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PHẠM LÊ NHẬT MINH

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IDENTIFYING THE HLA ALLELE FREQUENCY OF RENAL DONORS AND RECIPIENTS AND EVALUATING THE INFLUENCE OF HLA MISMATCHING RATES TO GRAFT SURVIVAL IN RENAL TRANSPLANTED PATIENTS

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Assoc-Prof Nguyễn Thị Thu Hoài, PhD

SUMMARY OF PHD DISSERTATION

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1	HLA Compatibility and Graft Survival Rates Among Related and Unrelated Donors in Renal Transplantation	**Nhat-Minh Le Pham**, Thinh Phuc Ong, Nguyen Lam Vuong, Thi Thu Hoai Nguyen	Transplantation Proceedings, 2024	SCI-e, ISSN/ eISSN: 0041-1345/ 1873-2623	0.8	Q3
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3	Frequency of Human Leukocyte Antigen (HLA) of unrelated renal donors and recipients	**Pham Le Nhat Minh**, Nguyen Thi Thu Hoai, Tran Van Bao	Vietnam Medical Journal, 2020	ISSN: 1859-1868		

CONTENTS

ABSTRACT

IDENTIFYING THE HLA ALLELE FREQUENCY OF RENAL DONORS AND RECIPIENTS AND EVALUATING THE INFLUENCE OF HLA MISMATCHING RATES TO GRAFT SURVIVAL IN RENAL TRANSPLANTED PATIENTS

Phạm Lê Nhật Minh

School of Biotechnology

International University, VNU-HCM

Background: HLA is the most diverse genetic system in humans, with inconsistent allele distribution among ethnic groups. Previous global research has shown that HLA plays a crucial role in graft survival after renal transplantation. The main risk factor for graft rejection is the rate of HLA allele mismatch between donors and recipients. However, there is limited research in Vietnam on HLA profiles of ESRD patients and their donors, as well as the impact of HLA matching rates on graft survival.

Aims: This study aims to analyze HLA profiles of healthy donors and ESRD patients and investigate the impact of HLA mismatching rates on graft survival in recipients after renal transplantation.

Methods: A prospective study was conducted in Cho Ray Blood Transfusion Center, Cho Ray Hospital in Ho Chi Minh City, Vietnam from March 2018 to December 2020. The study included 458 participants, consisting of healthy donors and ESRD patients. Participants were divided into two groups: unrelated group included unrelated donors-patients (URD) and related group included related donors-patients (RD). The URD group had 98 ESRD patients and 108 unrelated donors, while the RD group had 126 ESRD patients with their corresponding related donors. HLA typing was conducted using the PCR-SSO method with Luminex technology. Mismatching rates for HLA alleles were recorded for recipients and donor pairs in each group for five loci: HLA-DRB1, HLA-B, HLA-A, HLA-DQA1, and HLA-DQB1. The graft survival rates among 458 previous participants were monitored, including 82 recipients and donor pairs in URD group and

126 recipients and donor pairs in RD group (416/458). The recipients were followed up in post-transplantation in Cho Ray hospital and People's Hospital 115, Ho Chi Minh City, Vietnam. There were 124 recipients in RD group and 45 recipients in URD group at Cho Ray Hospital were monitored for changing some crutial laboratory indicators in pre- and post-transplant to investigate the graft function, such as: hemoglobin, BUN, serum creatinine, eGFR, proteinuria levels and the detection of BK virus infection.

Results: The study detected some certain alleles such as HLA-B*07 (*OR* = 1.951; *95% CI* = 1.032–3.688; *p* = 0.040), DQA1*06 (*OR* = 1.630; *95% CI* = 1.044–2.545; *p* = 0.031) and DQB1*03 (*OR* = 1.515; *95% CI* = 1.027–2.235; *p* = 0.036) were associated with susceptibility to ESRD while others like HLA-B*27 (*OR* = 0.175; *95% CI* = 0.039–0.793; *p* = 0.024) và DQB1*02 (*OR* = 0.337; *95% CI* = 0.154–0.736; *p* = 0.006) showed a decreased risk of developing ESRD. URD group had higher rates of HLA mismatch (MM). Meanwhile, RD group showed higher rates of both partial and complete matches for all HLA loci. An HLA mismatch of 9-10 MM was associated with a significantly higher risk of suspected graft rejection, being 7.99 times greater than the risk associated with an HLA mismatch of 5-8 MM with 1-2 DRB1 MM (p = 0.013). Over the 30-month follow-up, RD group showed significantly higher overall survival rate (p=0.0086) and better-free survival rate (p=0.0025) compared to URD group. In URD group, the donors older than five years increased the risk of suspected graft rejection by a hazard ratio of 4.2, while positive anti-HLA antibodies raised this risk with a hazard ratio of 4.5. Male-male donor-recipient pairs decreased the risk of suspected graft rejection by 88% when compared to female-female pairs. We monitored the changes some crucial laboratory data for recipients and observed that these data showed dramatic improvement post-transplantation in both groups. However, the recipients within RD group had a higher proportion of BK virus infections compared to recipients in the URD group.

Conclusions: Alleles HLA-B*07 (p = 0.040), -DQA1*06 (p = 0.031), and -DQB1*03 (p = 0.036) were identified as risk alleles for ESRD, while HLA-B*27 (p = 0.024) and -DQB1*02 (p = 0.006) were associated with a lower risk of ESRD. Over a 30-month follow-up, recipients in the RD group showed significantly higher overall survival (p = 0.0086) and better event free survival rates (p = 0.0025) compared to the URD group. The URD group had a higher incidence of HLA mismatches, while the RD group exhibited

more partial and complete matches across all HLA loci. An HLA mismatch of 9-10 MM was linked to a significantly increased risk of suspected graft rejection, being 7.99 times higher than a mismatch level of 5-8 MM with 1-2 DRB1 MM ($p = 0.013$). Both groups showed significant improvements for key laboratory values, including hemoglobin, BUN, serum creatinine, eGFR, urine protein levels, but the RD group had a higher prevalence of BK virus infections compared to the URD group.

Keywords: Allele; Human Leukocyte Antigen (HLA); Healthy donors; HLA mismatching; Graft survival; Recipients; Renal transplantation.

CHAPTER 1: GENERAL INTRODUCTION

1.1 Introduction

Organ transplantation is a great achievement of mankind. It is considered a fantastic progress in medicine. Nowadays, transplantation becomes the main part of the globalization procedure of the world. Organ transplantation can save lives in each country in the world with different economies, culture and social conditions. However, we have to face some problems in the new century on the transplantation.

Human leukocyte antigen (HLA) genes encode major histocompatibility complex proteins in humans and are responsible for immune system regulation. The association between HLA alleles and renal disorders has been described from many years ago. In recent years, the association between HLA alleles and ESRD has been proposed, as several of both HLA class I and class II alleles were found as protective or risk factors of ESRD in a variety of studies worldwide. The identification of such associated alleles is not only important for screening high risk ESRD patients, but also extends our understanding of the disease mechanism which could help to accelerate the development of more effective, safe and targeted therapies. Moreover, the susceptible alleles can be avoided when selecting optimal donors to increase the post-transplant long-term survival for ESRD patients.

In previous publications, HLA mismatching has been recorded as the critical issue for graft survival on renal transplantation. Furthermore, these studies also suggested risk factors related to graft survival and HLA alleles mismatching between donors and recipients on renal transplantation. However, there is not much information in Vietnam on the HLA profile of patients with ESRD as well as healthy donors, especially the relationship between the HLA mismatching on prior-renal transplantation and its influence to graft survival on post transplantation has not fully reported. The lack of this information in Vietnam causes lots of difficulties in finding matched donors in due time as well as performing early warning for clinicians to choose the matching pairs for renal transplantation and ensure the long graft survival as well as prevent the graft rejection for patients. Therefore, we would like to perform a study named ***"Identifying the HLA allele frequency of renal donors and recipients and evaluating the influence of HLA mismatching rates to graft survival in renal transplanted patients"***

1.2 Aims and Objectives of the study

This study aims to identify the HLA allele frequency of renal donors and recipients and evaluate the influence of HLA mismatching rates to graft survival in renal transplanted patients.

Objectives of the study included:

a. Determine the frequency of HLA alleles of renal donors and recipients
b. Analyze the compatibility of HLA between renal transplanted donors and recipients
c. Evaluate the influence of HLA mismatching on the graft survival rate in renal transplanted patients.

CHAPTER 2: STUDY SUBJECTS AND METHODOLOGY

2.1 Study subjects and methodology

A prospective study was conducted from March 2018 to December 2020. Participants collected samples at Cho Ray blood transfusion center-Cho Ray Hospital. Transplanted patients were followed up at Cho Ray Hospital and People's Hospital 115 in Ho Chi Minh City.

The Ethics review committee of Cho Ray Hospital, Ho Chi Minh City, Vietnam, approved this study (approval number: 1111/CN-HĐĐĐ) and People's Hospital 115, Ho Chi Minh City, Vietnam, approved this study (approval number: 1442/BVND115-NCKH).

There were 458 participants who joined in the study including healthy donors and ESRD patients (or recipients). The participants were divided into 2 groups: unrelated group included unrelated donors-recipients (URD) and related group included related donors-recipients (RD). Based on two groups, 98 ESRD patients and 108 unrelated donors, and 126 ESRD patients came with their 126 related donors. HLA typing was conducted using the PCR-SSO method with Luminex technology.

There were 82 donor-recipient pairs in the URD group and 126 donor-recipient pairs in the RD group who received kidney transplants out of 458 participants in the initial study (416/458). Mismatching rates for HLA alleles were recorded for recipients and donor pairs in each group for five loci: HLA-DRB1, HLA-B, HLA-A, HLA-DQA1, and HLA-DQB1.

We followed up 208 transplanted patients of RD and URD groups of which 126 patients in RD group and 82 patients came from URD group. These recipients were monitored to assess HLA incompatibility in the pre-transplant phase and the impact of HLA incompatibility on graft survival through follow-up and documentation of information in the patients' medical profiles at each follow-up visit, such as the free of suspected graft rejection rate; the free of graft loss; the overall survival rate; and the rate of survival without incidents of acute rejection and/or graft loss (the event-free survival rate) at one month, three months, six months, nine months, twelve months, fifteen months, eighteen months, twenty-one months,

twenty-four months, and thirty months post-kidney transplantation and within the study period. The recipients were followed up in post-transplantation in Cho Ray hospital and People's Hospital 115, Ho Chi Minh City, Vietnam

There were 124 recipients in RD group and 42 recipients in URD group at Cho Ray Hospital were recorded the changes of laboratory data in post-transplantation from March 2018 to December 2020 as for hemoglobin, BUN (Blood of Urea Nitrogen), Creatinine in serum, eGFR, protein level in urine, BK virus infection. Data were collected from the patients' medical profiles during the study period.

Clinical outcome definitions:

The suspected graft rejection rate refers to the clinical suspicion that a transplanted organ, such as a kidney, may be undergoing rejection by the recipient's immune system. Suspected graft rejection is typically based on clinical signs and symptoms, laboratory tests, and imaging findings suggesting possible rejection. These signs may include elevated serum creatinine levels (indicating decreased kidney function), fever, pain or tenderness over the transplant site, decreased urine output, swelling or fluid retention, and changes in blood pressure.

The graft loss rate was defined as an acute, irreversible decline in graft function that does not respond to immunosuppressive treatment and confirmed by biopsy.

The overall survival rate is determined by calculating the percentage of patients who are alive at the end of the follow-up period.

The event-free survival rate is the percentage of patients who are alive until the end of the follow-up period without suspected graft rejection or graft loss.

2.2 Workflow of the study

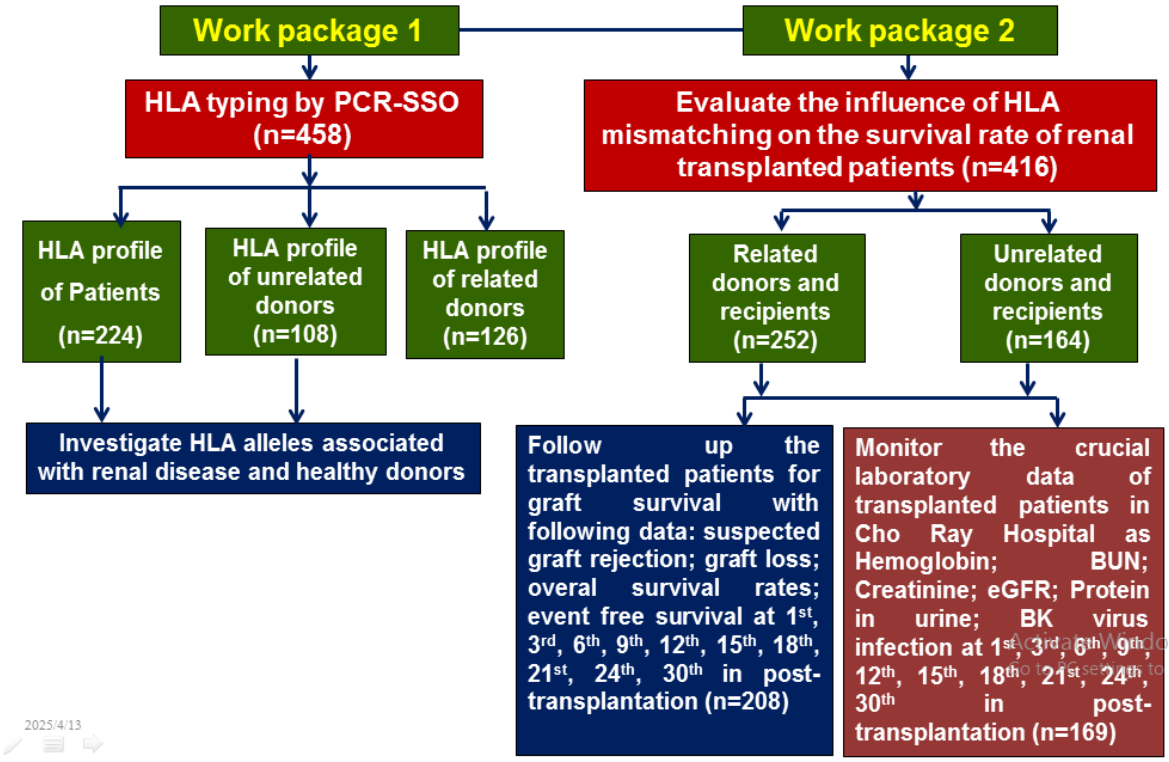

Figure 2.1: Workflow of the study

CHAPTER 3: RESULTS

3.1 Workflow of study result

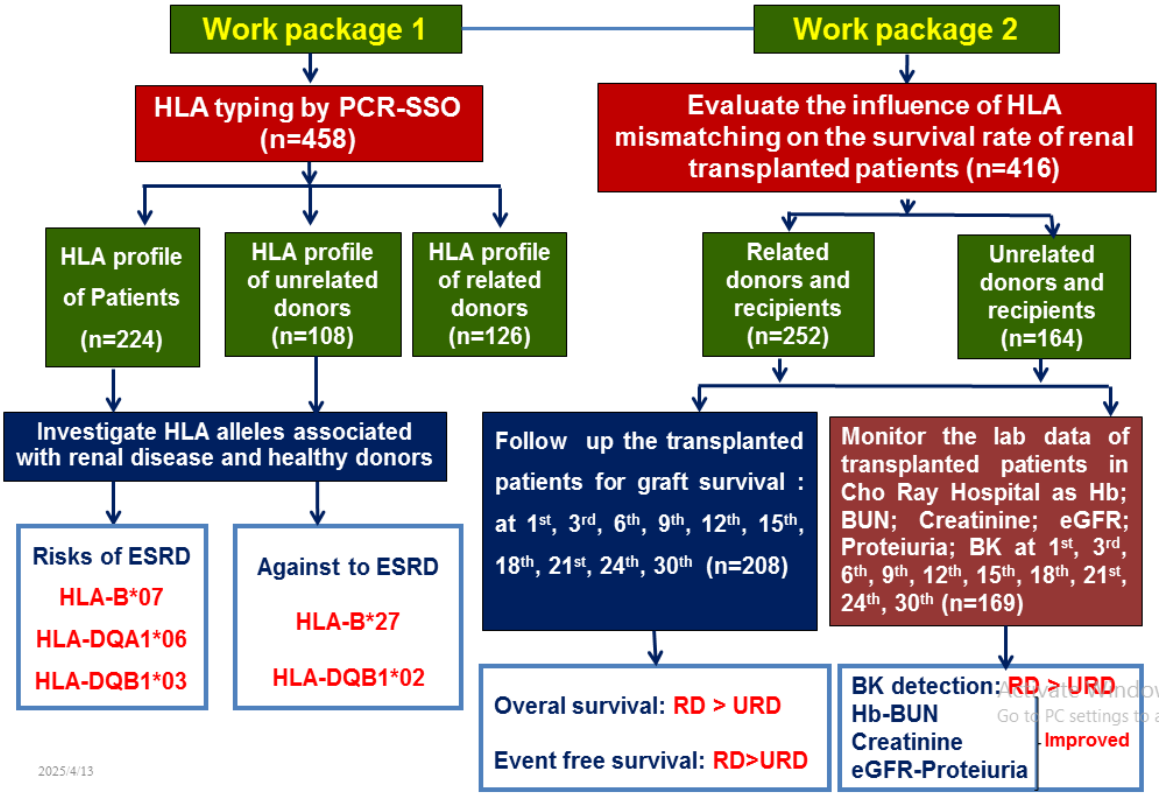

Figure 3.1: Workflow of study result

3.2 HLA alleles of unrelated donors-recipients and related donors-recipients and their association with ESRD patients and donors.

3.2.1 Demographic characteristics of participants

A total of 458 participants were enrolled in the study, of which 98 ESRD patients (recipients) and 108 unrelated donors, and 126 ESRD patients (recipients) came with their 126 related donors. Most ESRD patients were men (66.7% and 64.3%) with mean age of 34.1 ± 9.5 years and 41.0 ± 9.7 years, respectively. The majority of donors in URD group were men with mean age of 38.2 ± 11.9 years, while most donors in RD group were women at a higher age (mean: 52.1 ± 8.8 years) (Table 3.1).

Table 3.1: Demographic characteristics of participants

	Related group		Unrelated group	
	Donors (N=126)	**Recipients (N=126)**	**Donors (N=108)**	**Recipients (N=98)**
Age (years)				
Mean ± SD	52.1 ± 8.8	34.1 ± 9.5	38.2 ± 11.9	41.0 ± 9.7
Median (IQR)	54 (47 - 59)	33 (27 - 39)	36 (29 - 48)	40 (34 - 48)
Range	28 - 68	17 - 67	20 - 69	21 - 65
Age group (years)				
<18	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)
18-30	3 (2.4)	45 (35.7)	35 (32.4)	12 (12.2)
31-40	11 (8.7)	52 (41.3)	31 (28.7)	38 (38.8)
41-50	35 (27.8)	19 (15.1)	23 (21.3)	35 (35.7)
51-60	55 (43.7)	7 (5.6)	13 (12.0)	10 (10.2)
>60	22 (17.5)	1 (0.8)	6 (5.6)	3 (3.1)
Sex				
Male	57 (45.2)	84 (66.7)	69 (63.9)	63 (64.3)
Female	69 (54.8)	42 (33.3)	39 (36.1)	35 35.7)

3.2.2 HLA class I typing of donors and ESRD patients

HLA profiles were similar between s and donors. At the HLA-A and HLA-B loci, A*02, A*11, A*24 and B*15, B*07 were the most frequently found among both recipients (24.5%, 32.1%, 16.7%, 26.1%, 12.7%, respectively) and donors (22.4%, 29.8%, 18.2%, 23.4%, 9.9%). Allele HLA-B*7 was significantly higher in the ESRD patients than donors in URD group. Contrasly, allele HLA-B*27 was presented with a higher percentage in the donors than ESRD patients in URD group (Table 3.2).

Table 3.2: HLA class I typing of donors and ESRD patients

	Related group			Unrelated group		
	Donors (N=252)[1]	**Recipients (N=252)[1]**	**p-value**	**Donors (N=216)[1]**	**Recipients (N=196)[1]**	**p-value**
HLA-A						
1	7 (2.8)	4 (1.6)	0.367	3 (1.4)	4 (2.0)	0.611
2	64 (25.4)	68 (27.0)	0.685	42 (19.4)	43 (21.9)	0.532
3	2 (0.8)	1 (0.4)	0.570	4 (1.9)	1 (0.5)	0.246
11	74 (29.4)	82 (32.5)	0.441	65 (30.1)	62 (31.6)	0.735
23	1 (0.4)	0 (0.0)	-			
24	39 (15.5)	44 (17.5)	0.548	45 (20.8)	31 (15.8)	0.191
26	3 (1.2)	4 (1.6)	0.704	7 (3.2)	5 (2.6)	0.678
29	24 (9.5)	22 (8.7)	0.757	12 (5.6)	19 (9.7)	0.116
30	5 (2.0)	3 (1.2)	0.481	2 (0.9)	6 (3.1)	0.139
31	1 (0.4)	2 (0.8)	0.570	2 (0.9)	4 (2.0)	0.358
32	1 (0.4)	0 (0.0)	-	1 (0.5)	0 (0.0)	-
33	25 (9.9)	17 (6.7)	0.200	29 (13.4)	19 (9.7)	0.240
34	2 (0.8)	4 (1.6)	0.421	3 (1.4)	0 (0.0)	-
68	1 (0.4)	1 (0.4)	1.000	1 (0.5)	0 (0.0)	-
74	3 (1.2)	0 (0.0)	-	0 (0.0)	1 (0.5)	-
36				0 (0.0)	1 (0.5)	-
HLA-B						
7	30 (11.9)	28 (11.1)	0.780	17 (7.9)	28 (14.3)	**0.040**
13	12 (4.8)	13 (5.2)	0.837	13 (6.0)	8 (4.1)	0.375
14	1 (0.4)	0 (0.0)	-	1 (0.5)	0 (0.0)	-
15	62 (24.6)	66 (26.2)	0.682	48 (22.2)	51 (26.0)	0.368
18	6 (2.4)	4 (1.6)	0.526	4 (1.9)	2 (1.0)	0.488
27	6 (2.4)	9 (3.6)	0.435	12 (5.6)	2 (1.0)	**0.024**
35	14 (5.6)	14 (5.6)	1.000	9 (4.2)	2 (1.0)	0.068
37	2 (0.8)	2 (0.8)	1.000	4 (1.9)	0 (0.0)	-
38	17 (6.7)	14 (5.6)	0.579	10 (4.6)	16 (8.2)	0.146

	Related group			Unrelated group		
	Donors (N=252)[1]	**Recipients (N=252)[1]**	**p-value**	**Donors (N=216)[1]**	**Recipients (N=196)[1]**	**p-value**
39	7 (2.8)	6 (2.4)	0.779	3 (1.4)	3 (1.5)	0.905
40	12 (4.8)	16 (6.3)	0.438	20 (9.3)	17 (8.7)	0.835
41	1 (0.4)	0 (0.0)	-			-
44	2 (0.8)	3 (1.2)	0.655	6 (2.8)	1 (0.5)	0.113
46	18 (7.1)	20 (7.9)	0.736	18 (8.3)	22 (11.2)	0.324
48	5 (2.0)	5 (2.0)	1.000	2 (0.9)	3 (1.5)	0.580
51	10 (4.0)	8 (3.2)	0.632	8 (3.7)	10 (5.1)	0.490
52	1 (0.4)	4 (1.6)	0.213	4 (1.9)	2 (1.0)	0.488
53	1 (0.4)	1 (0.4)	1.000			
54	5 (2.0)	10 (4.0)	0.199	8 (3.7)	6 (3.1)	0.720
55	5 (2.0)	4 (1.6)	0.737	3 (1.4)	5 (2.6)	0.400
56	9 (3.6)	4 (1.6)	0.171	5 (2.3)	3 (1.5)	0.567
57	9 (3.6)	6 (2.4)	0.435	3 (1.4)	5 (2.6)	0.400
58	17 (6.7)	14 (5.6)	0.579	18 (8.3)	9 (4.6)	0.131
67	0 (0.0)	1 (0.4)	-			-
45			-	0 (0.0)	1 (0.5)	-

[1]Number of alleles

*Notes: The HLA allele was summarized by count and percentage for ESRD patients and unrelated and related donors. Frequency and percentage were used to describe categorical data. Allele frequencies of HLA-A, -B were computed by (n/2N)*100, of which n is the total count of an allele and N is the total number of individuals.*

3.2.3 HLA class II typing of donors and ESRD patients

At HLA-DRB1, HLA-DQA1 and HLA-DQB1 loci, DRB1*12, DRB1*09, DQA1*01, DQA1*06, DQB1*03 and DQB1*05 were the most common alleles in all study groups (34.3%, 11.0%, 32.2%, 27.8%, 57.1%, 22.5% among recipients and 28.2%, 12.0%, 36.1%, 22.6%, 50.0%, 27.7% among donors, respectively). In URD group, allele HLA-DQA1*6, -DQB1*3 were significantly higher in the ESRD patients (30.6%, 56.6%)

than donors (21.3%, 46.3%), contrasly allele HLA-DQB1*2 was presented with a higher percentage in the donors (12.5%) than ESRD patients (4.6%) (Table 3.3).

Table 3.3: HLA class II typing of donors and ESRD patients

	Related group			Unrelated group		
	Donors (N=252)[1]	**Recipients (N=252)[1]**	**p-value**	**Donors (N=216)[1]**	**Recipients (N=196)[1]**	**p-value**
HLA-DRB1						
1	1 (0.4)	1 (0.4)	1.000	1 (0.5)	0 (0.0)	-
3	12 (4.8)	9 (3.6)	0.505	14 (6.5)	6 (3.1)	0.115
4	27 (10.7)	32 (12.7)	0.489	18 (8.3)	22 (11.2)	0.324
7	13 (5.2)	8 (3.2)	0.270	14 (6.5)	8 (4.1)	0.283
8	8 (3.2)	9 (3.6)	0.805	7 (3.2)	9 (4.6)	0.481
9	30 (11.9)	31 (12.3)	0.891	26 (12.0)	19 (9.7)	0.447
10	22 (8.7)	25 (9.9)	0.646	14 (6.5)	15 (7.7)	0.643
11	5 (2.0)	10 (4.0)	0.199	3 (1.4)	8 (4.1)	0.106
12	73 (29.0)	84 (33.3)	0.290	59 (27.3)	69 (35.2)	0.085
13	11 (4.4)	6 (2.4)	0.224	12 (5.6)	4 (2.0)	0.077
14	13 (5.2)	9 (3.6)	0.386	16 (7.4)	13 (6.6)	0.759
15	33 (13.1)	25 (9.9)	0.265	24 (11.1)	19 (9.7)	0.639
16	4 (1.6)	3 (1.2)	0.704	8 (3.7)	3 (1.5)	0.186
18				0 (0.0)	1 (0.5)	-
HLA-DQA1						
1	86 (34.1)	80 (31.7)	0.570	82 (38.0)	64 (32.7)	0.261
2	13 (5.2)	8 (3.2)	0.270	14 (6.5)	7 (3.6)	0.186
3	56 (22.2)	60 (23.8)	0.672	41 (19.0)	40 (20.4)	0.716
4	12 (4.8)	19 (7.5)	0.198	8 (3.7)	8 (4.1)	0.843
5	25 (9.9)	22 (8.7)	0.646	25 (11.6)	17 (8.7)	0.333
6	60 (23.8)	63 (25.0)	0.756	**46 (21.3)**	**60 (30.6)**	**0.031**

	Related group			Unrelated group		
	Donors (N=252)[1]	**Recipients (N=252)[1]**	**p-value**	**Donors (N=216)[1]**	**Recipients (N=196)[1]**	**p-value**
HLA-DQB1						
1	0 (0.0)	3 (1.2)	-	1 (0.5)	0 (0.0)	-
2	16 (6.3)	15 (6.0)	0.853	**27 (12.5)**	**9 (4.6)**	**0.006**
3	135 (53.6)	145 (57.5)	0.370	**100 (46.3)**	**111 (56.6)**	**0.036**
4	15 (6.0)	17 (6.7)	0.715	9 (4.2)	12 (6.1)	0.370
5	67 (26.6)	58 (23.0)	0.354	62 (28.7)	43 (21.9)	0.116
6	19 (7.5)	14 (5.6)	0.370	17 (7.9)	21 (10.7)	0.321

[1]Number of alleles

*Notes: The HLA allele was summarized by count and percentage for ESRD patients and unrelated and related donors. Frequency and percentage were used to describe categorical data. Allele frequencies of HLA-DRB1, -DQA1, -DQB1 were computed by (n/2N)*100, of which n is the total count of an allele and N is the total number of individuals.*

3.2.4 Detection of susceptible and protective alleles

HLA-B*07 (OR = 1.951 (1.032-3.688)), DQA1*06 (OR = 1.630 (1.044-2.545)) and DQB1*03 1.515 (1.027-2.235)) were risk alleles of ESRD ($p < 0.05$). Conversely, HLA-B*27 (OR = 0.175 (0.039-0.793)), DQB1*02 (OR = 0.337 (0.154-0.736)) were found as protective alleles to ESRD progression (Table 3.4).

Table 3.4: Detection of susceptible and protective alleles

HLA alleles	OR (95% CI)	p-value	Notes
B*07	1.951 (1.032-3.688)	0.040	Risk of ESRD
B*27	0.175 (0.039-0.793)	0.024	Protective factor to ESRD
DQA1*06	1.630 (1.044-2.545)	0.031	Risk of ESRD
DQB1*02	0.337 (0.154-0.736)	0.006	Protective factor to ESRD
DQB1*03	1.515 (1.027-2.235)	0.036	Risk of ESRD

3.3 Evaluate the influence of HLA mismatching on the graft survival rate of renal transplanted patients among recipients-donors in RD and URD groups in post renal transplantation

A total of 208 transplanted pairs of unrelated and related donors-recipients among were monitored in post-transplantation, of which 82 ESRD patients and 82 unrelated donors in URD group, and 126 ESRD patients came with their 126 related donors in RD group.

3.3.1 Age compatibility

The majority of recipients in both RD and URD groups were adults aged 18-40 (Table 3.5). In RD group, donors were mainly in the middle age range of 41-60, while donors in the URD group remained in the adult range of 18-40. It can be inferred that there is an age disparity between donors and recipients. Specifically, in the RD group, donors are typically older than recipients by over 5 years, accounting for 77.8% of cases. On the other hand, in the unrelated donor group, recipients are generally older than donors by more than 5 years, representing 41.5% of cases.

Table 3.5: Age compatibility demographic characteristics

	Related group (N=126)	**Unrelated group (N=82)**
Recipient age (years)		
Mean ± SD	34.1 ± 9.5	41.2 ± 9.4
Median (IQR)	33 (27 - 39)	40 (34 - 48)
Min - Max	17 - 67	24 - 65
Recipient age group (years), n (%)		
<18	2 (1.6)	0 (0.0)
18-30	45 (35.7)	9 (11.0)
31-40	52 (41.3)	34 (41.5)
41-50	19 (15.1)	28 (34.1)
51-60	7 (5.6)	8 (9.8)
>60	1 (0.8)	3 (3.7)
Donor age (years)		
Mean ± SD	52.1 ± 8.8	37.4 ± 11.9
Median (IQR)	54 (47 - 59)	35 (27 - 47)
Min - Max	28 - 68	20 - 66

	Related group (N=126)	Unrelated group (N=82)
Donor age group (years), n (%)		
<18	0 (0.0)	0 (0.0)
18-30	3 (2.4)	29 (35.4)
31-40	11 (8.7)	25 (30.5)
41-50	35 (27.8)	16 (19.5)
51-60	55 (43.7)	8 (9.8)
>60	22 (17.5)	4 (4.9)
Donor-recipient age match, n (%)		
Equivalent (±5 years)	20 (15.9)	31 (37.8)
Donor is older (>5 years)	98 (77.8)	17 (20.7)
Recipient is older (>5 years)	8 (6.3)	34 41.5)

3.3.2 Gender compatibility

In general, the majority of recipients were male, with males making up roughly double the number of female recipients (66.7% versus 33.3%) (Table 3.6). Among RD group, the gender distribution was quite balanced, while among URD group, the proportion of male donors was also twice as high. As a result, there was a gender matching pattern where female-to-male matches accounted for the majority in the RD group (38.9%), while male-to-male matches were most common in the URD group (45.1%).

Table 3.6: Gender compatibility demographic characteristics

	Related group (N=126)	Unrelated group (N=82)
Recipient gender, n (%)		
Male	84 (66.7)	55 (67.1)
Female	42 (33.3)	27 (32.9)
Donor gender, n (%)		
Male	57 (45.2)	56 (68.3)
Female	69 (54.8)	26 (31.7)
Donor-recipient gender, n (%)		
Female-female	20 (15.9)	8 (9.8)
Male-female	22 (17.5)	19 (23.2)

	Related group (N=126)	Unrelated group (N=82)
Female-male	49 (38.9)	18 (22.0)
Male-male	35 (27.8)	36 45.1)

3.3.3 ABO and Rhesus blood group compatibility

The most common blood group among recipients in both groups is O, followed by B, A, and AB (Table 3.7). Similarly, the most prevalent blood group among donors is O, with B being the second most common, followed by A and AB. However, there's a disparity in the percentage of matching ABO blood group between the two groups. In terms of ABO compatibility, 83.3% of related donors were compatible with recipients compared to 75.6% in the URD group. Most of the participants were Rhesus positive.

Table 3.7: ABO and Rhesus blood group compatibility characteristics

	Related group (N=126)	Unrelated group (N=82)
Recipient ABO type, n (%)		
O	50 (39.7)	33 (40.2)
B	42 (33.3)	35 (42.7)
A	28 (22.2)	10 (12.2)
AB	6 (4.8)	4 (4.9)
Donor ABO type, n (%)		
O	68 (54.0)	51 (62.2)
B	34 (27.0)	24 (29.3)
A	21 (16.7)	6 (7.3)
AB	3 (2.4)	1 (1.2)
General ABO compatibility, n (%)		
Matched	105 (83.3)	62 (75.6)
Unmatched	21 (16.7)	20 (24.4)
ABO compatibility specifying, n (%)		
A-A	21 (16.7)	5 (6.1)
B-B	31 (24.6)	23 (28.0)
AB-AB	3 (2.4)	1 (1.2)
O-O	50 (39.7)	33 (40.2)
O-A	7 (5.6)	5 (6.1)
O-B	11 (8.7)	12 (14.6)

	Related group (N=126)	Unrelated group (N=82)
O-AB	0 (0.0)	1 (1.2)
A-AB	0 (0.0)	1 (1.2)
B-AB	3 (2.4)	1 (1.2)
Recipient Rhesus type, n (%)		
Positive	125 (99.2)	82 (100.0)
Negative	1 (0.8)	0 (0.0)
Donor Rhesus type, n (%)		
Positive	126 (100.0)	82 (100.0)
Negative	0 (0.0)	0 (0.0)

3.3.4 HLA and anti-HLA antibodies compatibility level

These are specific HLA loci that play a crucial role in the immune response and transplant compatibility: HLA-DRB1, HLA-A, HLA-B, HLA-DQA1, and HLA-DQB1. We observed three levels of matching: mismatch, partial match, and complete match on HLA (Table 3.8). Recipients and donors in URD group generally had higher rates of mismatch across all HLA loci compared to RD group. Conversely, recipients and donors in RD group had higher rates of partial match and complete match across all HLA loci compared to URD group. In terms of HLA matching levels per 10 alleles, RD group was more likely to exhibit higher levels of matching than URD group. When considering the percentage of HLA mismatch cases, RD group had a greater percentage of complete matches and fewer instances with high mismatches compared to URD group which show more cases with high mismatches (9-10 MM) (Table 4.8). Concerning anti-HLA antibodies presence, similar results were found between the two groups. Negative results accounted for approximately 60% while positive results were around 40%.

Table 3.8: HLA and anti-HLA antibodies compatibility level characteristics

	Related group (N=126)	Unrelated group (N=82)
HLA-DRB1, n (%)		
Mismatch	42 (33.3)	59 (72.0)
Partial match	59 (46.8)	21 (25.6)
Complete match	25 (19.8)	2 (2.4)
HLA-A, n (%)		
Mismatch	36 (28.6)	34 (41.5)

	Related group (N=126)	Unrelated group (N=82)
Partial match	59 (46.8)	39 (47.6)
Complete match	31 (24.6)	9 (11.0)
HLA-B, n (%)		
Mismatch	51 (40.5)	57 (69.5)
Partial match	55 (43.7)	24 (29.3)
Complete match	20 (15.9)	1 (1.2)
HLA-DQA1, n (%)		
Mismatch	38 (30.2)	43 (52.4)
Partial match	56 (44.4)	25 (30.5)
Complete match	32 (25.4)	14 (17.1)
HLA-DQB1, n (%)		
Mismatch	22 (17.5)	30 (36.6)
Partial match	55 (43.7)	40 (48.8)
Complete match	49 (38.9)	12 (14.6)
Level of HLA matching (per 10 alleles), n (%)		
0	0 (0.0)	6 (7.3)
1	7 (5.6)	18 (22.0)
2	21 (16.7)	14 (17.1)
3	20 (15.9)	18 (22.0)
4	19 (15.1)	14 (17.1)
5	19 (15.1)	5 (6.1)
6	12 (9.5)	5 (6.1)
7	7 (5.6)	2 (2.4)
8	5 (4.0)	0 (0.0)
9	3 (2.4)	0 (0.0)
10	13 (10.3)	0 (0.0)
Anti-HLA antibodies, n (%)		
Negative	77 (61.1)	50 (61.0)
Positive	49 (38.9)	32 (39.0)
HLA mismatch, n (%)		
0 MM	13 (10.3)	0 (0.0)
1-4 MM, 0 DRB1 MM	12 (9.5)	2 (2.4)
1-4 MM, 1-2 DRB1 MM	15 (11.9)	5 (6.1)

	Related group (N=126)	Unrelated group (N=82)
5-8 MM, 0 DRB1 MM	0 (0.0)	0 (0.0)
5-8 MM, 1-2 DRB1 MM	79 (62.7)	51 (62.2)
9-10 MM	7 (5.6)	24 29.3)

3.3.5 Association between the suspected graft rejection rate and patient's characteristics

In univariable Cox proportional hazard model, it was found in URD group that older unrelated donors (over 5 years older than the recipients) were associated with a higher risk of suspected graft rejection. This risk was 4.22 times higher compared to the group of donors who were of equivalent age (Table 3.9), and this difference was statistically significant ($p < 0.05$). The association between suspected graft rejection rates and gender was also examined in both two groups. A statistically significant result was found in the URD group, where male-male matches had a hazard ratio of 0.12 compared to female-female matches ($p=0.02$). This indicates a significant reduction in risk. The relationship between each specific HLA locus at all three levels of match and suspected graft rejection rates was also investigated, but no statistically significant relationship was found in either group. To examine the association between anti-HLA antibodies and suspected graft rejection rates, it was discovered that positive anti-HLA antibodies in unrelated donor transplants are associated with worse outcomes, increasing the risk by 4.5 times ($p=0.011$).

In multivariable Cox proportional hazard model (Table 3.10), an HLA mismatch (MM) of 9-10 MM was found to be associated with a higher risk of suspected graft rejection. Specifically, this risk was 7.99 times greater compared to an HLA mismatch level of 5-8 MM with 1-2 DRB1 MM with statistically significant ($p = 0.013$). Additionally, regarding HLA matching (per 10 alleles), a partial match with HLA-DQA1 was also linked to an increased risk of suspected graft rejection, with a hazard ratio of 2.94 times ($p < 0.05$). In multivariable Cox proportional hazard models, indicating that recipients with positive anti-HLA antibodies prior to transplantation had a significantly higher risk of suspected graft rejection, with a hazard ratio of 3.43 times ($p < 0.05$), compared to recipients with negative anti-HLA antibodies.

Table 3.9: Association between the suspected graft rejection rate and recipient's characteristics (Univariable Cox proportional hazard model)

	Related group			Unrelated group		
Outcomes	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Level of HLA matching (per 10 alleles)	1.04	0.89, 1.21	0.620	0.92	0.67, 1.26	0.587
HLA-DRB1						
Mismatch	—	—		—	—	
Partial match	2.00	0.71, 5.60	0.189	0.22	0.03, 1.69	0.146
Complete match	1.32	0.35, 4.92	0.680	0.00	0.00, Inf	0.998
HLA-A						
Mismatch	—	—		—	—	
Partial match	1.65	0.52, 5.27	0.398	1.57	0.46, 5.36	0.472
Complete match	2.61	0.79, 8.68	0.117	3.32	0.74, 14.9	0.118
HLA-B						
Mismatch	—	—		—	—	
Partial match	1.99	0.80, 4.93	0.138	0.90	0.28, 2.87	0.859
Complete match	0.37	0.04, 2.97	0.346	0.00	0.00, Inf	0.998
HLA-DQA1						
Mismatch	—	—		—	—	
Partial match	0.50	0.19, 1.36	0.176	1.01	0.34, 3.03	0.979
Complete match	0.76	0.27, 2.14	0.603	0.00	0.00, Inf	0.998
HLA-DQB1						
Mismatch	—	—		—	—	

	Related group			Unrelated group		
Outcomes	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Partial match	2.57	0.57, 11.5	0.217	1.92	0.59, 6.25	0.280
Complete match	1.85	0.39, 8.69	0.438	0.71	0.08, 6.46	0.764
Donor-recipient age match						
Equivalent (±5 years)	—	—		—	—	
Donor was older (>5 years)	***2.11***	***0.49, 9.07***	***0.315***	***4.22***	***1.05, 16.9***	***0.042***
Recipient was older (>5 years)	1.32	0.12, 14.5	0.823	1.50	0.36, 6.26	0.582
Donor-recipient sex						
Female-female	—	—		—	—	
Male-female	0.82	0.16, 4.07	0.808	0.88	0.23, 3.44	0.856
Female-male	1.16	0.31, 4.30	0.826	0.25	0.04, 1.48	0.125
Male-male	***1.32***	***0.34, 5.13***	***0.684***	***0.12***	***0.02, 0.71***	***0.020***
ABO compatibility						
Matched	—	—		—	—	
Unmatched	0.49	0.11, 2.10	0.338	0.87	0.24, 3.11	0.825
Anti-HLA antibodies						
Negative	—	—		—	—	
Positive	***1.24***	***0.54, 2.88***	***0.614***	***4.50***	***1.41, 14.3***	***0.011***

Table 3.10: Association between the suspected graft rejection rate and recipient's characteristics – (Multivariable Cox proportional hazard model)

	HR	**95% CI**	**p-value**
Group			
Related group	1	Ref	
Unrelated group	1.51	0.56, 4.04	0.417
HLA mismatch			
5-8 MM, 1-2 DRB1 MM	1	Ref	
0 MM	-	-	0.997
1-4 MM, 0 DRB1 MM	0.72	0.03, 17.1	0.839
1-4 MM, 1-2 DRB1 MM	1.42	0.28, 7.18	0.675
9-10 MM	***7.99***	***1.54, 41.4***	***0.013***
Level of HLA matching (per 10 alleles)	1.58	0.66, 3.79	0.305
HLA-DRB1			
Mismatch	1	Ref	
Partial match	0.78	0.21, 2.92	0.716
Complete match	NA	NA	NA
HLA-A			
Mismatch	1	Ref	
Partial match	1.14	0.36, 3.68	0.820
Complete match	3.13	0.40, 24.5	0.277
HLA-B			
Mismatch	1	Ref	
Partial match	0.76	0.24, 2.39	0.645
Complete match	0.00	0.00, Inf	0.997
HLA-DQA1			
Mismatch	1	Ref	
Partial match	0.46	0.14, 1.51	0.200
Complete match	0.18	0.02, 1.64	0.129
HLA-DQB1			
Mismatch	1	Ref	
Partial match	**2.94**	**1.22, 7.10**	***0.016***

	HR	95% CI	p-value
Complete match	NA	NA	NA
Donor-recipient age match			
Equivalent (±5 years)	1	Ref	
Donor is older (>5 years)	2.21	0.73, 6.76	0.162
Recipient is older (>5 years)	1.04	0.28, 3.94	0.950
Donor-recipient gender			
Female-female	1	Ref	
Male-female	1.17	0.37, 3.70	0.787
Female-male	0.88	0.30, 2.61	0.816
Male-male	1.01	0.31, 3.28	0.993
ABO blood group compatibility			
Matched	1	Ref	
Unmatched	0.80	0.26, 2.44	0.690
Anti-HLA antibodies			
Negative	1	Ref	
Positive	***3.43***	***1.42, 8.29***	***0.006***

3.3.6 Clinical outcomes on graft survival in transplanted patients

In order to evaluate and compare the graft survival of transplanted patients in URD and RD group over a 30-month follow-up period, we assessed multiple indicators including the free of suspected graft rejection rate, free of graft loss rate, the overall survival rate, and the event-free survival rate. The rate of clinical outcomes, including these multiple indicators were calculated by the Kaplan-Meier method and visualized by Kaplan-Meier plots by each group of RD and URD.

a. Free of suspected graft rejection rate

Grafts of transplanted patients from both RD and URD group exhibited comparable survival rates, as evidenced by the overlapping curves in figure 3.2. The likelihood of grafts remaining the free from suspected rejection gradually declines over time for both groups.

The free of suspected graft rejection rates for recipients in RD and URD groups were recorded at various time points post-transplantation: at 1, 3, 6, 9, 12, 15, 18, 21, 24, and 30 months, the rates were as follows: RD group: 97.6%, 94.4%, 90.4%, 89.5%, 85.7%, 83.7%, 82.6%, 81.2%, 81.2%, 76.9%; URD group: 92.7%, 87.8%, 86.5%, 85.1%, 83.3%, 83.3%, 83.3%, 83.3%, 83.3%, 80.1%, 80.1%.

There is no substantial disparity (p=0.75) in the suspected graft rejection rates between grafts from RD and URD groups during the observed period.

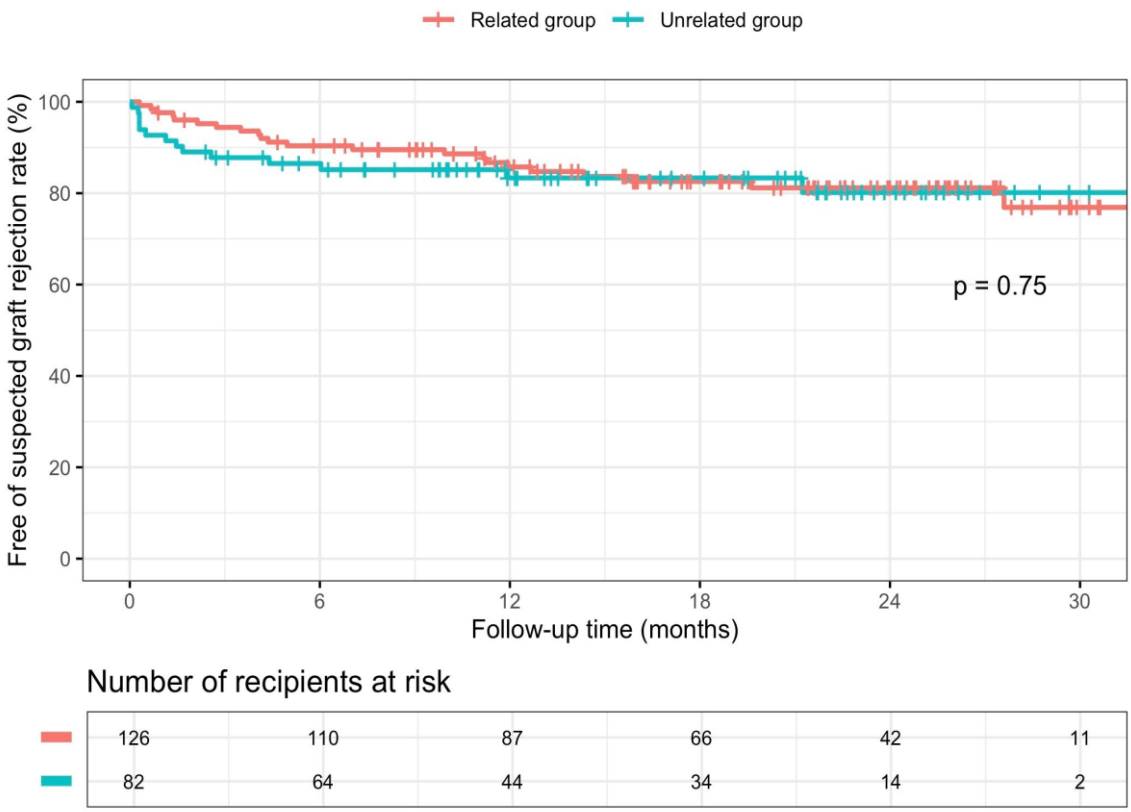

Figure 3.2: Kaplan-Meier curve of free of suspected graft rejection rate

b. The free of graft loss rate

Both two groups display excellent survival rates, with curves consistently remaining close to 100% throughout the majority of the observed period (Figure 3.3). Although there was a slight indication that grafts of recipients from URD group may experience a slightly higher rate of loss compared to those from RD group, this difference was not reach statistical significance (p=0.095).

The free of graft loss rates for recipients in RD and URD groups were recorded at various time points post-transplantation: at 1, 3, 6, 9, 12, 15, 18, 21, 24, and 30 months, the rates were as follows: RD group: 100%, 99.2%, 99.2%, 99.2%, 99.2%, 99.2%, 99.2%, 99.2%, 99.2%, 99.2%; URD group: 100%, 100%, 100%, 100%, 98.6%, 96.7%, 96.7%, 96.7%, 96.7%, 93.4%, 93.4%.

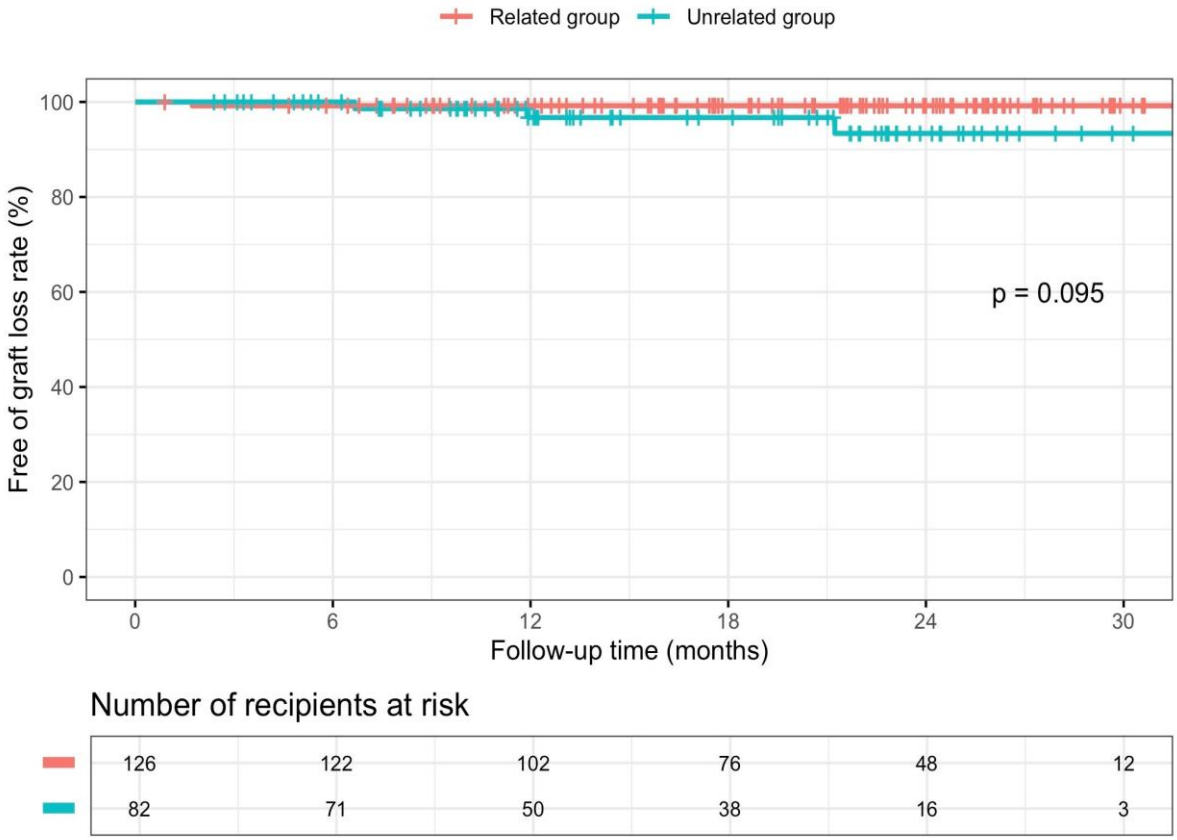

Figure 3.3: Kaplan-Meier curve of the free of graft loss rate

c. The overall survival rate

The overall survival rates of grafts of recipients from RD group were notably higher than those from unrelated donors throughout the 30-month follow-up period (Figure 3.4). While both groups exhibited high probabilities of survival, a more distinct contrast became evident as the follow-up period advances.

The overall survival rates for recipients in RD and URD groups were recorded at various time points post-transplantation: at 1, 3, 6, 9, 12, 15, 18, 21, 24, and 30 months, the rates were as follows: RD group: 100%, 100%, 100%, 100%, 100%, 100%, 100%, 100%,

100%, 100%; URD group: 100%, 100%, 100%, 98.7%, 97.3%, 94.1%, 94.1%, 94.1%, 94.1%, 94.1%, 94.1%.

Grafts of recipients from RD group demonstrated a significantly greater overall survival rate in comparison to grafts of recipients from URD group, with a statistically significant p-value of 0.0086.

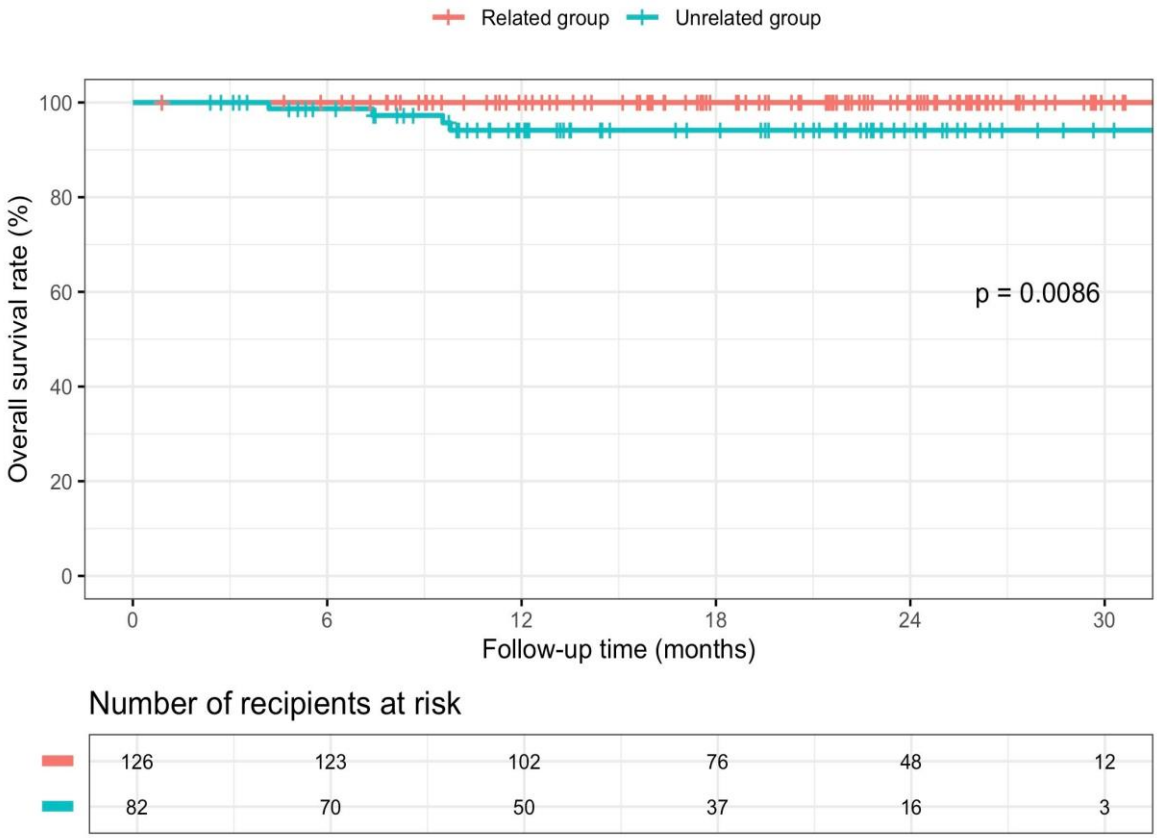

Figure 3.4: Kaplan-Meier curve of overall survival rate

d. The event-free survival rate

The survival curves demonstrated a decrease as the follow-up duration extends, suggesting an increase in graft loss events (Figure 3.5). Generally, recipients who receive grafts from donors in RD group exhibited higher rates of the event-free survival rate.

The event-free survival rates for recipients in RD and URD groups were recorded at various time points post-transplantation: at 1, 3, 6, 9, 12, 15, 18, 21, 24, and 30 months, the rates were as follows: RD group: 100%, 99.2%, 99.2%, 99.2%, 99.2%, 99.2%, 99.2%,

99.2%, 99.2%, 99.2%; URD group: 100%, 100%, 100%, 98.7%, 95.9%, 91.1%, 91.1%, 91.1%, 91.1%, 88%, 88%.

The statistically significant p-value of 0.0025 confirms a notable difference between the two groups.

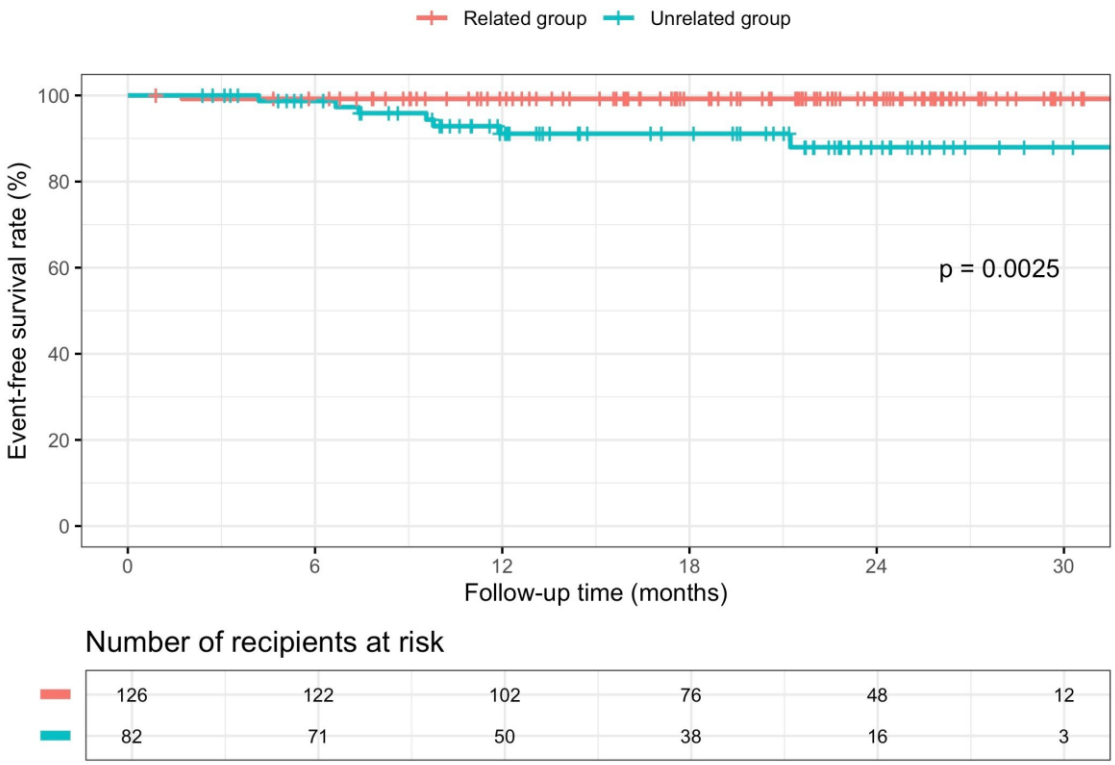

Figure 3.5: Kaplan-Meier curve of the event-free survival rate

3.3.7 Monitoring the crucial laboratory data in pre and post-transplantation of recipients

3.3.7.1 The Proportion of BK virus -postive recipients by follow-up period

It was observed that during the follow-up period, recipients in the RD group had a higher proportion of BK virus infection compared to recipients in the URD group.

3.3.7.2 Monitoring of hemoglobin level

Before transplantation, both groups had low hemoglobin levels (107±21 g/L, 105±23 g/L). In the URD group, hemoglobin levels remained low in the first but started to increase and reach normal range from the second month, similar to the RD group. At the

3rd, 6th, 12th, 24th, and 30th month follow-ups, both groups showed similar mean hemoglobin levels: RD group (122 ± 16 g/L;126 ±18 g/L;135 ±19g;134±18g/L;136±16g/L) and URD group (122 ±17 g/l;126 ±19 g/l;133±18g/l; 133±26 g/l;133±25g /l).

3.3.7.3 Monitoring of BUN level

We observed that both groups had high BUN levels before transplantation (59.1±20.2 mg/dL, 56.1±20.2 mg/dL). The BUN levels for both groups improved in the first few months after transplantation and reached the normal range by the third month for both groups.

3.3.7.4 Monitoring of serum creatinine level

We observed that both groups had high levels of serum creatinine before transplantation (9.38±2.44 mg/dL, 9.13±2.17 mg/dL). The levels reduced and reached within normal range from the first month after transplantation.

3.3.7.5 Monitoring of eGFR

We discovered that both groups had low levels of eGFR before transplantation (6.9±2.3 mL/min/l 73m2, 6.4±1.9 mL/min/l 73m2, respectively). Within the first month after transplantation, the levels of eGFR reached within normal range for both groups (mean of 66.6 ± 21.7 mL/min/l 73m2 in the RD group and 68.6 ± 22.1 mL/min/l 73m2 in the URD group).

3.3.7.6 Monitoring of proteinuria level

We observed that the levels of urine protein were high in both groups before transplantation (Mean of 379.1 ± 331.1 mg/dL in the RD group and 364.3 ± 330.6 mg/dL in the URD group). However, from the first month after transplantation, there was a decrease in urine protein levels for both groups (Mean of 49.3 ± 120.1 mg/dL in the RD group and 60.8 ± 164.6 mg/dL in the URD group). Furthermore, by the second month after transplantation, urine protein levels had decreased and returned to normal range for both groups

CHAPTER 4: DISCUSSION

4.1 HLA alleles of unrelated donors-recipients and related donors-recipients and their association with ESRD patients and donors

Several studies have shown an association between HLA alleles and end-stage renal disease (ESRD the findings have been across different countries. This suggests that susceptible HLA alleles may be specific to particular ethnic groups. Therefore, study aimed to investigate a wide range of both class I (-A, -B) and class II (-DR, -DQ) HLA alleles in Vietnamese ESRD patients and healthy donors, with the goal of contributing a better understanding of ESRD-related genetic factors among Vietnamese and Southeast Asians.

In our study, we discovered that HLA-B*07 was associated with ESRD (OR = 1.951 (1.032-3.688)). However this finding was not consistent with some studies in the Asian region. The inconsistencies listed above highlight that different populations and geographies can lead to the functional changes of alleles when it comes to ESRD. In study, HLA-B *27 was categorized as a protective factor against ESRD (OR=0.175 (0.039-0.793)) with $p<0.05$. In addition to the gold standard of HLA matching on loci -A, -B, and -DR in renal transplantation, the importance of matching HLA-DQ has been gradually recognized. In our study, we identified HLA-DQA1*06 as a significant susceptible allele for ESRD. However, this finding contradicts a study conducted by another authors which concluded that HLA-DQA1*06 was a protective allele. The discrepancy in findings could be attributed to differences in HLA typing between the two populations. In our research, we identified allele DQB1*03 as a risk factor for ESRD, which is consistent with previous studies conducted on patients from Turkey and China. On the other hand, we found that the frequencies of HLA-DQB1*02 were significantly higher in the control group compared to the ESRD group. This allele was identified as protective factors against ESRD in our study.

In summary, the most common alleles found in each HLA locus were consistent with those observed in the general Vietnamese population and other countries in East and Southeast Asia. We identified HLA-B*07, DQA1*06, and DQB1*03 as alleles that predispose individuals to ESRD. Conversely, we found that HLA-B*27 and DQB1*02 are associated with a reduced risk of developing ESRD.

4.2 Evaluate the influence of HLA mismatching on the graft survival rate of renal transplanted patients among recipients-donors in RD and URD groups in post renal transplantation

4.2.1 Age compatibility and its influence on the suspected graft rejection rate in transplanted patients

The analysis of our data revealed an interesting age discrepancy between donors and recipients in our study population. Specifically, we found that related donors were generally older than the recipients. In fact, 77.8% of related donors were more than five years older than their recipients, whereas only 20.7% of unrelated donors had this age difference. Remarkably, in univariable Cox proportional hazard model, this age disparity had a significant impact on graft outcomes in the unrelated donor group. Specifically, when the donor was more than five years older than the recipient, there was a 4.22 times higher risk of suspected graft rejection ($p < 0.05$). This suggests that minimizing the age discrepancy between donors and recipients is crucial in unrelated donor transplants to reduce the risk of suspected graft rejection and improve overall renal transplant outcomes.

4.2.2 Gender compatibility and its influence on the suspected graft rejection rate in transplanted patients

The data revealed that the majority of recipients in both groups were male, accounting for 66.7% of the total. Interestingly, there was a balanced sex distribution among related donors, but unrelated donors had a higher proportion of males, leading to different patterns of sex matching. Female-to-male matches were most common in the related donor group (38.9%), while male-to-male matches were predominant in the unrelated donor group (45.1%). A noteworthy observation was made in the unrelated donor group, where it was found that male-to-male matches had a significantly lower hazard ratio compared to female-to-female matches (HR=0.12; p=0.02). This suggests an 88% lower risk of suspected graft rejection in male-male matches compared to female-female matches within the unrelated donor group. These findings underscore the importance of considering gender matching when evaluating potential donors and recipients for renal transplantation procedures.

4.2.3 ABO and Rhesus blood group compatibility and influence on the suspected graft rejection rate in transplanted patients

ABO, Rhesus compatibility does not appear to have a significant impact on the suspected graft rejection rates in our study population, it remains an important consideration in renal transplantation. Additional studies investigating other potential factors influencing graft survival are warranted to enhance our understanding of this complex process.

4.2.4 HLA and HLA antibody mismatch rates and influences on the suspected graft rejection rate in transplanted patients

Our study revealed that unrelated donors had higher rates of mismatch across all HLA loci compared to related donors while related donors showed higher rates of both partial and complete matches across all loci. However, despite these disparities, our analysis did not find any statistically significant relationship between specific HLA locus match levels and suspected graft rejection rates.

In the multivariable Cox proportional hazards model, an HLA mismatch (MM) of 9–10 MM was associated with a significantly higher risk of suspected graft rejection. Specifically, this risk was 7.99 times greater compared to an HLA mismatch level of 5–8 MM with 1–2 DRB1 MM, which was statistically significant ($p = 0.013$). Additionally, in terms of HLA matching (per 10 alleles), a partial match with HLA-DQA1 was also linked to an increased risk of suspected graft rejection, with a hazard ratio of 2.94 compared to a complete mismatch ($p < 0.05$).

In univariable Cox proportional hazard model, we observed similar proportions of anti-HLA antibodies presence in both groups, with approximately 60% testing negative and 40% testing positive. Upon examining the association between anti-HLA antibodies and the suspected graft rejection rates, we found that positive anti-HLA antibodies in unrelated donor transplants were associated with worse outcomes, increasing the risk by 4.5 times ($p=0.011$). In multivariable Cox proportional hazards models, indicating that recipients with positive anti-HLA antibodies prior to transplantation had a significantly higher risk of suspected graft rejection, with a hazard ratio of 3.43 ($p < 0.05$), compared to recipients with negative anti-HLA antibodies.

In summary, our study underscores the significance of HLA matching in determining compatibility but also highlights the potential impact of anti-HLA antibodies on graft survival outcomes. The findings further emphasize the importance of assessing these factors when evaluating renal transplantation suitability to help optimize patient care and long-term success-transplantation.

4.2.5 Clinical outcomes on graft survival in transplanted patients

Our study reveals that while the suspected graft rejection rate and the free of graft loss rate were comparable among unrelated and related group on renal transplantations, there was a distinct advantage in terms of the overall and event-free survival for recipients who received kidneys from related donors. These findings contributed to our understanding of transplantation outcomes based on different types of living donations.

4.2.6 Monitoring the crucial factors in pre and post-transplantation and their influences to graft function in transplanted patients

4.2.6.1 The proportion of BK virus-positive recipients

In our study, we observed that transplanted patients within RD group had a higher proportion of BK virus infections in their blood compared to patients in the URD group during the 30-month follow-up period. This indicates that there may be a relationship between relatedness and an increased likelihood of developing BK virus infections post-transplantation. In summary, BK virus infection poses considerable challenges for kidney transplant recipients and can affect graft survival rates. Regular monitoring and early detection through laboratory screening are essential for proper management and reducing immunosuppression as needed.

4.2.6.2 Hemoglobin level

This study demonstrates that while initially both patient groups exhibited low pre-transplantation hemoglobin levels, it was observed that following renal transplantation, hemoglobin was found to improve progressively in both groups. By ensuring optimal hemoglobin levels post-transplantation, healthcare providers can improve patient outcomes and reduce the risk of negative long-term consequences related to anemia after renal transplantation.

4.2.6.3 BUN level

After renal transplantation, BUN levels improved during the initial months for both groups. The BUN levels reached within the normal range at three months post-transplantation for both two groups. This finding suggests that renal transplantation can effectively improve renal function and subsequently lead to a reduction in BUN levels over time. These findings emphasize the positive impact of renal transplantation on improving kidney function as reflected by normalized BUN levels. Monitoring these changes is crucial for assessing renal health post-transplantation and ensuring positive outcomes for patients.

4.2.6.4 Serum creatinine level

Following transplantation, the levels of serum creatinine levels reached within the normal range in two groups by the first month post-transplantation. These findings highlight that renal transplantation has a positive impact on reducing serum creatinine levels and improving renal function over time for both related and unrelated groups of patients. Monitoring these changes is crucial for assessing renal health post-transplantation and ensuring positive outcomes for patients.

4.2.6.5 eGFR level

There was a notable improvement in eGFR levels for groups. Specifically, within the first month post-transplantation, the eGFR levels reached within the normal range for both groups. These findings indicate that renal transplantation led to a significant improvement in renal function as evidenced by the normalization of eGFR levels within just one month after transplantation for both related and unrelated groups. It is crucial to note that monitoring eGFR levels post-transplantation is essential for assessing renal health and ensuring successful outcomes for renal transplant recipients.

4.2.6.6 Proteinuria level

After renal transplant, there was a significant decrease in urine protein levels from the first month onwards for both groups. Moreover, our study found that from the second month post-transplantation, urine protein levels decreased further and returned to normal ranges for both groups. These outcomes are in strong agreement with previous studies on post-transplantation changes in urinary protein, observed in both related and unrelated groups. By validating these results, we can further emphasize the significance of monitoring urinary proteins as a crucial component of evaluating kidney function after transplantation.

CHAPTER 5: CONCLUSION AND RECOMMENDATION

The results of the study met the objectives of the thesis. There were 458 participants in the study, including 98 ESRD patients and 108 unrelated donors, as well as 126 ESRD patients who came with their related donors. The most frequent alleles in each HLA locus were similar to those found in the general Vietnamese population and other countries in South-east Asia. HLA-B*07 ($p = 0.040$), -DQA1*06 ($p = 0.031$), and -DQB1*03 ($p = 0.036$) were found as susceptible alleles for ESRD, while HLA-B*27 ($p = 0.024$) and -DQB1*02 ($p = 0.006$) were associated with a decreased risk of ESRD.

A total of 416 participants were examined graft survival rates in RD and URD groups. This included 126 pairs in RD and 82 pairs in URD groups. Throughout the 30-month follow-up, recipients in RD group exhibited significantly higher the overall survival rate ($p= 0.0086$) and better event-free survival rate ($p= 0.0025$) compared to URD group. The URD group exhibited higher rates of HLA mismatches (MM), while the RD group demonstrated higher rates of both partial and complete matches across all HLA loci. An HLA mismatch of 9-10 MM was associated with an increased risk of the suspected graft rejection. Specifically, this risk was 7.99 times higher compared to an HLA mismatch level of 5-8 MM with 1-2 DRB1 MM ($p = 0.013$). In URD group, unrelated donors older than five years increased the risk of suspected graft rejection by a hazard ratio of 4.22, while positive anti-HLA antibodies also raised this risk with a hazard ratio of 4.5. Male-male donor-recipient pairs significantly decreased the risk of the suspected graft rejection by 88% when compared to female-female pairs.

There were 124 transplanted patients in RD group and 45 transplanted patients in URD group at Cho Ray hospital were followed up the changes of some crucial laboratory data in post-transplantation to investigate graft function as for hemoglobin, BUN, creatinine in serum, eGFR, Protein level in urine, detection of BK virus infection. Throughout the 30-month follow-up period, we observed a significant improvement after renal transplantation in both groups. Renal transplanted patients in the RD group had a higher prevalence of BK virus infections compared to those in the URD group.

Additional research with higher resolution and a larger sample size, preferably multi-center, should be carried out to confirm our findings. It is important to conduct

further research to investigate the mechanisms behind these observations and develop strategies for improved donor selection and matching in renal transplantation. Continuous monitoring and recording of information during follow-up examinations after renal transplantation are essential. Patient monitoring should adhere to the hospital's treatment plan and the guidelines of the Ministry of Health./.