, or a true biological association of the variant with disease status. These possibilities should be considered when interpreting our findings, and future studies with larger, well-controlled cohorts and case–control designs are needed to confirm the genetic profile of *ABCB1* rs1045642 in SLE.[44,45]

## Conclusion

The genotype distribution of the *ABCB1* rs1045642 polymorphism among SLE patients in Bandung City was AA 10.71%, AG 61.91%, and GG 27.38%, with a significant deviation from Hardy–Weinberg equilibrium. Due to this deviation, association analyses with therapeutic outcome (LLDAS) were not conducted. Instead, we provide a descriptive profile of the cohort and highlight that treatment outcomes in SLE are multifactorial, influenced by clinical characteristics, medication adherence, and appropriateness of therapy, in addition to genetic variation. This study represents the first report of *ABCB1* rs1045642 genotype distribution in Indonesian SLE patients and contributes baseline data for future research with larger, well-controlled cohorts.

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## Declaration Of Conflicting Interests

The authors declared no potential conflicts of interest in this study.

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