Original Article

HLA mismatch between deceased donors and kidney transplant recipients: a retrospective study from January 2019 to December 2021

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Abstract:

Introduction: *One factor influencing graft function and survival in deceased donor kidney transplantation is human leukocyte antigen (HLA) mismatch between donors and recipients. Up-to-date data of HLA mismatch grades according to kidney allocation criteria of the Organ Donation Centre, Thai Red Cross Society (ODC-TRC) allocation criteria remains unclear.* ***Objective:*** *The study aimed to determine the HLA mismatch between deceased donors and kidney transplant recipients.* ***Materials and Methods:*** *Demographic and laboratory data of deceased donors and kidney transplant recipients from January 2019 to December 2021 from the ODC-TRC Program were analyzed.* ***Results:*** *Among 767 deceased kidney donors, their age ranged from 3 to 66 years and the ratio of males and females in deceased donors was 3.65:1, similar to a related study. The common HLA-A and HLA-B antigens were A2, A11, A24 and A33, and B46, B13, B75 and B18, respectively. HLA-DR15, DR12, DR14 and DR4 were commonly found. No significant difference was observed when HLA frequencies were compared with a related study ($p > 0.05$). Among 1,476 transplanted kidney recipients, BDR1 was the most common mismatch grade (35.23%), followed by BDR2 (33.87%), BDR3 (16.40%), BDR0 (10.44%), and BDR4 groups (4.06%), respectively. Regarding the BDR0 kidney transplant recipients, 92 of 1,476 (6.23%) recipients were ABDR = 0:0:0 (76 from pooled and 16 from retrieval centers).* ***Conclusion:*** *This study showed the mismatch at the HLA-A, -B, and -DR loci between donors and recipients in kidney transplantation. Emphasizing additional loci for HLA mismatch in the national kidney allocation system would be beneficial in reducing the risks of allosensitization and immunosuppression therapy.*

Keywords : ● *HLA antigen* ● *Mismatch* ● *Deceased donors* ● *Kidney transplantation*

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นิพนธ์ต้นฉบับ

HLA mismatch ระหว่างผู้บริจาคที่เสียชีวิตและผู้ป่วยที่ได้รับการปลูกถ่ายไต: การศึกษาย้อนหลังตั้งแต่ มกราคม พ.ศ. 2562 ถึงธันวาคม พ.ศ. 2564

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บทคัดย่อ

บทนำ *ปัจจัยที่ส่งผลต่อหน้าที่และการอยู่รอดของกราฟท์หลังจากการปลูกถ่ายไตจากผู้บริจาคไตสมองตาย คือ ความแตกต่างของ human leukocyte antigen (HLA) mismatch ระหว่างผู้บริจาคไตและผู้ป่วยที่ได้รับไต จนถึงปัจจุบันข้อมูลของเกรด HLA mismatch จากข้อมูลของการจัดสรรไต ศูนย์รับบริจาคอวัยวะ สภากาชาดไทย (ODC-TRC) ยังไม่เป็นที่ชัดเจน* ***วัตถุประสงค์*** *การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาเกี่ยวกับ HLA mismatch ระหว่างผู้บริจาคไตสมองตายและผู้ป่วยที่ได้รับไต* ***วัสดุและวิธีการ*** *ดำเนินการวิเคราะห์ข้อมูลทั่วไปและผลการตรวจทางห้องปฏิบัติการของผู้บริจาคไตสมองตายและผู้ป่วยที่ได้รับไต จากระบบของ ODC-TRC ตั้งแต่เดือนมกราคม พ.ศ. 2562 ถึงเดือนธันวาคม พ.ศ. 2564* ***ผลการศึกษา*** *จากผู้บริจาคไตสมองตายจำนวน 767 ราย พบว่า ช่วงอายุที่พบบ่อย คือ 3 ปี ถึง 66 ปี และสัดส่วนของเพศชายต่อเพศหญิงเท่ากับ 3.65:1 ซึ่งใกล้เคียงกับที่เคยมีรายงานไว้ แอนติเจน HLA-A และ HLA-B ที่พบบ่อยคือ A2, A11, A24 และ A33, และ B46, B13, B75 และ B18 ตามลำดับ HLA-DR15, DR12, DR14 และ DR4 พบได้บ่อย เมื่อเปรียบเทียบความถี่ของแอนติเจน HLA กับที่เคยมีรายงานไว้ไม่พบความแตกต่างกัน ($p > 0.05$) ในผู้ป่วยที่ได้รับไตจำนวน 1,476 รายพบว่า HLA mismatch ชนิด BDR1 พบบ่อยที่สุด (35.23%) รองลงมาคือ BDR2 (33.87%), BDR3 (16.40%), BDR0 (10.44%) และ BDR4 (4.06%) ตามลำดับ สำหรับผู้ป่วยที่ได้รับไตแบบ BDR0 นั้น 92 รายจาก 1,476 ราย (6.23%) เป็น ABDR = 0:0:0 (76 รายจาก pooled และ16 รายจาก retrieval centers)* ***สรุป*** *การศึกษานี้แสดงถึง HLA-A, -B และ -DR mismatch ระหว่างผู้บริจาคไตสมองตายกับผู้ป่วยที่ได้รับการปลูกถ่ายไต การพิจารณา HLA mismatch ที่ loci อื่นเพิ่มเติมในระบบการจัดสรรไตของประเทศจะช่วยในการลดความเสี่ยงต่อการเกิด allosensitization และการใช้ยากดภูมิคุ้มกันต่อไป*

คำสำคัญ : ● *การตรวจชนิด HLA* ● *ความไม่ตรงกัน* ● *ผู้บริจาคไตสมองตาย* ● *การปลูกถ่ายไต*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2565;32:193-200.

Introduction

The Organ Donation Centre (ODC) and the National Blood Centre (NBC) of Thai Red Cross Society (TRC) are the organizations involved in enrolling patients with end-stage renal diseases requiring deceased donor kidney transplantation and testing ABO blood group and human leukocyte antigen (HLA) compatibilities between donor and recipient.[1] In general, HLA-A, -B, and -DR typing results of the waited-listed patients in each transplant center are submitted and registered in the ODC-TRC kidney allocation program. When receiving notification from the transplant coordinators, the negative results of infectious markers in deceased donors are confirmed by the NBC-TRC, the HLA-A, -B, and -DR typing of the deceased donor will be examined. The donor ABO blood group, Rh(D), and HLA typing results are submitted to the kidney allocation program to search for the sequences of patients' scores. The serum samples of waited-listed patients with the highest overall score from HLA-A, -B, and -DR mismatches, panel reactive antibody (PRA) and renal waiting time can be selected for HLA crossmatch with donor T and B lymphocytes. Patients with negative HLA crossmatch could be crucially transplanted.[2,3]

The degree of HLA mismatch for deceased donor kidney transplantation is the number of broad antigen specificities (as defined by serological nomenclature)[3] mismatched at the HLA-A, -B, and -DR loci. A totally HLA mismatched transplant is referred to as a 2:2:2, while a 0:0:0 transplant would indicate no mismatched at any three loci.[4-7] The Organ Procurement and Transplant Network (OPTN) and Eurotransplant provide antecedence points for candidates for HLA-A, -B and -DR or HLA-DR matching with deceased donors based on the recipient benefits, especially in reducing the incidence of acute graft rejection and improving graft survival.[5,6]

Regarding the ODC-TRC for kidney allocation criteria, one kidney of the deceased donor will be allocated to waited-listed patients in the retrieval team and the other kidney to pooled waited-listed patients among transplant centers.[8] Pretransplant factors influencing the testing time of HLA crossmatch in deceased donor kidney transplantation were previously reported and the appropriate medium for spleen and lymph node transportation to the laboratory was suggested to reduce the problem of cell viability.[3] However, data of HLA mismatch grades between deceased donors and recipients according to current kidney allocation criteria remains unclear. This retrospective study aimed to determine the HLA mismatch between deceased donors and kidney transplant recipients from January 2019 to December 2021.

Materials and Methods

Study populations

The populations used in this retrospective study included the demographic and laboratory data of deceased donors and kidney transplant recipients obtained from the ODC-TRC Program from January 1, 2019 to December 31, 2021.

Data analysis

Regarding the ODC-TRC criteria, all DNA-based HLA-A, -B, and -DR typing results of deceased donors and waited-listed patients 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)[9] and the HLA dictionary.[10]

Statistical analysis

Descriptive analysis was conducted to characterize the baseline demographic data of deceased donors and kidney transplant recipients and expressed in numbers and percentages. HLA-A, -B, and -DR antigen frequencies of deceased donors were analyzed as antigen frequency (AF) using the following formula: %AF = (sum of each antigen/ 2N) × 100 for the different antigen frequencies. HLA-A, -B, and -DR antigen frequencies were compared with a related study, previously reported[11] and analyzed by paired *t*-test using SPSS Software (Version 16.0; SPSS Inc., Chicago, IL, USA). A *p*-value of less than 0.05 was considered to be significantly different.

Results

The data from the ODC-TRC Program, from January 1, 2019 to December 31, 2021, included 767 deceased kidney donors and 1,476 kidney transplant recipients. Among 767 deceased donors, ages ranged from 3 to 66 years, and the most common age group was 41 to 50 years (26.08%), followed by 51 to 60 years (19.69%), and 31 to 40 years (19.30%), consecutively. For kidney transplant recipients, ages ranged from 8 to 83 years, and the most common age group was 51 to 60 years (27.03%), followed by 41 to 50 years (26.76%), and 31 to 40 years (21.61%), successively. Male to female ratio among deceased donors and kidney transplant recipients were 602/165 (3.65:1) and 911/565 (1.61:1), as shown in Table 1.

HLA-A, -B and DR antigen frequencies among deceased donors are summarized in Table 2. Antigen frequencies commonly observed more than 5% in each HLA locus were HLA-A2, A11, A24, and A33: HLA-B46, B13, B75, B58, B18, B51, and B60; HLA-DR15, DR12, DR14, DR4, DR9, DR7, and DR17. The details of antigen frequencies are shown in Table 2. Frequencies of HLA-A, -B, and -DR antigens among deceased donors from 2019 to 2021 were compared with the data previously reported from 1996 to 2018, without significant difference ($p > 0.05$).

The HLA-B and -DR mismatch grades between deceased donors and kidney transplant recipients in this study are shown in Table 3 and Figure 1. Among 1,476 transplanted kidney recipients, BDR1 was the most common mismatch grade (35.23%), followed by BDR2 (33.87%), BDR3 (16.40%), BDR0 (10.44%) and BDR4 groups (4.06%), consecutively. Of the 604 kidney transplant recipients in the retrieval transplant centers, BDR2 was the most common (15.24%), followed by BDR3 (10.64%), BDR1 (9.82%), BDR4 (3.31%), and BDR0 groups (1.90%), sequentially. In addition, among 872 kidney transplant recipients in the pooled transplant centers, BDR1 was the most common (25.41%), followed by BDR2 (18.63%), BDR0 (8.54%), BDR3 (5.76%), and BDR4 groups (0.75%), consecutively. Regarding the BDR0 kidney transplant recipients (data not shown), 92 of 1,476 (6.23%) recipients were ABDR = 0:0:0 (76 from pooled and 16 from retrieval centers).

Discussion

Regarding the kidney allocation criteria, the HLA compatibilities among patients and deceased kidney donors are mainly involved in graft survival and function.[12-15] Notably, HLA matching is recommended to reduce allosensitization and donor-specific antibody

Table 1 Characteristics of study populations

Characteristics	Deceased donors		Kidney transplant recipients	
	Number (n = 767)	%	Number (n = 1,476)	%
Sex				
- Male	602	78.49	911	61.72
- Female	165	21.51	565	38.28
Age range (years)				
- 1-20	127	16.56	49	3.32
- 21-30	124	16.17	124	8.40
- 31-40	148	19.30	319	21.61
- 41-50	200	26.08	395	26.76
- 51-60	151	19.69	399	27.03
- 61-70	17	2.22	157	10.64
- > 70	0	0.00	33	2.24

Table 2 Antigen frequencies of HLA-A, -B and -DR among deceased kidney donors in this study (2019-2021) compared with a previous study (1996-2018)

Antigen	Frequency in study period (%)		Antigen	Frequency in study period (%)		Antigen	Frequency in study period (%)	
	1996-2018	2019-2021		1996-2018	2019-2021		1996-2018	2019-2021
A1	1.9	1.89	B7	3.58	3.19	DR1	0.45	0.33
A2	28.07	27.84	B8	0.66	0.26	DR4	9.62	9.58
A3	0.68	0.39	B13	8.92	9.97	DR7	7.7	8.22
A11	29.29	27.58	B18	6.63	6.58	DR8	1.88	1.69
A23	0.07	0.00	B27	3.83	3.65	DR9	10.91	8.74
A24	18.56	19.69	B35	3.78	3.45	DR10	1.92	2.09
A26	1.63	1.76	B37	0.48	0.59	DR11	5.75	4.56
A29	0.72	0.72	B38	3.46	4.37	DR12	15.91	16.43
A30	2.08	1.69	B39	2.94	3.71	DR13	2.47	2.41
A31	1.2	0.65	B41	0.05	0.07	DR14	8.96	10.23
A32	0.27	0.13	B44	4.5	5.15	DR15	23.38	24.84
A33	12.06	13.56	B45	0.02	0.07	DR16	5.25	4.43
A34	1.36	1.17	B46	15.93	15.12	DR17	5.79	6.45
A66	0.02	0.00	B47	0.02	0.00			
A68	0.84	1.30	B48	0.81	0.59			
A74	1.24	1.63	B49	0.02	0.00			
			B50	0.05	0.20			
			B51	5.39	5.34			
			B52	2.31	1.69			
			B53	0.05	0.07			
			B54	0.7	0.65			
			B55	1.77	1.76			
			B56	1.81	1.76			
			B57	1.18	1.11			
			B58	6.29	7.89			
			B60	6.45	5.28			
			B61	3.44	3.52			
			B62	5.89	4.37			
			B63	0.29	0.20			
			B65	0.09	0.07			
			B67	0.05	0.00			
			B71	0.29	0.32			
			B72	0.02	0.07			
			B75	7.63	8.08			
			B76	0.34	0.39			
			B77	0.32	0.46			
			B81	0.02	0.00			

Table 3 HLA mismatch between deceased donors and kidney transplant recipients

HLA mismatch grade[12]	Number of recipients from		Total
	Retrieved	Pooled	
- BDR 0	28 (1.90%)	126 (8.54%)	154 (10.44%)
- BDR 1	145 (9.82%)	375 (25.41%)	520 (35.23%)
- BDR 2	225 (15.24%)	275 (18.63%)	500 (33.87%)
- BDR 3	157 (10.64%)	85 (5.76%)	242 (16.40%)
- BDR 4	49 (3.31%)	11 (0.75%)	60 (4.06%)
- BDR 4 A0	7 (0.47%)	2 (0.14%)	9 (0.61%)
- BDR 4 A1	25 (1.69%)	5 (0.34%)	30 (2.03%)
- BDR 4 A2	17 (1.15%)	4 (0.27%)	21 (1.42%)
Total	**604 (40.91%)**	**872 (59.09%)**	**1,476 (100.0%)**

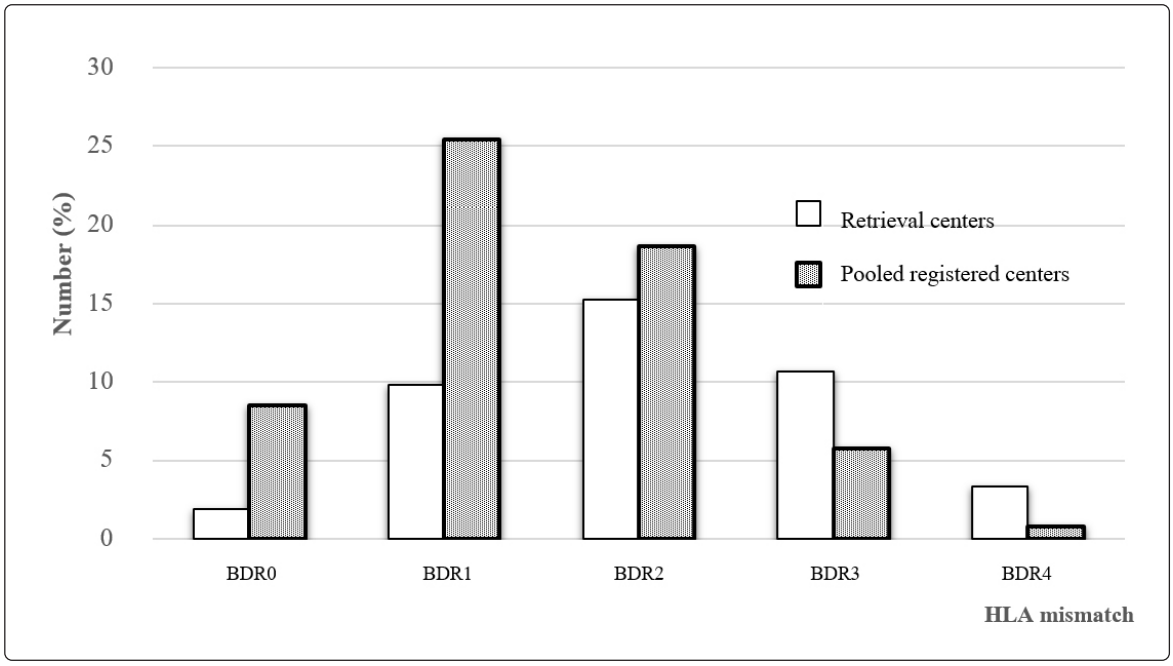

Figure 1 Percentage of HLA mismatch between deceased donors and kidney transplant recipients

production after kidney transplantation.[13] A related study conducted among more than 1,000 deceased donor kidney transplants in the USA revealed that patients receiving HLA-A, -B, and -DR matched kidney transplantation had one-year graft survival and half-life at better than HLA mismatch.[16] Moreover, patients with ABDR zero mismatch (0:0:0) had a lower risk of graft failure than patients with an increased number of HLA mismatches.[17,18]

In this retrospective study, we reported the HLA mismatch between deceased donors and kidney transplant recipients according to the information obtained from the ODC-TRC Program. The ratio of males to females among deceased donors was 3.65:1, and their age ranges were similar to a related study reported by Ounjai, et al. in 2019.[11] Additionally, HLA-A, -B, and -DR antigen frequencies among 767 donors showed no significant difference compared with the frequencies among 2,209 donors, a study covering the years 1996 to 2018.[11] The rare antigens including HLA-A23, A66, B47, B49, B67 and B81 were not found in this study, which may be due to their low incidence among Thai population.

For HLA mismatch grades, BDR1 was frequently found (35.23%) among 1,476 kidney transplant recipients, similar to 872 recipients in the pooled transplant centers. In contrast, BDR2 was higher than BDR1 among 604 recipients in the retrieval transplant centers, which might have been due to the lower numbers of waited-list patients registered in each retrieval center than in the pooled transplant centers. The high number of waited-list patients have a better chance of finding HLA-matched grades than the low number of patients. This reflects the chance of finding a better BDR mismatch grade in the pooled transplant centers. Among 92 of 154 BDR0 kidney transplant recipients were ABDR = 0:0:0 (data not shown in table) and the most were from the pooled transplant centers. A related study revealed that HLA-A, -B, -DR, and HLA-DQ mismatches could be implemented in the kidney allocation scheme to minimize the subsequent risk of sensitization, especially among patients listed for repeat transplantation.[19-21] In addition, HLA-DP typing was suggested for donor and patient before transplantation to reduce the HLA-DP DSA formation.[22] In addition, related studies reported that one patient with only HLA-C mismatch and a patient with anti-Cw5 antibody experienced renal allograft rejection.[23,24] Therefore, to improve the patient's graft outcome after kidney transplantation, the assessment to increase the number of HLA mismatches at all loci is suggested for new kidney allocation criteria.

Conclusion

This study showed the mismatch at the HLA-A, -B, and -DR loci between donors and recipients in deceased donor kidney transplantation. Emphasizing additional loci for HLA mismatch grade in the national kidney allocation criteria would be beneficial in reducing the risks of allosensitization and immunosuppression therapy.

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