

Original article

HLA class II allele and haplotype frequencies in deceased kidney donors and the significance of HLA-DQ matching on allograft survival: a retrospective study from January 2019 to December 2024

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Abstract:

Introduction: Data on HLA-A, -B, and -DR allele frequencies in deceased kidney donors were reported, but HLA-DQB1 frequencies were not. HLA-DQB1 mismatch has been associated to increase the risk of graft rejection and is linked to DRB1 mismatch. **Objective:** This retrospective study aimed to determine the allele and haplotype frequencies of HLA-DRB1 and -DQB1, and to investigate whether HLA-DQB1 matching is associated with allograft survival in deceased kidney donors. **Materials and Methods:** HLA class II allele data from 1,557 deceased kidney donors between January 1, 2019, to December 31, 2024, were obtained and analyzed for HLA-DRB1 and -DQB1 allele frequencies from the ODC-TRC Program. HLA-DRB1-DQB1 haplotypes were deduced based on known linkage patterns of HLA-DRB1 and -DQB1 alleles in HLA-DR51, -DR52 and -DR53. The haplotype frequencies were calculated using Unequivocal haplotype assignment and the formula: (haplotype count ÷ 2N) × 100, where N is the number of individuals in the population. Data on graft outcomes provided from Thai Transplantation Society. Among 75 patients with zero HLA-ABDR mismatch and either HLA-DQ match or mismatch were analyzed. **Results:** Overall, 13 HLA-DRB1 alleles were detected among 1,557 deceased donors. Of these, DRB1*15 was the most frequent, followed by DRB1*12, DRB1*14, and DRB1*09, respectively. Additionally, seven HLA-DQB1 alleles were identified. The most common were DQB1*05, followed by DQB1*03 (DQ7), DQB1*02, and DQB1*03 (DQ9), respectively. Five HLA-DRB1-DQB1 haplotype frequencies, including DRB1*15-DQB1*05, DRB1*12-DQB1*03 (DQ7), DRB1*09-DQB1*03 (DQ9), DRB1*14-DQB1*05, and DRB1*07-DQB1*02, were frequently observed. Graft losses occurred in two patients, one with zero and one with a single HLA-DQ mismatch. Kaplan–Meier survival analysis showed that patients with two HLA-DQ mismatches had the lowest graft survival rates, and the difference among groups was statistically significant. **Conclusion:** This study identified HLA-DRB1 and -DQB1 allele and haplotype frequencies among deceased kidney donors, providing additional background information relevant to kidney allocation criteria.

Keywords : ● HLA alleles ● Haplotypes ● Deceased donors ● Kidney transplantation

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นิพนธ์ต้นฉบับ

ความถี่ของ HLA Class II allele และ haplotype ในผู้บริจาคไตสมองตาย และความสำคัญของ HLA-DQ matching กับ การปลูกถ่ายอวัยวะ: การศึกษาย้อนหลังตั้งแต่เดือนมกราคม 2562 ถึงธันวาคม 2567

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บทคัดย่อ

บทนำ ข้อมูลของ human leukocyte antigen (HLA) ซึ่งเป็นความถี่อัลลีล HLA-A, -B, และ -DR ในผู้บริจาคไตสมองตายนั้นมีรายงานไว้ แต่ยังไม่มีความถี่อัลลีลของ HLA-DQB1 ซึ่งในการปลูกถ่ายอวัยวะ HLA-DQB1 mismatch ส่งผลต่อการเพิ่มความเสี่ยงต่อการปฏิเสธอวัยวะและเกี่ยวข้องกับ HLA-DRB1 mismatch **วัตถุประสงค์** เพื่อศึกษาข้อมูลย้อนหลังความถี่อัลลีลและ haplotypes ของ HLA-DRB1 และ -DQB1 และ HLA-DQB1 matching มีผลต่อ graft survival ในผู้บริจาคไตสมองตายหรือไม่ **วัสดุและวิธีการ** เก็บข้อมูลผลการตรวจทางห้องปฏิบัติการในผู้บริจาคไตสมองตายจำนวน 1,557 ราย จากโปรแกรมของ ODC-TRC ตั้งแต่วันที่ 1 มกราคม พ.ศ. 2562 ถึงวันที่ 31 ธันวาคม พ.ศ. 2567 รวบรวมผลตรวจและวิเคราะห์ความถี่อัลลีลของ HLA-DRB1 และ -DQB1 รวมทั้งคำนวณเป็น HLA-DRB1-DQB1 haplotype frequencies ด้วยวิธี Unequivocal haplotype assignment และหาความถี่ด้วยสูตร : $(\text{haplotype count} \div 2N) \times 100$ โดย N คือจำนวนของผู้บริจาคไตสมองตาย **ผลการศึกษา** ผู้บริจาคไตสมองตาย จำนวน 1,557 ราย พบอัลลีล HLA-DRB1 จำนวน 13 ชนิด อัลลีลที่พบบ่อยคือ DRB1*15, DRB1*12, DRB1*14 และ DRB1*09 พบอัลลีล HLA-DQB1 จำนวน 7 ชนิดที่พบบ่อย คือ DQB1*05 รองลงมาคือ DQB1*03 (DQ7), DQB1*02, และ DQB1*03 (DQ9) ตามลำดับ ความถี่อัลลีลทั้ง HLA-DRB1 และ -DQB1 ที่พบครั้งนี้ใกล้เคียงกับที่เคยมีรายงานไว้ในคนไทย การศึกษานี้ความถี่ของ HLA-DRB1-DQB1 haplotypes ที่พบบ่อย 5 แบบ คือ DRB1*15-DQB1*05, DRB1*12-DQB1*03 (DQ7), DRB1*09-DQB1*03 (DQ9), DRB1*14-DQB1*05 และ DRB1*07-DQB1*02 เมื่อวิเคราะห์ข้อมูลของ graft outcome ในผู้ป่วยที่ได้รับไตแบบ HLA-ABDR ตรงกันทั้งหมด และ HLA-DQ ตรงกัน หรือ HLA-DQ ไม่ตรงกัน จำนวน 75 ราย พบว่า ผู้ป่วยที่มี graft loss จำนวน 2 ราย มี 1 รายเป็น HLA-DQB1 ตรงกัน และอีก 1 รายเป็น HLA-DQB1 ไม่ตรงกัน 1 อัลลีล จากการวิเคราะห์ graft survival ด้วยวิธี Kaplan-Meier แสดงให้เห็นว่าผู้ป่วยที่มี HLA-DQB1 ไม่ตรงกัน 2 อัลลีล มีความแตกต่างอย่างมีนัยสำคัญทางสถิติเมื่อเทียบกับกลุ่มอื่น **สรุป** การศึกษานี้ได้รายงานความถี่อัลลีล และ haplotypes ของ HLA-DRB1 และ -DQB1 ในผู้บริจาคไตสมองตายเพื่อใช้เป็นข้อมูลเพิ่มเติมที่เป็นประโยชน์สำหรับการจัดสรรไตต่อไป

คำสำคัญ : ● อัลลีล HLA ● Haplotypes ● ผู้บริจาคไตสมองตาย ● การปลูกถ่ายไต

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2569;36:21-30.

Introduction

For deceased donor kidney transplantation, ABO blood group and human leukocyte antigen (HLA) compatibility between donor and recipient improves graft function and outcomes and reduces the risk of sensitization.¹ First, the HLA-A, -B, and -DR typing results of wait-listed patients at each transplant center are submitted and registered according to the kidney allocation criteria of the Organ Donation Centre, Thai Red Cross Society (ODC-TRC) program. When the ODC-TRC transplant coordinators are notified of a deceased donor, HLA-A, -B, and -DR typing is performed, and the negative results of infectious markers are confirmed by the National Blood Centre, Thai Red Cross Society (NBC-TRC). Subsequently, patients on the waitlist are ranked according to a composite score that includes HLA-A, -B and -DR typing, panel reactive antibody (PRA), patient age, and duration of waiting time. Those with the highest scores are selected for HLA crossmatching using recipient serum against donor T and B lymphocytes, according to donor ABO blood group, Rh(D), and HLA typing. Patients with the highest scores and a negative HLA crossmatch are prioritized for transplantation.^{3,4} Subsequently, patients on the waitlist are ranked according to a composite score that includes HLA-A, -B, and -DR typing, panel reactive antibody (PRA) levels, patient age, and duration of waiting time.

Data from the Collaborative Transplant Study in 1985 revealed that the kidney transplant success rate was higher when there was no mismatch of HLA-B and -DR than when there was a mismatch⁵, consistent with related studies in deceased donor kidney transplants.^{6,7} Nevertheless, there is limited data on HLA typing results in deceased kidney donors at other HLA loci, including HLA-C, -DOB1, and -DPB1, which may be due to the limited availability of reagents and techniques used and their high cost. A related study revealed that when there was also one HLA-B mismatch, patients with one or two HLA-C mismatches had a significantly

higher incidence of rejection compared with those with no HLA-C mismatch when there was also one HLA-B mismatch.⁸

According to data from the Southeastern Organ Procurement Foundation, HLA-DQ matching showed no effect among 12,050 deceased donor transplants;⁹ however, a significantly increased risk of rejection was observed when HLA-DQ mismatching occurred in combination with HLA-DR mismatches.¹⁰ Moreover, recipients with DQ mismatch developed de novo donor-specific antibodies (dnDSAs) after kidney transplantation. The immunogenetic potential of HLA-DQ mismatch exhibited a significantly higher rate of late graft rejection and graft survival compared with recipients who did not develop dnDSAs.¹¹ Therefore, incorporating HLA-A, -B, -DR, and -DQ typing results for both wait-listed patients and deceased donors has been recommended in kidney allocation schemes to reduce the risk of sensitization, particularly in patients undergoing repeat transplantation.¹⁰⁻¹³

Data on HLA-A, -B, and -DR frequencies in deceased donors from the ODC-TRC were reported in 2019, showing no significant differences compared with the Thai stem cell donor registry; however, HLA-DQ frequencies were not included.¹⁴ In 1996, polymerase chain reaction sequence-specific primer (PCR-SSP) testing was first applied for HLA-A, -B, -DRB1, and -DOB1 typing in deceased donors. Since 2017, real-time PCR has been implemented for deceased donor typing to reduce turnaround time, with supplementary HLA-C and -DPB1 typing results also available.¹⁵ To strengthen the kidney allocation system of the ODC-TRC, this retrospective study aimed to determine the distribution of *HLA-DRB1* and *-DOB1* alleles and haplotypes in deceased kidney donors from January 2019 to December 2024, and to compare graft outcomes between recipients of DOB1-matched and DOB1-mismatched deceased donor kidney transplants.

Materials and Methods

Study populations

This retrospective study protocol was approved by the Research Ethics Committee, National Blood Centre, Thai Red Cross Society, Bangkok, Thailand (COA No. NBC EC 12/2025).

The study population comprised laboratory data from total 1,557 deceased kidney donors obtained through the ODC-TRC Program between January 1, 2019, and December 31, 2024. Eligible organ donors were required to be less than 60 years of age, to have been declared brain dead. Donors with active infections, malignancies and chronic diseases (including diabetes mellitus, cardiovascular disease, renal disease, hypertension, hepatic disease, or alcohol dependence) were excluded. All organs considered for transplantation were required to demonstrate adequate functional status and to be free of transmissible pathogens, such as hepatitis B virus and HIV. Organ procurement was conducted exclusively after consent for donation had been obtained from the donor's family or legal next of kin. HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQB1, and -DPB1 typing was performed using real-time PCR (LinkSeq™ HLA Typing Kits, One Lambda, Inc., CA, USA).¹⁵ The laboratory is accredited under ISO 15189:2022 medical laboratory standards. Among 2,709 patients who were registered with HLA-A, -B, -DR, and -DQ typing results and received kidneys from 1,468 deceased donors between January 2019 and December 2024, 75 patients received zero HLA-ABDR mismatch donors (0:0:0). In addition, graft outcome among 75 patients who received deceased donor kidney transplants with zero HLA-ABDR mismatch and either HLA-DQ match or mismatch were analyzed.

Data analysis

Regarding the ODC-TRC criteria, all DNA-based HLA-A, -B, and -DRB1 typing results of deceased donors were converted to serologically defined split antigens. The assignment of split antigens was performed based on the IPD-IMGT/HLA database (<http://www.ebi.ac.uk/ipd/imgt/hla>)¹⁶ and the HLA dictionary.¹⁷

Statistical analysis

HLA class II allele analysis results were collected in a database (Microsoft Access 11.0; Microsoft Corporation, Seattle, WA, USA). *HLA-DRB1* and *-DQB1* allele frequencies of deceased donors were analyzed as allele frequency (AF) using the following formula: %AF = (sum of each individual allele/ 2N) × 100. *HLA-DRB1* and *-DQB1* haplotype frequencies among 1,557 deceased kidney donors were determined using unequivocal haplotype assignment, according to the data reported among Thai populations.¹⁸ This approach was based on the known linkage patterns of *HLA-DRB1* and *-DQB1* alleles within the HLA-DR51, -DR52 and -DR53- associated haplotypes previously described in the Thai population. When multiple allele combinations were compatible with the typing results, the haplotype most frequently reported in the population was assigned as the most likely haplotype. In addition, to model time-to-graft loss and recipient survival after kidney transplantation, Kaplan-Meier (K-M) survival curves were generated using IBM SPSS Statistics version 23 and presented with Microsoft® Word 2019.

Results

The data from the ODC-TRC Program, from January 1, 2019, to December 31, 2024, included 1,557 deceased kidney donors. The distribution of *HLA-DRB1* and *HLA-DQB1* alleles was defined by real-time PCR low-resolution typing among deceased kidney donors, as shown in Table 1. Overall, 13 *HLA-DRB1* alleles were detected among deceased kidney donors. Of these, *DRB1*15* (23.92%), *DRB1*12* (16.02%), *DRB1*14* (9.83%), and *DRB1*09* (9.57%) were the most frequent, consistent with a related study.¹⁴ The *DRB1*03* (DR18) allele was not observed in this study because it was a rare allele hardly found in Thais. Additionally, seven *HLA-DQB1* alleles were identified. The most common *DQB1* alleles among deceased kidney donors were *DQB1*05* (40.59%), followed by *DQB1*03* (DQ7) (16.60%), *DQB1*02* (13.46%), and *DQB1*03* (DQ9) (10.92%), respectively.

Table 1 Distributions of *HLA-DRB1* and *-DQB1* alleles among deceased kidney donors

Alleles	Frequency (n = 1,557)	
	Observed	%
<i>DRB1</i> allele		
<i>DRB1*01</i>	6	0.19
<i>DRB1*03(DR 17)</i>	193	6.20
<i>DRB1*04</i>	287	9.22
<i>DRB1*07</i>	267	8.57
<i>DRB1*08</i>	47	1.51
<i>DRB1*09</i>	298	9.57
<i>DRB1*10</i>	64	2.06
<i>DRB1*11</i>	160	5.14
<i>DRB1*12</i>	499	16.02
<i>DRB1*13</i>	72	2.31
<i>DRB1*14</i>	308	9.89
<i>DRB1*15</i>	745	23.92
<i>DRB1*16</i>	168	5.40
<i>DQB1</i> allele		
<i>DQB1*02</i>	419	13.46
<i>DQB1*03(DQ7)</i>	517	16.60
<i>DQB1*03(DQ8)</i>	149	4.79
<i>DQB1*03(DQ9)</i>	340	10.92
<i>DQB1*04</i>	134	4.30
<i>DQB1*05</i>	1264	40.59
<i>DQB1*06</i>	291	9.34

The *DRB1*-*DQB1* haplotype frequencies among deceased kidney donors are shown in Table 2. Five haplotypes, including *DRB1*15-DQB1*05*, *DRB1*12-DQB1*03* (DQ7), *DRB1*09-DQB1*03* (DQ9), *DRB1*14-DQB1*05*, and *DRB1*07-DQB1*02*, were frequently observed among this study population. The rare haplotype frequencies of *DRB1*03* (DR17)-*DQB1*03* (DQ7), *DRB1*04-DQB1*05*, *DRB1*07-DQB1*05*, *DRB1*08-DQB1*03* (DQ7), *DRB1*12-DQB1*06*, and *DRB1*03* (DR17)-*DQB1*03* (DQ9) were also observed. The distribution of *DRB1*-*DQB1* haplotype frequencies among 1,557 deceased kidney donors was analyzed by using unequivocal haplotype assignment and sorted from low to high frequencies, as shown in Figure 1.

Among 2,709 patients who were registered with HLA-A, -B, -DR, and -DQ typing results and received kidneys

from 1,468 deceased donors between January 2019 and December 2024, 75 patients received zero HLA-ABDR mismatch donors (0:0:0). Of these, 54 patients had zero HLA-DQ mismatches, 19 patients had one HLA-DQ mismatch, and 2 patients had two HLA-DQ mismatches. Regarding graft survival in these patients, one patient with zero HLA-DQ mismatch and one patient with one HLA-DQ mismatch experienced graft rejection with graft loss at day 436 and 552, respectively. Survival of renal allografts in 75 patients with zero HLA-ABDR mismatch donors, stratified by HLA-DQ match and mismatch. Patients with two HLA-DQ mismatched alleles had a lower survival rate than the other groups. The difference among the three groups was statistically significant, as determined by the univariate Chi-squared analysis (log-rank test, *p*-value = 0.049), as shown in Figure 2.

Table 2 HLA-DRB1 and DQB1 haplotype frequencies among deceased donors (n = 1,557)

Haplotype	Observed	Haplotype frequency (%)
DRB1*01-DQB1*05	6	0.19
DRB1*03(DR17)-DQB1*02	192	6.17
DRB1*03(DR17)- DQB1*03(DQ7)	1	0.03
DRB1*04-DQB1*04	129	4.14
DRB1*04-DQB1*05	1	0.03
DRB1*04- DQB1*03(DQ7)	11	0.35
DRB1*04- DQB1*03(DQ8)	146	4.69
DRB1*07-DQB1*02	227	7.29
DRB1*07-DQB1*05	1	0.03
DRB1*07- DQB1*03(DQ9)	38	1.22
DRB1*08-DQB1*04	4	0.13
DRB1*08-DQB1*06	42	1.35
DRB1*08- DQB1*03(DQ7)	1	0.03
DRB1*09- DQB1*03(DQ8)	2	0.06
DRB1*09- DQB1*03(DQ9)	296	9.51
DRB1*10-DQB1*05	64	2.06
DRB1*11-DQB1*05	5	0.16
DRB1*11-DQB1*06	3	0.10
DRB1*11- DQB1*03(DQ7)	152	4.88
DRB1*12-DQB1*05	183	5.88
DRB1*12-DQB1*06	1	0.03
DRB1*12- DQB1*03(DQ7)	315	10.12
DRB1*13-DQB1*05	2	0.06
DRB1*13-DQB1*06	42	1.35
DRB1*13- DQB1*03(DQ7)	28	0.90
DRB1*14-DQB1*05	288	9.25
DRB1*14-DQB1*06	12	0.39
DRB1*14- DQB1*03(DQ7)	8	0.26
DRB1*15-DQB1*05	550	17.66
DRB1*15-DQB1*06	192	6.17
DRB1*15- DQB1*03(DQ7)	3	0.10
DRB1*16-DQB1*05	168	5.39
DRB1*03(DR17)-DQB1*03(DQ9)	1	0.03

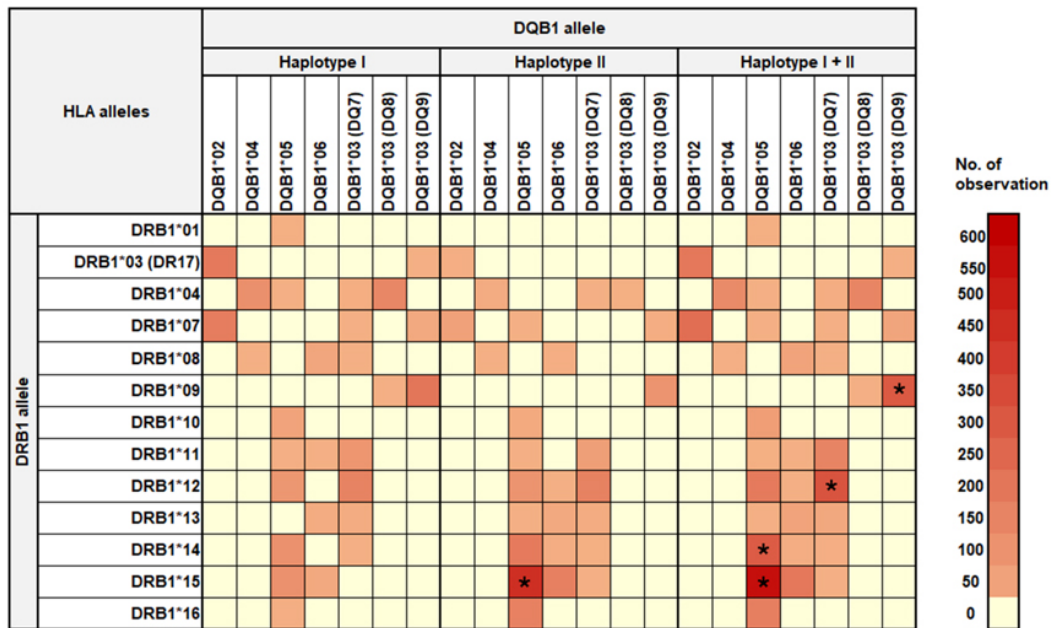


Figure 1 HLA-DRB1-DQB1 haplotype frequencies among deceased kidney donors. Haplotypes observed more than 250 times are marked with an asterisk (*) in a box. Haplotype I represents the frequencies observed in this study, Haplotype II represents previously published data from Thai population⁸, and Haplotype I+II indicates the combined dataset from both studies. DRB1*15-DQB1*05, DRB1*12-DQB1*03 (DQ7), DRB1*09-DQB1*03 (DQ9) and DRB1*14-DQB1*05 were most frequently observed among the Thai population

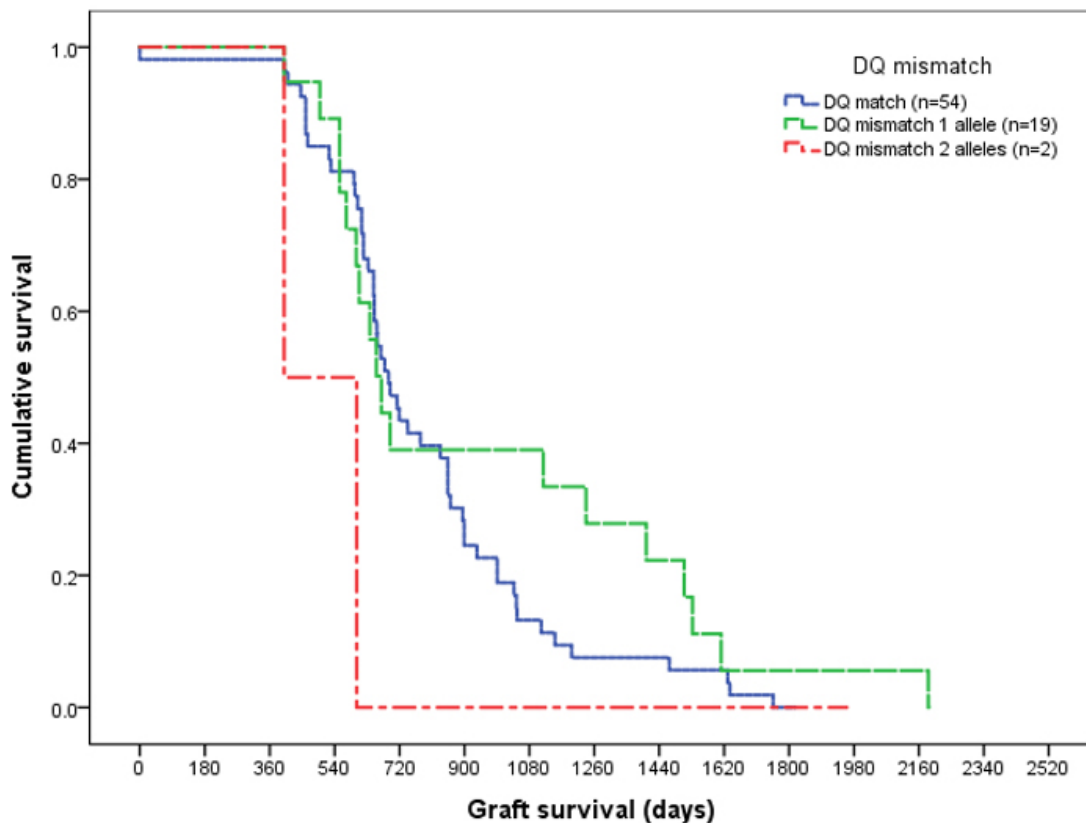


Figure 2 Kaplan-Meier curves comparing graft survival among patients with DQ match, DQ mismatch-1, and DQ mismatch-2 alleles.

Discussion

In this retrospective study, we analyzed the frequencies of HLA class II alleles, including *HLA-DRB1* and *-DQB1* alleles, among 1,557 deceased kidney donors over a period of 5 years (2019-2024). Regarding *HLA-DRB1* alleles, their frequencies were similar to related studies in deceased kidney donors and the Thai Stem Cell Donor Registry.^{14,19} *HLA-DRB1* and *-DQB1* frequencies were consistent with other reports in Thai populations. The frequencies of *HLA-DRB1*12* and *HLA-DRB1*15* alleles were frequently found in different Thai populations, including deceased kidney donors, present-day Thais, and Northeast Thais.^{20,21} *HLA-DRB1*03* (DR18) allele was not observed in this study, confirming that it is a rare allele in Thai populations. Further studies of larger sample sizes are recommended.

Concerning *HLA-DQB1* alleles, their frequencies were similar to related studies in Thai populations.^{20,21} The frequencies of *HLA-DQB1*05* and *HLA-DQB1*03* (DQ7) alleles were most frequently observed among deceased kidney donors and the other groups, including present-day Thais and Northeast Thais.^{18, 20-21} Even though *HLA-DRB1* and *HLA-DQB1* alleles are in strong linkage disequilibrium within different populations, associations between *HLA-DRB1* and *DQB1* alleles are usually weak or limited to some haplotypes.²² Particular allelic combinations, referred to as conserved haplotypes, have been well documented in Thai populations.^{18, 20-21}

In this study, we also analyzed the distribution of the DRB1-DQB1 haplotype frequencies among 1,557 deceased kidney donors. We found that two common haplotypes, including DRB1*15-DQB1*05 and DRB1*12-DQB1*03 (DQ7), were identified, corresponding to the predominant *DRB1* and *DQB1* alleles, this study population. Similar results were also reported in healthy Thai individuals and patients with knee osteoarthritis aged over 45 years.²³ Further studies focusing on HLA-DRB1-DQB1 haplotypes may provide an impact on susceptibility or resistance to disease in Thai populations. An unusual HLA-DRB1*15:01-DQB1*02:01 haplotype has

been reported in a healthy candidate for stem cell donation. The subsequent analysis of the relatives revealed that its formation has most likely occurred within or beyond the generation, which might be due to a crossing-over event during spermatogenesis.²⁴ A limitation of this study is that we could not confirm the definite pattern of uncommon DRB1-DQB1 haplotypes found among deceased kidney donors. Because DRB1-DQB1 haplotypes are typically inherited together and their frequencies vary across different ethnic populations, it is possible that these uncommon haplotypes may have arisen through recombination or crossing-over events. To ensure accurate haplotype assignment, confirmatory testing using third generation sequencing or family-based phasing method is recommended.

HLA-DQ antibodies are frequently detected after kidney transplantation and are more strongly associated with adverse graft outcomes than other HLA antibodies.²⁵ In Thailand, HLA-DQB1 typing results are not currently included in the ODC-TRC kidney allocation criteria, we analyzed graft survival among 75 patients with HLA-ABDR match, incorporating HLA-DQ typing. Graft loss occurred in two patients: one with HLA-DQ match and the other with one HLA-DQ mismatch. The causes of graft rejection in these cases may be attributable to other HLA loci (e.g., HLA-C, -DQA1, -DPB1), patient and donor age, donor-specific antibodies, or treatment factors. To improve compatibility at other HLA loci, new strategies such as allele or epitope matching are recommended to reduce sensitization risks and enhance kidney allocation criteria.²⁶⁻²⁷ An additional study with a larger sample size is suggested.

Conclusion

HLA-A, -B, -DR, and -DQ typing results for both wait-listed patients and deceased donors have been recommended in kidney allocation schemes to reduce the risk of sensitization. HLA-DQB1 typing results are not currently included in the ODC-TRC kidney allocation criteria. This retrospective study identified *HLA-DRB1*

and -*DOB1* allele and haplotype frequencies among deceased kidney donors, providing background information to improve compatibility. Patients with HLA-ABDR match but with two HLA-DQ mismatches showed a lower graft survival rate than the fully matched group.

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