Research Article
Evaluation of Human Leukocyte Antigen Class I and Class II in End-Stage Renal Disease Occurrence in Indonesian Transplantation Patients

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Background. Genetic studies of end-stage renal disease (ESRD), including those of human leukocyte antigen (HLA) genes, have been reported in several populations but have not yet been evaluated in Indonesia. Some studies have reported that these genes had a substantial role in ESRD. This study aims to analyze the association between HLA genes and ESRD within the Indonesian community.

Method. A retrospective study to investigate HLA class I and II alleles to find out the distribution of HLA-A, -B, -C, -DPB1, -DQB1, and -DRB1 in renal transplant recipients and to ascertain their role in susceptibility to ESRD was performed on totally 149 subjects, consisting of 69 ESRD patients and 80 healthy controls. HLA typing was determined using Luminex techniques. The allele and haplotype frequencies were compared between ESRD patients and controls. Result. High-frequency alleles were HLA-A*24 (43.6%), B*15 (38.2%), C*08 (30.8%), DRB1*12 (47.3%), DQB1*03 (50.6%), and DPB1*13 (22.5%). HLA-A*24 (p = 0.01) and HLA-B*35 (p = 0.02) were associated with a protective effect, with OR 0.53 (95% CI 0.34–0.86) and 0.31 (95% CI 0.11–0.88), respectively. There were some two-locus haplotypes associated with susceptibility to ESRD, such as B*15-DRB1*12, B*13-DRB1*15, A*02-B*15, A*02-C*08, and B*13-DQB1*05. HLA-A*24-B*13-DRB1*15 and A*24-B*13-DRB1*15 appear to be associated with susceptibility to ESRD. Conclusion. The allele groups of HLA-A*24 and HLA-B*35 are associated with protection from ESRD. Meanwhile, HLA-B*13-DRB1*15 and A*24-B*13-DRB1*15 are the most frequent HLAs associated with ESRD in two-locus and three-locus haplotype, respectively.

1. Introduction

The incidence of ESRD in the world is increasing as well as in Indonesia. The Indonesian Renal Registry showed that ESRD incidence rose from 9649 in 2010 to 30831 in 2017. At the same time, the prevalence of ESRD increased from 11484 in 2010 to 77892 in 2017. The causes of kidney disease are mainly due to hypertension and diabetes mellitus, with the 1-year survival rate of 83%, while the 5-year survival rate was 51.9%. The leading cause of death in 37% of cases was cardiovascular disorders [1].

End-stage renal disease (ESRD) is suspected to be influenced by genetic and nongenetic factors. Many genetic factors cause ESRD, and human leukocyte antigen (HLA) is an essential factor. HLA is encoded by the major histocompatibility complex (MHC) located on chromosome 6p21.3. The HLA molecule binds and presents peptide to T lymphocytes in cell-mediated immune response and plays a crucial role in shaping the T-cell repertoire and is also associated with allograft rejection [2, 3]. The correlation of HLA polymorphism with ESRD can be caused by HLA association with the aetiology and the progression of kidney
2. Methods

2.1. Population Samples. This study was observational and retrospective. The data were collected from the biomolecular laboratory databases of Dr. Saiful Anwar General Hospital from 2017 to 2020. We investigated HLA class I and II alleles to determine the distribution of HLA-A, HLA-B, HLA-C, HLA-DPB1, HLA-DQB1, and HLA-DRB1 and to ascertain their role in susceptibility to ESRD in patients considering renal transplantation and healthy controls. The inclusion criteria were the subjects had complete HLA typing data from 6 loci, not family related, and Indonesian population.

2.2. DNA Extraction. DNA was isolated from whole blood containing Acid Citrate Dextrose (ACD) solution, using a Genomic DNA Isolation kit, according to the manufacturer’s instructions (Qiagen). In brief, 20 μL of Qiagen protease and 200 μL of whole blood were added into a 1.5 mL microcentrifuge tube. 200 μL of buffer (AL) was added and then incubated at 56°C for 10 minutes, and 200 μL of ethanol (100%) was added and centrifuged. The mixture was transferred into a QIAamp mini spin column, the tube was centrifuged, the QIAamp mini spin column was placed in a clean 2 mL collection tube, and the tube containing the filtrate was discarded. 500 μL of buffer (AW1) was added and centrifuged, then the QIAamp mini spin column was placed in a clean 2 mL collection tube, and the tube containing the filtrate was discarded. The procedure was repeated with 500 μL of buffer (AW2), and then, the QIAamp mini spin column was placed in a clean 1.5 mL microcentrifuge tube. Then, 200 μL of elusion buffer (AE) was added and centrifuged, the QIAamp mini spin column was discarded, and the microcentrifuge tube containing the eluted DNA was stored at −80°C.

2.3. DNA Typing. HLA typing of loci HLA-A, HLA-B, HLA-C, HLA-DPB1, HLA-DQB1, and HLA-DRB1 was performed by Luminex Labscan 100 using the sequence-specific oligonucleotide probes (SSO) method. In summary, 2 μL of the target DNA is amplified using a group-specific primer. The PCR product is denatured and allowed to rehybridize to complementary DNA probes conjugated to fluorescein coded microspheres. A flow analyzer, the LABScan™ 100, identified the fluorescent intensity of PE (phycoerythrin) on each microsphere. The HLA Fusion software (ONE LAMBDA, INC, USA) will analyze the HLA typing for allele identification based on the reaction pattern compared to patterns associated with published HLA gene sequences.

2.4. Statistical Analysis. HLA allele, two-locus, and three-locus haplotype frequencies were performed by direct counting in percentage. Two-locus haplotype frequencies in this study will be compared with the two-locus haplotype from the other population because more studies reported the two-locus haplotype than the three-locus haplotype. However, the three-locus haplotype (HLA-ABDR) was considered more relevant in this regard, so we also performed the three-locus haplotype in this study. The association between HLA allele with ESRD was estimated with Odds Ratio (OR) and 95% confident intervals, with p < 0.05 was considered statistically significant. Odds Ratio (OR) value greater than one was deemed positive or susceptible to ESRD, meanwhile OR values less than one were considered protective to ESRD. The exact test was used to evaluate the assumption of Hardy–Weinberg Equilibrium (HWE). The software for statistical analysis was the SPSS version 23 and OpenEpi. The institutional ethics board of Dr. Saiful Anwar General Hospital has approved the study (ethical number 400/141/K.3/302/2020).

3. Results

3.1. Characteristics of Study Participants and Hardy–Weinberg Equilibrium Tests. The study collected HLA data from 81 ESRD and 87 control participants. According to the inclusion criteria, 69 ESRD patients and 80 donors, a total of 149 subjects, were selected. There was a male predominance among the control group (63.8%) and ESRD group (51.3%). The allele number of HLA-A, HLA-B, HLA-C, HLA-DPB1, HLA-DQB1, and HLA-DRB1 in ESRD patients and donors are summarized in column charts shown in Figure 1. The HWE tests of the HLA-A, -B, -C,-DRB1, -DQB1, and -DRP1 loci showed p > 0.05.

3.2. Allele Frequencies at HLA-A, HLA-B, HLA-C, HLA-DPB1, HLA-DQB1, and HLA-DRB1 Loci in Renal Transplant Recipients and Donors. The high-frequency alleles of HLA class I was HLA-A*24 (35.5% in ESRD, 50.6% in control group, and 43.60% in both groups), HLA-B*15 (37.70% in ESRD, 38.20% in control group, and 38.20% in both groups), and HLA-C*08 (31.20% in ESRD, 30% in control group, and 30.80% in both groups). Table 1 shows the class I HLA types with frequency >1% in the ESRD or control groups. If the frequency is 1% or less, the data were not performed. According to Table 1, HLA-A*24 (p = 0.01) and HLA-B*35 (p = 0.02) were associated with a protective effect, with OR 0.537 (95%CI 0.34–0.86) and 0.316 (95%CI 0.11–0.88), respectively.
Figure 1: Numbers of HLA-A, HLA-B, HLA-C, HLA-DPB1, HLA-DQB1, and HLA-DRB1 allele groups in ESRD patients, control, and both groups.

Table 1: HLA class I allele frequency.

| HLA subtype | Alleles | ESRD | Control | OR | OR 95% CI | p value |
|-------------|---------|------|--------|----|----------|---------|
| HLA-A       | A*01    | 0    | 2      | 1.30 | —        | —       |
|             | A*02    | 22.50| 14.40 | 1.726| 0.95–3.13| 0.10    |
|             | A*11    | 24.60| 20.60 | 1.258| 0.73–2.17| 0.49    |
|             | A*24    | 35.50| 50.60 | 0.537| 0.34–0.86| 0.01*   |
| HLA-B       | A*02    | 1.40 | 0      | —   | —        | —       |
|             | A*31    | 1.40 | 0      | —   | —        | —       |
|             | A*33    | 6.50 | 8.10  | 0.789| 0.33–1.91| 0.76    |
|             | A*34    | 4.30 | 5.10  | 1.409| 0.42–4.72| 0.80    |
|             | A*74    | 2.20 | 0      | —   | —        | —       |
| HLA-C       | B*07    | 2.90 | 4.20  | 1.164| 0.29–4.74| 1       |
|             | B*08    | 1.40 | 0      | —   | —        | —       |
|             | B*13    | 5.10 | 3.10  | 2.796| 0.71–11.03| 0.23    |
|             | B*15    | 37.70| 38.80 | 0.956| 0.60–1.53| 0.94    |
|             | B*18    | 15.90| 16     | 1.098| 0.52–2.31| 0.95    |
|             | B*27    | 5.80 | 8      | 1.169| 0.43–3.20| 0.96    |
|             | B*35    | 3.60 | 17     | 0.316| 0.11–0.88| 0.02*   |
| HLA-DPB1    | B*38    | 5.80 | 11     | 0.834| 0.33–2.14| 0.89    |
|             | B*39    | 2.90 | 2      | 1.30 | 2.358   | 0.43–13.08| 0.55    |
|             | B*40    | 5.80 | 8      | 5    | 1.169   | 0.43–3.20| 0.96    |
|             | B*44    | 2.90 | 12     | 7.50 | 0.368   | 0.12–11.17| 0.13    |
|             | B*51    | 5.10 | 11     | 6.90 | 0.724   | 0.27–19.12| 0.69    |
|             | B*52    | 0.70 | 2      | 1.30 | 0.577   | 0.05–6.43| 1       |
|             | B*56    | 2.20 | 2      | 1.30 | 1.756   | 0.29–10.66| 0.86    |
|             | B*58    | 2.20 | 1      | 0.60 | 3.533   | 0.36–34.36| 0.52    |
| HLA-DQB1    | C*01    | 4.30 | 2      | 1.20 | 3.977   | 0.69–51.79| 0.15    |
|             | C*03    | 10.10| 13     | 8.10 | 1.277   | 0.58–2.82| 0.68    |
|             | C*04    | 14.50| 29     | 18.10| 0.735   | 0.40–1.36| 0.41    |
|             | C*06    | 2.20 | 3      | 1.90 | 1.163   | 0.23–5.86| 1       |
| HLA-DRB1    | C*07    | 40.29| 50     | 31.30| 0.93    | 0.57–1.53| 0.87    |
|             | C*08    | 31.20| 48     | 30   | 1.056   | 0.64–1.73| 0.93    |
|             | C*12    | 0.40 | 2      | 1.30 | 1.162   | 0.16–8.36| 1       |
|             | C*14    | 3.60 | 9      | 5.60 | 0.631   | 0.21–1.93| 0.59    |
|             | C*15    | 3.60 | 9      | 1.90 | 1.967   | 0.46–8.39| 0.57    |

*p < 0.05. HLA types with frequency >1% were performed in ESRD or control groups. HLA: human leukocyte antigen; ESRD: end-stage renal disease.

Table 2 indicates the class II HLA types with frequency >1% in the ESRD or control groups. The high-frequency alleles of HLA class II were HLA-DRB1*12 (44.20% in ESRD, 50% in control group, and 47.30% in both groups), HLA-DQB1*03 (49.30% in ESRD, 51.90% in control group, and 50.6% in both groups), and HLA-DPB1*13 (22.50% in ESRD, 22.50% in control group, and 22.5% in both groups). HLA class II was not associated with ESRD.

Table 3 shows the association of two-locus haplotypes with ESRD with a significant odds ratio between the two groups (p value < 0.05). There are some haplotypes associated with susceptibility to ESRD, namely, B*15–DRB1*12, B*13–DRB1*15, A*02–B*15, A*02–C*08, and B*13–DQB1*05. Meanwhile, the other haplotypes are associated with protection from ESRD.

Table 4 indicates the association of the three-locus haplotypes with ESRD with a significant odds ratio between the two groups (p value < 0.05). Two haplotypes are associated with susceptibility to ESRD, where the highest OR is HLA-A*24–B*13–DRB1*15 (OR = 8.171), followed by HLA-DQB1*12 and HLA-DPB1*35–DRB1*15 is negatively associated with ESRD.

4. Discussion

Aside from its essential role in determining donor-recipient immune compatibility in organ transplantation, HLA genotyping is performed routinely as part of the diagnostic work-up of certain autoimmune diseases. The HLA genotyping also has contributed to understanding several diseases’ pathogenesis, including ESRD [3].

Our study observed that the ESRD participants consisted of 51.3% males and 48.7% females. It is similar to the research by Panigrahi et al. [4] and Tuladhar et al. [5], which reported that most ESRD patients were males.

The data of HLA alleles in our study showed heterogeneity in both HLA class I or class II. The number of HLA-B alleles is higher than HLA-A and HLA-C in HLA class I. Meanwhile, HLA class II indicated that the number of HLA-DPB1 alleles is higher than HLA-DR and HLA-DQB1. The heterogeneity of HLA alleles results in amino acid substitutions that predominantly involve peptide binding sites for the effective display of a broad peptide to CD4+ and CD8+ T cells. As of July 2018, the polymorphisms of HLA-A, HLA-B, and HLA-C had 9,341 different proteins and 5,355 proteins in the polymorphisms of HLA-DR, HLA-DQ, and HLA-DP [3].

The high frequency of HLA-A*24 in our study is also observed similarly in South Indian, northern Indian, and Bangladeshi Bengali populations [5–7]. The frequent alleles such as HLA-A*02 and A*11 were also observed by Ali...
et al., and this HLA correlated with the Bangladeshi Bengali population. The most common alleles in Nepal, such as HLA-B*15 and DRB1*12 [5], were also found in high frequencies in our study. Pradana et al. stated that the Indonesian HLA profile had high variation at HLA-

### Table 2: HLA class II allele frequency.

| HLA subtype | Alleles | ESRD | Control |
|-------------|---------|------|---------|
|             | n      | %    | n      | %      | OR    | OR 95% CI | p value |
| **HLA-DRB1** |        |      |        |        |       |        |         |
| DRB1*03     | 5      | 3.60 | 2      | 1.30   | 2.97  | 0.567–15.56 | 0.34 |
| DRB1*04     | 6      | 4.30 | 7      | 4.40   | 0.994 | 0.326–3.03  | 1    |
| DRB1*07     | 9      | 6.50 | 14     | 8.80   | 0.728 | 0.305–1.74  | 0.62 |
| DRB1*08     | 7      | 5.10 | 4      | 2.50   | 2.084 | 0.597–7.28  | 0.39 |
| DRB1*09     | 4      | 2.90 | 3      | 1.90   | 1.562 | 0.344–7.10  | 0.84 |
| **HLA-DQB1** |        |      |        |        |       |        |         |
| DQB1*02     | 11     | 8    | 17     | 10.70  | 0.729 | 0.329–1.61  | 0.56 |
| DQB1*03     | 68     | 49.30| 83     | 51.90  | 0.901 | 0.572–1.42  | 0.74 |
| DQB1*04     | 5      | 3.60 | 6      | 3.70   | 0.965 | 0.288–3.23  | 1    |
| DQB1*05     | 33     | 23.90| 31     | 19.30  | 1.308 | 0.752–2.28  | 0.42 |
| DQB1*06     | 21     | 15.20| 23     | 14.40  | 1.069 | 0.563–2.03  | 0.97 |
| **HLA-DPB1** |        |      |        |        |       |        |         |
| DPB1*01     | 5      | 3.60 | 6      | 3.80   | 0.965 | 0.288–3.23  | 1.00 |
| DPB1*02     | 20     | 14.50| 13     | 8.10   | 1.917 | 0.915–4.01  | 0.12 |
| DPB1*03     | 8      | 5.80 | 15     | 9.40   | 0.595 | 0.244–1.45  | 0.35 |
| DPB1*04     | 29     | 21   | 34     | 21.30  | 0.986 | 0.564–1.72  | 1.00 |
| DPB1*05     | 24     | 17.40| 26     | 16.30  | 1.085 | 0.591–1.99  | 0.91 |
| DPB1*13     | 31     | 22.50| 36     | 22.50  | 0.998 | 0.578–1.72  | 1.00 |
| **HLA-DQA1** |        |      |        |        |       |        |         |
| DQA1*01     | 5      | 3.60 | 6      | 3.80   | 0.965 | 0.288–3.23  | 1.00 |
| DQA1*02     | 20     | 14.50| 13     | 8.10   | 1.917 | 0.915–4.01  | 0.12 |
| DQA1*03     | 8      | 5.80 | 15     | 9.40   | 0.595 | 0.244–1.45  | 0.35 |
| DQA1*04     | 29     | 21   | 34     | 21.30  | 0.986 | 0.564–1.72  | 1.00 |
| DQA1*05     | 24     | 17.40| 26     | 16.30  | 1.085 | 0.591–1.99  | 0.91 |
| DQA1*13     | 31     | 22.50| 36     | 22.50  | 0.998 | 0.578–1.72  | 1.00 |

HLA types with frequency >1% were performed in ESRD or control groups. HLA: human leukocyte antigen; ESRD: end-stage renal disease.

### Table 3: Association of two-locus haplotypes with ESRD.

| Haplotypes | ESRD | Control |
|------------|------|---------|
|            | n    | %    | n    | %    | p value | OR | OR 95%CI |
| **HLA-A and HLA-B** |      |      |      |      |         |    |          |
| A*02-B*15  | 26   | 9.42 | 14   | 2.19 | 0.022  | 2.273 | 1.162–4.446 |
| A*24-B*35  | 5    | 1.81 | 24   | 3.59 | 0.002  | 0.238 | 0.089–0.635 |
| **HLA-A and HLA-C** |      |      |      |      |         |    |          |
| A*02-C*08  | 22   | 7.97 | 10   | 1.56 | 0.014  | 2.685 | 1.249–5.774 |
| A*24-C*08  | 27   | 9.78 | 53   | 8.28 | 0.020  | 0.546 | 0.333–0.896 |
| **HLA-A and HLA-DRB1** |      |      |      |      |         |    |          |
| A*24-DRB1*12 | 51  | 18.48| 87   | 13.59| 0.015  | 0.607 | 0.410–0.897 |
| **HLA-A and HLA-DQB1** |      |      |      |      |         |    |          |
| A*24-DQP1*03 | 53  | 19.20| 85   | 13.28| 0.042  | 0.657 | 0.445–0.969 |
| **HLA-B and HLA-C** |      |      |      |      |         |    |          |
| B*35-C*04  | 5    | 1.81 | 24   | 3.75 | 0.001  | 0.228 | 0.086–0.605 |
| **HLA-B and HLA-DRB1** |      |      |      |      |         |    |          |
| B*15-DRB1*12 | 61  | 22.10| 39   | 6.09 | 0.001  | 2.044 | 1.317–3.172 |
| **HLA-A and HLA-DQA1** |      |      |      |      |         |    |          |
| B*35-DQA1*06 | 01  | 5    | 1.81 | 27   | 0.037  | 0.329 | 0.120–0.903 |
| B*35-DQA1*03 | 5    | 1.81 | 27   | 2.66 | 0.037  | 0.329 | 0.120–0.903 |
| B*35-DQA1*05 | 8    | 2.90 | 1    | 0.16 | 0.021  | 9.522 | 1.184–76.610 |

HLA: human leukocyte antigen; ESRD: end-stage renal disease.
Some two-locus haplotypes were associated with susceptibility to ESRD in our study, such as HLA-A*02-B*15, A*02-C*08, B*15-DRB1*12, B*13-DRB1*15, and B*13-DQB1*05. This result is different from the research by Hamdi that reported the association of two-locus haplotypes HLA-A*01-DRB1*13 and HLA-A*30-DRB1*03 with ESRD in Saudi Arabian population [20]. In Venezuela, a study by Rivera et al. stated that the haplotypes positively associated with ESRD were HLA-A*02-B*51, HLA-A*02-B*53, HLA-A*23-B*38, and HLA-A*68-B*38 [21].

According to our data, HLA-A*02-B*15-DRB1*12 and HLA-A*24-B*13-DRB1*15 were three-locus haplotypes associated with susceptibility to ESRD. HLA-A*24-B*13-DRB1*15 had a strong association with ESRD with OR 8.171. Nevertheless, the study by Cao et al. in the Cantonese community, a representative southern population of China, showed that HLA-A*11-B*27-DRB1*04 in ESRD patients is significantly higher than that in the controls [11].

Based on the data of HLA and ESRD given above, there are different results in different studies and populations. This difference may be influenced by the disease that causes kidney abnormalities. HLA has substantial risk factors in most immune-mediated renal disorders. Together with other genetic and environmental factors, HLA causes loss of tolerance and autoimmune-mediated inflammation of the kidney [3, 22]. For example, Karnes et al. reported that HLA-DRB1*04 and HLA-DQB1*03:02 had an association with diabetic kidney disease. The association of HLA-DQB1*03:02 and ESRD or kidney transplantation was weak (OR = 1.4), but this HLA had the risk of type 1 diabetes and diabetic kidney disease with OR 7.1 [23].

The limitations of our study were the small number of ESRD and healthy control participants. Further research with a more significant number of samples is needed. However, our research is expected to give a piece of information on the association between HLA and ESRD, especially in Indonesia, thus allowing the management of chronic kidney disease patients with HLA susceptibility more precisely and effectively.

### 5. Conclusions

The result of this study showed heterogeneity in both HLA class I or class II antigens, and some HLA polymorphisms have an association with ESRD in the Indonesian population. HLA-A*24 and HLA-B*35 are associated with protection from ESRD, whereas HLA-B*13-DRB1*15 is the most frequent HLA related to susceptibility to ESRD in...
the two-locus haplotype and HLA-A∗24-B∗13-DRB1∗15 in the three-locus haplotype.

**Data Availability**

The database for the study can be acquired from the principal investigator, Hani Susianti, hanisusianti.fk@ub.ac.id.

**Conflicts of Interest**

The authors declare no conflicts of interest.

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