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# Frequency of human leukocyte antigen compatibility and graft rejection in kidney transplant patients from living donors

## *Frecuencia de compatibilidad antígeno leucocitario humano y rechazo de injerto en pacientes trasplantados de riñón de donador vivo*

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## Abstract

**Objective:** *The aim of the present research was to identify the frequency of Human Leukocyte Antigen compatibility and graft rejection in kidney transplant patients from related donors during the period from 2019 to 2022 in one of the most important tertiary medical facilities in Mexico.* **Methods:** *A cross-sectional design was used to identify the HLA compatibility of transplanted patients registered from January 1, 2019, to December 31. The included patients were young adults aged 18-45, beneficiaries of social security provide by the government who were transplanted.* **Results:** *A total of 690 patients were transplanted during the period from 2019 to 2022. The graft survival rate was 98.67%; in just four years, a total of 9 kidney transplantectomy were performed,5 of them were transplants from unrelated relatives. Only 1 of these shared at least 2 class 1 antigens, while the rest did not share any. The related family members shared at least 1 and up to 3 class 1. In the 6-month post-transplant period, 30.25% of the patients experienced some type of renal dysfunction.* **Conclusion:** *It can be concluded that HLA compatibility is a good predictor for preventing rejection in kidney transplants from related and unrelated living donors. Efforts should be made to identify the best donor options among all future donors and explore the possibility of exchanging donors, especially unrelated living donors, among recipients on the waiting list. This is to ensure better adaptability and graft survival in patients.*

***Keywords:*** *End-stage renal disease. Kidney transplant. Human leukocyte antigen. Compatibility. Graft survival.*

## Resumen

**Objetivo:** *El objetivo del estudio fue identificar la frecuencia de compatibilidad Antígeno Leucocitario Humano y el rechazo de injerto en pacientes trasplantados de riñón de donador relacionado en el periodo del 2019 a 2022 en uno de los hospitales más importantes de tercer nivel de atención en México.* **Método:** *Se realizó un diseño de tipo transversal, para identificar la compatibilidad HLA de los pacientes trasplantados registradas del 1 enero del 2019 al 31 de diciembre de 2022. Los pacientes incluidos fueron adultos jóvenes de 18-45 años, derechohabientes con seguridad social por parte del gobierno, que fueron trasplantados.* **Resultado:** *Se obtuvo un total de 690 pacientes trasplantados en el periodo comprendido de 2019 a 2022. La supervivencia del injerto fue del 98.67%, tan solo en los 4 años se realizaron un total de 9 trasplantectomías de riñón, el resto*

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*de ellos, hasta la fecha ha tenido una supervivencia del injerto normofuncionante. En el periodo post trasplante de 6 meses, el 30.25% de los pacientes presentaron algún tipo de disfunción renal.* **Conclusión:** *Se puede concluir que la compatibilidad de HLA es un buen predictor para que no se dé el rechazo en trasplantes de riñón de donares vivos relacionados y no relacionados. Habría que hacer un esfuerzo por identificar las mejores opciones de donantes entre todos los futuros donadores y explorar la posibilidad de intercambiar donantes, sobre todo de donantes vivos no relacionados, entre los receptores en lista de espera, esto con la finalidad de asegurar una mejor adaptabilidad y supervivencia de los injertos en los pacientes.*

***Palabras clave:*** *Enfermedad renal terminal. Trasplante de riñón. Antigeno leucocitario humano. Compatibilidad. Supervivencia del injerto.*

## Introduction

Chronic Kidney Disease (CKD) has become a public health problem in recent years. Due to this, some developed countries spend around 3% of their annual health budget on its management[1]. Before the SARS-CoV-2 pandemics, the reported international prevalence was 13.4%, with approximately 4 to 7 million patients with End-Stage Renal Disease (ESRD) needing replacement therapy (dialysis, hemodialysis, or a kidney transplant)[2].

When a patient chooses transplantation as a kidney replacement measure, they undergo a thorough medical and psychosocial evaluation process. Both the donor and the recipient must undergo a series of tests to ensure compatibility and the safety of both. These blood tests, to evaluate compatibility and ensure the safety of the procedure, include the donor's and recipient's blood type, Rh factor (positive or negative), crossmatch test, Human Leukocyte Antigen (HLA) test, a panel of preformed antibodies, renal function tests, hepatitis tests, HIV tests, immunization tests, tests for transmissible diseases, and liver function tests[3].

HLA are proteins present on the surface of human body cells, and they play a crucial role in the immune system. These antigens are particularly important in the context of organ transplants, as the immune system uses HLA to distinguish between self and non-self cells and tissues[4].

When a kidney transplant is performed, it is essential that the donor's and recipient's HLA are as compatible as possible. Lack of compatibility can trigger an immune response in the recipient, which could result in the rejection of the transplanted kidney. Therefore, careful HLA compatibility testing is conducted before performing a transplant[5].

There are three main classes of HLA: Class I, Class II, and Class III. Classes I and II are the most relevant in organ transplants, as they are expressed on the surface of the cells that form tissues and organs. HLA class I and class II play essential roles in antigen presentation and immune response activation[6].

HLA Class I main components are HLA-A, HLA-B, and HLA-C, which functions are the presentation of endogenous antigens, the activation of Cytotoxic T Cells (CD8+) and the immune surveillance[7,8].

HLA Class II main components are HLA-DR, HLA-DQ and HLA-DP which functions are the presentation of exogenous antigens, the activation of Helper T Cells (CD4+) and the regulation of the immune response[7,8].

The importance of HLA in transplants is that this compatibility is essential for the success of organ and tissue transplants. Incompatibility can lead to transplant rejection by the recipient[7-9].

In summary, human leukocyte antigens play a critical role in kidney transplants by determining compatibility between the donor and the recipient. Finding adequate HLA compatibility helps reduce the risk of transplanted organ rejection and improves the long-term success of kidney transplants[10-12].

The aim of the present research was to identify the frequency of HLA compatibility and graft rejection in kidney transplant patients from related donors during the period from 2019 to 2022 at the in one of the most important tertiary medical facilities in Mexico.

## Materials and methods

A cross-sectional study design was used to identify the HLA compatibility of transplanted patients registered from January 1, 2019, to December 31, 2022, in one of the most important tertiary medical facilities in Mexico. Data collection was conducted through the review of medical records of all transplanted patients during this period, including only patients who met the inclusion criteria. The patients were young adults aged 18-45, beneficiaries of social security provide by the government treated at the transplant unit of the Medical Center from 2019-2022 who received a kidney transplant. Patients treated at a transplant unit who received a kidney transplant from a related or unrelated living

**Tabla 1.** Sociodemographic characteristics of transplanted patients

| | | |
|---|---|---|
| Age (average years) (n, %) | 29.57 ± 5 | |
| 18-25 | 148 | (21.45%) |
| 26-30 | 276 | (40.00%) |
| 31-35 | 172 | (24.93%) |
| 36-40 | 66 | (9.57%) |
| 41-45 | 28 | (4.06%) |
| Sex | | |
| Male | 499 | (72%) |
| Female | 191 | (28%) |
| Educational level (n, %) | | |
| PhD or Master degree | 7 | (1.05%) |
| Bachelor's degree, engineering, or technical degree | 173 | (25.98%) |
| Bachelor's degree, engineering, or technical degree dropout | 25 | (3.75%) |
| High school | 193 | (28.98%) |
| High school dropout | 41 | (6.16%) |
| Middle School | 164 | (24.62%) |
| Middle School dropout | 17 | (2.55%) |
| Primary School | 37 | (5.56%) |
| Primary School dropout | 7 | (1.05%) |
| Illiterate | 2 | (0.30%) |
| Marital status (n, %) | | |
| Single | 305 | (44.46%) |
| Married | 282 | (41.11%) |
| Common-law | 85 | (12.39%) |
| Divorced | 13 | (1.90%) |
| Widowed | 1 | (0.15%) |
| Ocupation (no, %) | | |
| Employee | 401 | (58.65%) |
| Retired | 95 | (13.93%) |
| Homemaker | 76 | (11.14%) |
| Unemployed | 54 | (7.92%) |
| Student | 40 | (5.87%) |
| Farmer | 9 | (1.32%) |
| Fisherman | 1 | (0.15%) |
| Family history of ESRD (n., %) | | |
| No | 553 | (80.61%) |
| Yes | 133 | (19.39%) |
| Type of donor (n., %) | | |
| LRD | 557 | (80.72%) |
| LUD | 133 | (19.28%) |

LRD: Living related donor; LUD: living unrelated donor.

donor were included. Patients who received a kidney transplant from a cadaveric donor were excluded. Patients with medical records that were incomplete by 80% were eliminated.

HLA measurement at the transplant unit was performed by serology. This method is based on antigen-antibody reactions and uses sera with specific antibodies against HLA antigens. HLA serology allows the identification of class I (HLA-A, HLA-B, HLA-C) and class II (HLA-DR, HLA-DQ, HLA-DP) HLA antigens.

The collected information will be entered into a database created in Excel® (Microsoft, Redmond, WA, USA), and data processing will be conducted using Epi Info 7.2.4 (Centers for Disease Control and Prevention, Atlanta, GA, USA). A statistical analysis was carried out using central tendency measures, frequencies, and means.

## *Ethical considerations*

The project has been approved by the local health ethics and research committee 1301 of the hospital, with institutional registration number R-2022-1301-224, COFEPRIS registration 17 CI 14 039 114, and CONBIOETICA registration 14 ECI 20190123.

## Results

A total of 690 patients received transplants from living donors during the period from 2019 to 2022. Of these patients, 133 received a graft from unrelated living donors (non-direct blood relatives), and the remaining 557 patients received grafts from related living donors (direct blood relatives). Table 1 shows the sociodemographic characteristics of the 690 transplanted patients.

The majority of donors were women, regardless of whether they were related or unrelated donors. The average age was 40.53 years, with the most predominant age range being 36 to 40 years (26.21%). Table 2 shows some of the sociodemographic characteristics of the donors.

The HLA compatibility between recipients and related living donors was higher in patients whose donors were their mothers, with haplotype compatibility in 73 patient-donor pairs. Of the 20 patients with identical HLA compatibility between siblings, only one was from an identical twin. Table 3 shows the frequency of HLA types identified in patients and related living donors, according to the type of donor.

Donations from unrelated living donors were more common between spouses, with 16 wives and 17 husbands generally sharing a class 1 antigen, while 24 husbands and 36 wives shared a class 2 antigen. Table 4 shows the frequency of HLA types identified in patients and unrelated living donors, according to the type of donor.

The graft survival rate was 98.67%; over the four years, a total of 9 transplantectomy were performed. The remaining patients have had normofunctioning graft survival to date. In the 6-month post-transplant period, 30.25% (206 patients) experienced some type of renal dysfunction. Out of the 9 patients with kidney rejection, 5 of them were transplants from unrelated relatives. Only 1 of these shared at least 2 class 1 antigens, while the rest did not share any. They only shared between 1 to 4 class 2 antigens. The related family members shared at least 1 and up to 3 class 1 antigens and between 2 to 6 class 2 antigens. Table 5 shows the number of rejections according to the HLA identified in patients and donors.

The average hospital stay for the 690 patients was 9 days, with a range of hospitalizations from 1 day to 90 days. There were 20 deaths identified during the hospitalization period, with an average time of death occurring 276 days (9 months) after hospital discharge. Two patients died during their hospital stay, and the patient with the longest time since discharge lived for 988 days (32 months/2.5 years).

**Tabla 2.** Sociodemographic characteristics of donors

| | | |
|---|---|---|
| Age (average years) (n, %) | 40.53 ± 13.57 | |
| ≤ 25 | 69 | (10.10%) |
| 26-30 | 204 | (29.87%) |
| 31-35 | 171 | (25.04%) |
| 36-40 | 179 | (26.21%) |
| 41-45 | 60 | (8.78%) |
| Sex | | |
| Male | 292 | (56.48%) |
| Female | 379 | (43.52%) |
| Type of donor LRD (n, %) | 557 | (80.72%) |
| Mother | 154 | (22.32%) |
| Father | 89 | (12.90%) |
| Brother | 121 | (17.54%) |
| Sister | 131 | (18.99%) |
| Cousin (male) | 5 | (0.72%) |
| Cousin (female) | 7 | (1.01%) |
| Uncle | 10 | (1.45%) |
| Aunt | 17 | (2.46%) |
| LUD | 133 | (19.28%) |
| Friend (female) | 14 | (2.03%) |
| Friend (male) | 20 | (2.90%) |
| Sister-in-law | 4 | (0.58%) |
| Brother-in-law | 7 | (1.01%) |
| Wife | 38 | (5.51%) |
| Husband | 25 | (3.62%) |
| Partner | 17 | (2.46%) |

LRD: Living related donor; LUD: living unrelated donor.

## Discussion

HLA compatibility was much higher in patients whose donors were related living donors compared to unrelated living donors. HLA compatibility with mothers and siblings was superior to that with any other donors.

Identical HLA always came from the patients' siblings and resulted in a 100% survival rate. The dysfunctions in the transplanted kidneys continued to be present at a median rate of 30% of patients, but these dysfunctions may not always be due to HLA compatibility, but to other factors that have not been analyzed in this study.

Of the 9 transplantectomy performed, 5 were from unrelated living donors (spouses, stepfathers, friends), and 4 were from related living donors (mother, sister, uncle). The latter mostly shared only one class 1 antigen and between 2 to 6 class 2 antigens. This indicates that while HLA is a predictor for determining if the graft will function properly, more in-depth studies are needed to identify the

**Tabla 3.** HLA in patients and related living donors

| | Madre | Padre | Hermano | Hermana | Primo | Prima | Tío | Tía |
|---|---|---|---|---|---|---|---|---|
| Identical HLA | 0 | 0 | 10 | 10 | 0 | 0 | 0 | 0 |
| Haplotype | | | | | | | | |
| 1 | 73 | 27 | 33 | 35 | 0 | 1 | 1 | 2 |
| 2 | 2 | 0 | 15 | 10 | 0 | 0 | 0 | 0 |
| Antigens | | | | | | | | |
| Class_1 | 97 | 67 | 59 | 71 | 3 | 1 | 9 | 14 |
| 0 | 1 | 3 | 2 | 8 | 0 | 3 | 0 | 1 |
| 1 | 22 | 9 | 14 | 23 | 1 | 1 | 5 | 4 |
| 2 | 20 | 21 | 16 | 16 | 1 | 0 | 0 | 3 |
| 3 | 39 | 25 | 22 | 15 | 0 | 0 | 3 | 5 |
| 4 | 9 | 6 | 7 | 9 | 1 | 0 | 0 | 2 |
| 5 | 4 | 5 | 0 | 2 | 0 | 0 | 0 | 0 |
| 6 | 3 | 1 | 0 | 6 | 0 | 0 | 1 | 0 |
| Class_2 | 102 | 70 | 65 | 83 | 5 | 2 | 8 | 15 |
| 0 | 0 | 1 | 1 | 4 | 0 | 0 | 0 | 0 |
| 1 | 7 | 1 | 3 | 5 | 1 | 2 | 0 | 1 |
| 2 | 10 | 11 | 12 | 10 | 2 | 1 | 0 | 1 |
| 3 | 16 | 11 | 10 | 13 | 0 | 1 | 2 | 3 |
| 4 | 21 | 10 | 13 | 20 | 2 | 1 | 2 | 4 |
| 5 | 18 | 15 | 11 | 12 | 0 | 0 | 3 | 3 |
| 6 | 13 | 5 | 8 | 9 | 0 | 0 | 0 | 2 |
| 7 | 7 | 7 | 5 | 1 | 0 | 0 | 1 | 1 |
| 8 | 6 | 3 | 1 | 8 | 0 | 0 | 0 | 0 |
| 9 | 2 | 7 | 1 | 3 | 0 | 0 | 0 | 0 |
| 10 | 2 | 0 | 1 | 2 | 0 | 0 | 0 | 0 |

**Tabla 4.** HLA in patients and unrelated living donors

| | Amiga | Amigo | Cuñada | Cuñado | Esposa | Esposo | Pareja |
|---|---|---|---|---|---|---|---|
| Identical HLA | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Haplotype | | | | | | | |
| 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Antigens | | | | | | | |
| Class_1 | 11 | 12 | 2 | 4 | 17 | 16 | 10 |
| 0 | 3 | 6 | 0 | 1 | 9 | 3 | 2 |
| 1 | 5 | 9 | 1 | 2 | 9 | 11 | 6 |
| 2 | 1 | 2 | 1 | 1 | 7 | 3 | 4 |
| 3 | 2 | 1 | 0 | 1 | 1 | 2 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Class_2 | 11 | 20 | 4 | 5 | 36 | 24 | 12 |
| 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 2 | 4 | 1 | 0 | 3 | 3 | 2 |
| 2 | 2 | 4 | 1 | 1 | 8 | 9 | 1 |
| 3 | 2 | 4 | 2 | 1 | 10 | 7 | 4 |
| 4 | 3 | 4 | 0 | 1 | 9 | 1 | 2 |
| 5 | 1 | 3 | 0 | 1 | 4 | 3 | 3 |
| 6 | 1 | 1 | 0 | 0 | 1 | 1 | 0 |
| 7 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 9 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Tabla 5.** Frequency of renal dysfunction and graft survival

| Dysfunction | n | % |
|---|---|---|
| Yes<br>Transplantectomy | 206<br>9 | 30.25<br>1.32 |
| No | 473 | 69.46 |
| Total | 679 | 100 |

specific types of antigens that, when combined, provide greater accuracy in predicting graft survival.

Studies that have analyzed human leukocyte antigen indicate that transplants performed between donors and recipients with identical HLA antigens carry a significantly lower immunological risk than those from donors with non-compatible HLA[12]. Conducting such studies demonstrates that analyzing HLA molecular mismatch should further improve organ allocation compatibility and stratify immunological risk[13,14]. In Mexico, the situation is similar, as studies conducted in the country have shown that HLA compatibility is important for graft survival. Matching at least two haplotypes is a good predictor for this[15-17].

We need to rethink the donor selection system through HLA, as suggested by Holscher C. and Jackson K., who propose a new model to redirect donors who are not entirely compatible by finding another recipient for that donor, akin to a donor exchange among patients. This would aim to achieve better compatibility[11,18].

The major strength of our study is the census-type sample size, which helps ensure a large sample power and makes the results much more valid and reliable.

The primary limitation of our study was the HLA measurement, as the most precise technique for identifying HLA antigens involves molecular methods such as polymerase chain reaction (PCR) and DNA sequencing, which were not used for identification. This could result in less precise measurements, potentially introducing bias in the classification.

## Conclusion

Patients undergoing transplantation must follow a series of protocols to ensure the success of the transplant, as it is a costly procedure for both institutions and patients. The analysis of HLA and its compatibility between donor and recipient can help predict if the graft will perform successfully post-surgery and during the patient's discharge. However, we should not rely solely on this procedure to guide donor decision-making.

It can be concluded that HLA compatibility is a good predictor for preventing rejection in kidney transplants from both related and unrelated living donors. Efforts should be made to identify the best donor options among all future donors and explore the possibility of exchanging donors, especially unrelated living donors, among recipients on the waiting list. This would aim to ensure better adaptability and graft survival in patients.

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None.

## Conflicts of interest

None.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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