Rev Colomb Cir. 2024;39:268-79
https://doi.org/10.30944/20117582.2491

ORIGINAL ARTICLE

Relationship between HLA compatibility and graft loss in renal transplant from a deceased donor: An analysis by propensity score matching in Colombia

Relación entre la compatibilidad del HLA y la pérdida del injerto en trasplante renal de donante cadavérico: Un análisis por *propensity score matching* en Colombia

Nicolás Lozano-Suárez, MD[1], Andrea García-López, MD[1], Andrea Gómez-Montero, MD[1], Fernando Girón-Luque, MD[1]

1 Colombiana de Trasplantes, Bogota, Colombia.

Abstract

Introduction. In Colombia, only 24% of patients on the waiting list received a renal transplant, most of them from cadaveric donors. HLA A-B-DR is considered for organ allocation, but recent evidence suggests that HLA A-B is not associated with transplant outcomes. The objective of this study was to evaluate the relevance of HLA A-B-DR on graft survival in kidney transplant recipients.

Methods. Retrospective cohort study that included 1337 kidney transplant recipients with a cadaveric donor in Colombiana de Trasplantes from 2008 to 2023. A Propensity Score Matching (PSM) was applied to adjust the covariates in comparison groups for compatibility, and the relationship of HLA A-B-DR with kidney graft survival was evaluated using the log rank test and Cox regression.

Results. There were 38.7% female patients, with median age of 47 years, and BMI 23.8 kg/m^2. After adjusting the covariates with PSM for the comparison groups, HLA A-B matching was not significantly related to graft loss, with HR of 0.99 (95% CI 0.71-1.37) and 0.75 (95% CI 0.55-1.02), respectively. Only HLA DR matching was significant for graft loss with an HR of 0.67 (95% CI 0.46-0.98).

Conclusions. This study suggests that HLA A-B matching does not significantly influence graft loss, whereas HLA DR matching does improve graft survival in renal transplantation with a cadaveric donor.

Keywords: organ transplantation; kidney transplantation; graft rejection; HLA antigens; survival analysis; propensity score.

Received: 08/31/2023 - Accepted: 11/03/2023 - Published online: 01/17/2024
Corresponding author: Andrea García-López, Av. Carrera 30 # 47 A - 47, Bogotá, D.C., Colombia. Tel.: +57 3005024618.
Email: aegarcia@colombianadetrasplantes.com
Cite as: Lozano-Suárez N, García-López A, Gómez-Montero A, Girón-Luque F. Relación entre la compatibilidad del HLA y la pérdida del injerto en trasplante renal de donante cadavérico: Un análisis por propensity score matching en Colombia. Rev Colomb Cir. 2024;39:268-79. https://doi.org/10.30944/20117582.2491

Resumen

Introducción. En Colombia, solo un 24 % de los pacientes en lista recibieron un trasplante renal, la mayoría de donante cadavérico. Para la asignación de órganos se considera el HLA A-B-DR, pero la evidencia reciente sugiere que el HLA A-B no está asociado con los desenlaces del trasplante. El objetivo de este estudio fue evaluar la relevancia del HLA A-B-DR en la sobrevida del injerto de los receptores de trasplante renal.

Métodos. Estudio de cohorte retrospectivo que incluyó 1337 trasplantados renales con donante cadavérico en Colombiana de Trasplantes, desde 2008 a 2023. Se aplicó un *propensity score matching* (PSM) para ajustar las covariables en grupos de comparación por compatibilidad y se evaluó la relación del HLA A-B-DR con la sobrevida del injerto renal por medio de la prueba de *log rank* y la regresión de Cox.

Resultados. Los pacientes fueron mujeres en un 38,7 %, con mediana de edad de 47 años y de índice de masa corporal de 23,8 kg/m^2. Tras ajustar por PSM las covariables para los grupos de comparación, la compatibilidad del HLA A-B no se relacionó significativamente con la pérdida del injerto, con HR de 0,99 ($IC_{95\%}$ 0,71-1,37) para HLA A y 0,75 ($IC_{95\%}$ 0,55-1,02) para HLA B. Solo la compatibilidad por HLA DR fue significativa para pérdida del injerto con un HR de 0,67 ($IC_{95\%}$ 0,46-0,98).

Conclusión. Este estudio sugiere que la compatibilidad del HLA A-B no influye significativamente en la pérdida del injerto, mientras que la compatibilidad del HLA DR sí mejora la sobrevida del injerto en trasplante renal con donante cadavérico.

Palabras clave: trasplante de órganos; trasplante de riñón; rechazo de injerto; antígenos HLA; análisis de supervivencia; puntaje de propensión.

Introduction

Kidney transplant is the best option in patients with chronic kidney disease (CKD) in advanced stages [1,2]. According to the report of the transplant donation network, by 2022 in Colombia there were 3328 patients on the waiting list for a kidney transplant and 822 of these procedures were performed, that is, only 24% of patients were benefited, demonstrating a gap between the number of organs available for transplant and the demand for an organ. On the other hand, more than 70% of kidney transplants in Colombia are from a cadaveric donor and less than 30% from a living donor [3]. Allocating organs from deceased donors involves evaluating patients on the waiting list and awarding points based on factors such as age, time on the list, blood group compatibility, and human leukocyte antigen (HLA) DR, B, and A [4].

Human leukocyte antigens (HLA) are a group of proteins found on cell surfaces and are encoded by histocompatibility complex (MHC) genes [5]. They are essential for immunological surveillance, allowing the recognition of own, pathogenic or tumor cells [6]. HLAs are divided into class I, II and III according to their chemical and biological properties, but only class I (HLA-A, B and C) and II (HLA-DR, DQ and DP) play a relevant role in the transplant immunology [7]. These are especially relevant in the development of specific antibodies for HLA antigens, since the generation of this type of antibodies can lead to rapid rejection of the organ [6].

Previous studies demonstrate that HLA compatibility or incompatibility (mismatch) are relevant factors for long-term kidney graft outcomes. Among the most distinguished are those published by the collaborative transplant study (CTS), where the usefulness and importance of HLA in kidney transplantation of adult [8,9] or pediatric patients [10,11], with a cadaveric donor [11-13] or with a living donor [11,14,15]. Initially, health systems such as in the United States considered these factors in organ allocation, but found significant difficulty in finding perfect matches, which was worse in ethnic minorities [16]. Furthermore, recent evidence that HLA A and B matching is not significantly associated with graft

loss [16,17] led to the removal of these factors from the organ allocation model in the country, leaving only HLA DR matching [18,19].

Given the importance of kidney transplantation by cadaveric donors in Colombia, the gap between supply and demand of organs and the changes in the evidence on HLA compatibility and transplant outcomes, the main objective of this study was to evaluate by means of a propensity score matching the association between HLA A, B, and DR compatibility and graft survival of kidney transplant patients with a cadaveric donor, adjusting the covariates age, sex, BMI, etiology of CKD, type of previous dialysis, cold ischemia time, cadaveric donor with extended criteria and type of induction.

Methods

Study of a retrospective cohort of kidney transplant patients in Colombiana de Transplantes, with a cadaveric donor, from July 2008 to May 2023. Sampling was consecutive at convenience. Minor patients and patients for whom information on HLA compatibility could not be retrieved were excluded. Patients with partial or complete HLA DR, B, and A compatibility were grouped.

The primary outcome was graft loss, defined as definitive return to dialysis after transplant. Pre-transplant clinical characterization variables were included, such as comorbidities (high blood pressure, diabetes, chronic lung disease, and surgical history), age, sex, BMI, type of previous dialysis (hemodialysis, peritoneal or pre-dialysis), etiology of chronic kidney disease (congenital, unknown, diabetes, glomerular, arterial hypertension, obstructive and other). Additionally, variables related to the transplant were evaluated, such as the type of induction (Alemtuzumab, Basiliximab, Antithymocyte Globulin, and others), the number of transplants, the cold ischemia time, the HLA A, B, and DR compatibility, and the qualitative result of the transplant. PRA for HLA I and II. Expanded criteria included donors aged ≥ 60 years or > 50 years with any of the following: blood creatinine > 1.5 mg/dl, a history of arterial hypertension, or a cause of cardiovascular death [20].

Although observational studies are relevant due to the large amount of historical data that can be collected, they run the risk of presenting systematic differences in the characteristics of the comparison groups, which can bias the results obtained [20-22]. Therefore, for the statistical analysis it was considered to use a propensity score matching (PSM), which by means of a score (propensity score-PS) groups and stratifies the comparison groups so that they have similar covariates, reducing confusion bias. in the results [22].

The PSM was used to adjust the comparison groups, with partial or complete matching and without HLA A, B, and DR matching, following the step methodology described by Zhao et al. [22]. First, multiple imputation was performed using the MICE package [23]. Second, the groups in the PSM were adjusted for statistically and clinically significant variables. Statistically significant variables were obtained through logistic regression with automatic selection by AIC (Akaike information criterion) for each exposure group (Partial or full HLA DR compatibility). Clinically significant variables included immunological and clinical aspects that are associated with graft survival (age, sex, donor with expanded criteria, PRA I-II, and cold ischemia).

In the third step, the "nearest neighbor" and "optimal" clustering methods were tested. The robustness and balance of the grouping was then verified by means of a standardized mean difference (SMD) less than 0.25, a variance ratio (VR) between 0.5-2 and a graphical evaluation; The grouping method with the best balance was chosen [22,24,25]. Finally, the groups adjusted by PSM were obtained, to which descriptive and bivariate statistics were applied, comparing patients with and without compatibility by HLA A, B, DR.

Depending on the distribution of the variables, the Students' t test and the Mann Whitney U test were used for numerical variables, and the chi square and Fisher tests were used for categorical variables. A Kaplan-Meier survival analysis was performed for graft loss and kidney survival was compared in patients with and without compatibility using the log rank test. Additionally, a Cox

model was created to quantify the association of compatibility in the main outcome, describing the hazard ratios (HR) with their respective confidence interval and p-value. Statistical significance was defined with a p value less than 0.05. All analyzes were performed in R Studio statistical software version 4.2.2.

Results

During the observation time, 1455 kidney transplants were performed with a cadaveric donor, 1337 recipients were included in the analysis and 118 patients were excluded because HLA compatibility information could not be recovered. The included patients were 38.7% female, with a median age of 47 years and a BMI of 23.8 kg/m^2 (Table 1). Among the history, arterial hypertension (71%), diabetes mellitus (17.9%), and surgical history (91.6%) were prevalent. The etiology of CKD was unknown in 46.2%, and the most common type of dialysis was hemodialysis (59.2%) compared to peritoneal (35.8%). The patients had a positive Antibody Reactive Panel (ARP) I and II in 60% and 20.9% were expanded criteria donors, with a median cold ischemia of 15 hours and induction with antithymocyte globulin in 58% of cases.

HLA A compatibility

When comparing patients with partial or total HLA A compatibility and those with complete incompatibility, significant differences were found in the prevalence of hypertension (p=0.02), surgical history (p<0.001), cold ischemia time (p=0.001), type of peritoneal dialysis (p=0.03), and type of induction with antithymocyte globulin (p=0.01). When grouping by PSM, two groups of 385 patients each were created, with all variables balanced and without significant differences in the bivariate analysis.

When comparing the kidney graft survival of the patients, a one-year survival rate of 84.6% (95%CI 81-88.4%) and a five-year survival rate of 78% (95%CI 73.1-83.0%) was calculated for patients with compatibility and 85.5% (95%CI 82-89.2%) and 75.3% (95%CI 69.9-81.2%) respectively for patients with HLA A incompatibility (Figure 1). When performing the log rank test, no statistically significant differences were found (p=0.9) and in the Cox regression an HR of 0.99 (95% CI 0.71-1.37; p=0.95) was estimated.

HLA B compatibility

Statistically significant differences were found when comparing patients with HLA B compatibility (partial or total) and incompatibility in the prevalence of hypertension (p=0.01), surgical history (p<0.001), frequency of transplants with expanded criteria (p=0.002), cold ischemia time (p=0.005), diabetic etiology (p=0.02), type of induction with antithymocyte globulin (p=0.008) and with basiliximab (p=0.02). After applying the PSM technique, two groups of 448 patients were formed. The only variable that could not be balanced and had significant differences in the bivariate analysis was the number of transplants (p=0.03).

In the survival analysis, graft survival was found in patients with HLA B compatibility at one year of 87% (95%CI 84.9-91.1%) and at 5 years of 79.6% (95%CI 74.9-91.1%) (Figure 2), while in patients with incompatibility there was a one-year survival of 82% (95%CI 78.3-85.8%) and a five-year survival of 73% (95%CI 68-85.8%). But the difference was not statistically significant when applying the log rank test (p=0.065). Given that it was not possible to balance the number of transplants by PSM, it was included in the Cox regression, showing an HR for HLA B compatibility of 0.75 (95%CI 0.55-1.02; p=0.072).

HLA DR compatibility

The variables with statistically significant differences between patients with and without HLA DR compatibility were BMI (p<0.001), cold ischemia (p=0.004) and types of induction with basiliximab (p=0.02), antithymocyte globulin. (p=0.01) and another scheme (p=0.009). After the application of the PSM, two groups of 278 patients each were created, without significant differences in the bivariate analysis and with all variables balanced.

Table 1. Descriptive and bivariate analysis of the total population and the groups adjusted by propensity score matching for compatibility/incompatibility according to HLA A, B and DR.

		HLA A compatibility without PSM			HLA A compatibility with PSM			HLA B compatibility without PSM		
	Total	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
	(n=1337)	(n=952)	(n=385)		(n=385)	(n=385)		(n=889)	(n=448)	
Age (years)a										
Mean (SD)	45.7 (13.8)	45.7 (13.7)	45.6 (14.0)	0.908	46.0 (13.6)	45.6 (14.0)	0.805	45.8 (13.5)	45.5 (14.3)	0.924
Median [IQR]	47 [37-56]	47 [37-56]	47 [37-56]		46 [36-56]	47 [37-56]		47 [37-56]	48 [36-57]	
Sex, n (%)b										
Male	820 (61.3%)	591 (62.1%)	229 (59.5%)	0.411	234 (60.8%)	229 (59.5%)	0.768	542 (61.0%)	278 (62.1%)	0.744
Female	517 (38.7%)	361 (37.9%)	156 (40.5%)		151 (39.2%)	156 (40.5%)		347 (39.0%)	170 (37.9%)	
BMI (kg/m^2)a										
Mean (SD)	24.1 (4.19)	24.1 (4.20)	24.2 (4.19)	0.550	24.2 (4.15)	24.2 (4.19)	0.980	24.2 (4.32)	23.9 (3.93)	0.499
Median [IQR]	23.8 [21.2-26.7]	23.7 [21.1-26.6]	23.9 [21.3-26.8]		24 [21.3-26.7]	23.9 [21.3-26.8]		23.9 [21-26.9]	23.7 [21.2-26.4]	
History, n (%)b										
HTA	951 (71.1%)	695 (73.0%)	256 (66.5%)	0.020*	267 (69.4%)	256 (66.5%)	0.440	652 (73.3%)	299 (66.7%)	0.014*
DM	239 (17.9%)	169 (17.8%)	70 (18.2%)	0.914	61 (15.8%)	70 (18.2%)	0.442	150 (16.9%)	89 (19.9%)	0.203
COPD	20 (1.5%)	14 (1.5%)	6 (1.6%)	1	4 (1.0%)	6 (1.6%)	0.750	13 (1.5%)	7 (1.6%)	1
AMI	29 (2.2%)	18 (1.9%)	11 (2.9%)	0.372	4 (1.0%)	11 (2.9%)	0.117	21 (2.4%)	8 (1.8%)	0.628
CVD	19 (1.4%)	14 (1.5%)	5 (1.3%)	1	4 (1.0%)	5 (1.3%)	1	14 (1.6%)	5 (1.1%)	0.671
Immune	105 (7.9%)	75 (7.9%)	30 (7.8%)	1	30 (7.8%)	30 (7.8%)	1	71 (8.0%)	34 (7.6%)	0.883
Surgical	1225 (91.6%)	894 (93.9%)	331 (86.0%)	<0.001*	333 (86.5%)	331 (86.0%)	0.916	834 (93.8%)	391 (87.3%)	<0.001*
Number of transplanta										
Mean (SD)	1.02 (0.186)	1.02 (0.185)	1.03 (0.189)	0.270	1.02 (0.161)	1.03 (0.189)	0.247	1.02 (0.203)	1.02 (0.148)	0.899
Median [IQR]	1 [1-1]	1 [1-1]	1 [1-1]		1 [1-1]	1 [1-1]		1 [1-1]	1 [1-1]	
Positive PRA I, n (%)b	807 (60.4%)	577 (60.6%)	230 (59.7%)	0.816	242 (62.9%)	230 (59.7%)	0.415	545 (61.3%)	262 (58.5%)	0.348
Positive PRA II, n (%)b	809 (60.5%)	578 (60.7%)	231 (60.0%)	0.857	239 (62.1%)	231 (60.0%)	0.605	545 (61.3%)	264 (58.9%)	0.435
Extended criteria, n (%)b	280 (20,9 %)	193 (20,3 %)	87 (22,6 %)	0,383	90 (23,4 %)	87 (22,6 %)	0,864	164 (18,4 %)	116 (25,9 %)	0,002*
Cold ischemia (hours)a										
Mean (SD)	14,0 (8,38)	14,6 (8,05)	12,7 (9,01)	0,001*	13,2 (8,55)	12,7 (9,01)	0,456	14,6 (7,83)	12,9 (9,26)	0,005*
Median [IQR]	15 [10.3-20]	15 [10.3-20]	14 [0.4-19]		14 [7-19]	14 [0.4-19]		15 [10.5-20]	14 [0.4-20]	
Etiology, n (%)b										
Hipertensive	136 (10.2%)	98 (10.3%)	38 (9.9%)	0.894	37 (9.6%)	38 (9.9%)	1	100 (11.2%)	36 (8.0%)	0.082
Glomerular	223 (16.7%)	160 (16.8%)	63 (16.4%)	0.907	78 (20.3%)	63 (16.4%)	0.192	153 (17.2%)	70 (15.6%)	0.511
Diabetic	189 (14.1%)	134 (14.1%)	55 (14.3%)	0.989	50 (13.0%)	55 (14.3%)	0.674	112 (12.6%)	77 (17.2%)	0.028*
Congenital	73 (5.5%)	54 (5.7%)	19 (4.9%)	0.866	22 (5.7%)	19 (4.9%)	0.748	50 (5.6%)	23 (5.1%)	0.806
Obstructive	39 (2.9%)	28 (2.9%)	11 (2.9%)	1	6 (1.6%)	11 (2.9%)	0.326	24 (2.7%)	15 (3.3%)	0.622
Other	59 (4.4%)	45 (4.7%)	14 (3.6%)	0.464	18 (4.7%)	14 (3.6%)	0.588	43 (4.8%)	16 (3.6%)	0.356
Unknown	618 (46.2%)	433 (45.5%)	185 (48.1%)	0.428	174 (45.2%)	185 (48.1%)	0.470	407 (45.8%)	211 (47.1%)	0.690
Type of dialysis, n (%)b										
Hemodialysis	791 (59.2%)	550 (57.8%)	241 (62.6%)	0.117	233 (60.5%)	241 (62.6%)	0.604	525 (59.1%)	266 (59.4%)	0.957
Peritoneal	478 (35.8%)	358 (37.6%)	120 (31.2%)	0.030*	125 (32.5%)	120 (31.2%)	0.757	323 (36.3%)	155 (34.6%)	0.572
Preanalysis	89 (6.7%)	63 (6.6%)	26 (6.8%)	1	27 (7.0%)	26 (6.8%)	1	53 (6.0%)	36 (8.0%)	0.186
Induction type, n (%)b										
Basiliximab	138 (10.3%)	108 (11.3%)	30 (7.8%)	0.066	31 (8.1%)	30 (7.8%)	1	104 (11.7%)	34 (7.6%)	0.025*
Antithymocyte Globulin	776 (58.0%)	533 (56.0%)	243 (63.1%)	0.019*	238 (61.8%)	243 (63.1%)	0.765	493 (55.5%)	283 (63.2%)	0.008*
Other	16 (1.2%)	12 (1.3%)	4 (1.0%)	0.952	7 (1.8%)	4 (1.0%)	0.543	8 (0.9%)	8 (1.8%)	0.254

SD: Standard deviation; IQR: Interquartile range; BMI: Body Mass Index; HTA: Hypertension; DM: Diabetes Mellitus; COPD: Chronic Obstructive Pulmonary Disease; AMI: Acute Myocardial Infarction; CVD: Cerebrovascular Disease.
[a]Mann Whitney U test bChi square test *Statistically significant result with p<0.05.
Source: Authors' own elaboration.

Table 1 (continued)

		HLA A compatibility with PSM			HLA DR compatibility without PSM			HLA DR compatibility with PSM		
	Total	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
	(N=1337)	(n=448)	(n=448)		(n=1059)	(n=278)		(n=278)	(n=278)	
Age (years)a										
Mean (SD)	45,7 (13,8)	45.3 (14.2)	45.5 (14.3)	0.698	46.0 (13.5)	44.4 (14.5)	0.140	44.9 (14.2)	44.4 (14.5)	0.797
Median [IQR]	47 [37-56]	47 [36-56]	48 [36-57]		47 [37- 56]	46 [35- 56]		45 [36-56]	46 [35-56]	
Sex, n (%)b										
Male	820 (61,3 %)	272 (60.7%)	278 (62.1%)	0.731	659 (62.2%)	161 (57.9%)	0.212	172 (61.9%)	161 (57.9%)	0.386
Female	517 (38,7 %)	176 (39.3%)	170 (37.9%)		400 (37.8%)	117 (42.1%)		106 (38.1%)	117 (42.1%)	
BMI (kg/m^2)a										
Mean (SD)	24,1 (4,19)	23.9 (4.33)	23.9 (3.93)	0.649	24.3 (4.24)	23.3 (3.93)	<0.001*	23.2 (4.07)	23.3 (3.93)	0.570
Median [IQR]	23,8 [21,2-26,7]	23.4 [21-26.8]	23.7 [21.2-26.4]		24 [21.4-26.9]	23 [20.8-25.9]		23 [20.3-2.6]	23 [20.8-25.9]	
History, n (%)b										
HTA	951 (71,1 %)	302 (67.4%)	299 (66.7%)	0.886	763 (72.0%)	188 (67.6%)	0.169	192 (69.1%)	188 (67.6%)	0.784
DM	239 (17,9 %)	81 (18.1%)	89 (19.9%)	0.550	191 (18.0%)	48 (17.3%)	0.833	61 (21.9%)	48 (17.3%)	0.199
COPD	20 (1,5 %)	8 (1.8%)	7 (1.6%)	1	16 (1.5%)	4 (1.4%)	0.996	0 (0%)	4 (1.4%)	0.132
AMI	29 (2,2 %)	10 (2.2%)	8 (1.8%)	0.811	25 (2.4%)	4 (1.4%)	0.479	7 (2.5%)	4 (1.4%)	0.542
CVD	19 (1,4 %)	6 (1.3%)	5 (1.1%)	1	14 (1.3%)	5 (1.8%)	0.754	3 (1.1%)	5 (1.8%)	0.721
Immune	105 (7,9 %)	36 (8.0%)	34 (7.6%)	0.900	84 (7.9%)	21 (7.6%)	0.933	23 (8.3%)	21 (7.6%)	0.875
Surgical	1225 (91,6 %)	398 (88.8%)	391 (87.3%)	0.536	975 (92.1%)	250 (89.9%)	0.305	261 (93.9%)	250 (89.9%)	0.120
Number of transplanta										
Mean (SD)	1,02 (0,186)	1.00 (0.0945)	1.02 (0.148)	0.033*	1.03 (0.205)	1.01 (0.0847)	0.228	1.00 (0.0600)	1.01 (0.0847)	0.564
Median [IQR]	1 [1-1]	1 [1-1]	1 [1-1]		1 [1-1]	1 [1-1]		1 [1-1]	1 [1-1]	
Positive PRA I, n (%)b	807 (60,4 %)	275 (61.4%)	262 (58.5%)	0.413	641 (60.5%)	166 (59.7%)	0.858	165 (59.4%)	166 (59.7%)	1
Positive PRA II, n (%)b	809 (60,5 %)	274 (61.2%)	264 (58.9%)	0.539	643 (60.7%)	166 (59.7%)	0.813	168 (60.4%)	166 (59.7%)	0.931
Extended criteria, n (%)b	280 (20,9 %)	111 (24,8 %)	116 (25,9 %)	0,758	223 (21,1 %)	57 (20, 5%)	0,905	57 (20.5%)	57 (20.5%)	1
Cold ischemia (hours)a										
Mean (SD)	14,0 (8,38)	13,3 (8,25)	12,9 (9,26)	0,740	13,7 (8,33)	15,2 (8,48)	0,004*	14.7 (7.68)	15.2 (8.48)	0.221
Median [IQR]	15 [10,3-20]	14 [8.5-19]	14 [0.4-20]		14.5 [9-19]	16 [11-21]		15 [11-19]	16 [11-21]	
Etiology, n (%)b										
Hipertensive	136 (10,2 %)	43 (9.6%)	36 (8.0%)	0.479	112 (10.6%)	24 (8.6%)	0.399	26 (9.4%)	24 (8.6%)	0.882
Glomerular	223 (16,7 %)	71 (15.8%)	70 (15.6%)	1	185 (17.5%)	38 (13.7%)	0.154	54 (19.4%)	38 (13.7%)	0.086
Diabetic	189 (14,1 %)	60 (13.4%)	77 (17.2%)	0.137	146 (13.8%)	43 (15.5%)	0.535	48 (17.3%)	43 (15.5%)	0.646
Congenital	73 (5,5 %)	29 (6.5%)	23 (5.1%)	0.475	57 (5.4%)	16 (5.8%)	0.924	11 (4.0%)	16 (5.8%)	0.430
Obstructive	39 (2,9 %)	13 (2.9%)	15 (3.3%)	0.847	30 (2.8%)	9 (3.2%)	0.875	5 (1.8%)	9 (3.2%)	0.416
Other	59 (4,4 %)	25 (5.6%)	16 (3.6%)	0.200	50 (4.7%)	9 (3.2%)	0.363	10 (3.6%)	9 (3.2%)	1
Unknown	618 (46,2 %)	207 (46.2%)	211 (47.1%)	0.840	479 (45.2%)	139 (50.0%)	0.176	124 (44.6%)	139 (50.0%)	0.234
Type of dialysis, n (%)b										
Hemodialysis	791 (59,2 %)	266 (59.4%)	266 (59.4%)	1	619 (58.5%)	172 (61.9%)	0.335	180 (64.7%)	172 (61.9%)	0.537
Peritoneal	478 (35,8 %)	155 (34.6%)	155 (34.6%)	1	386 (36.4%)	92 (33.1%)	0.332	82 (29.5%)	92 (33.1%)	0.410
Preanalysis	89 (6,7 %)	37 (8.3%)	36 (8.0%)	1	65 (6.1%)	24 (8.6%)	0.176	26 (9.4%)	24 (8.6%)	0.882
Induction type, n (%)b										
Basiliximab	138 (10,3 %)	31 (6.9%)	34 (7.6%)	0.796	120 (11.3%)	18 (6.5%)	0.023*	14 (5.0%)	18 (6.5%)	0.584
Antithymocyte Globulin	776 (58,0 %)	288 (64.3%)	283 (63.2%)	0.781	634 (59.9%)	142 (51.1%)	0.010*	152 (54.7%)	142 (51.1%)	0.444
Other	16 (1,2 %)	8 (1.8%)	8 (1.8%)	1	8 (0.8%)	8 (2.9%)	0.009*	7 (2.5%)	8 (2.9%)	1

SD: Standard deviation; IQR: Interquartile range; BMI: Body Mass Index; HTA: Hypertension; DM: Diabetes Mellitus; COPD: Chronic Obstructive Pulmonary Disease; AMI: Acute Myocardial Infarction; CVD: Cerebrovascular Disease.
[a]Mann Whitney U test bChi square test *Statistically significant result with p<0.05.
Source: Authors' own elaboration.

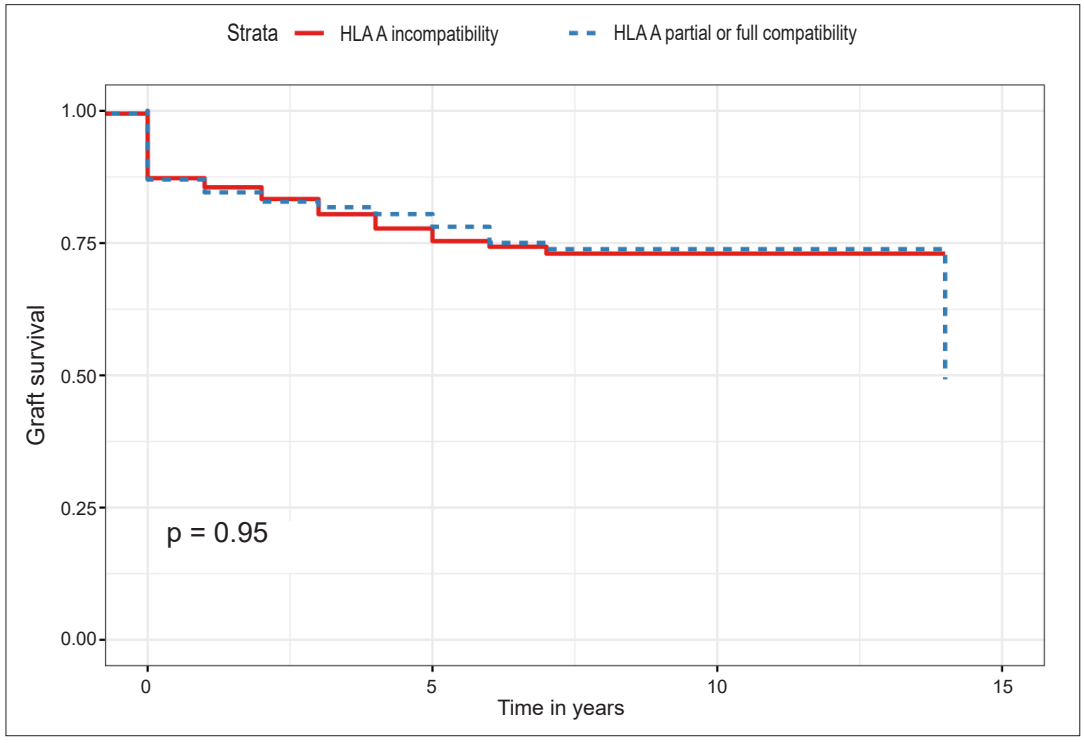

Figure 1. Kaplan Meier curve for graft survival in patients with HLA A compatibility/incompatibility.
Source: Authors' own elaboration.

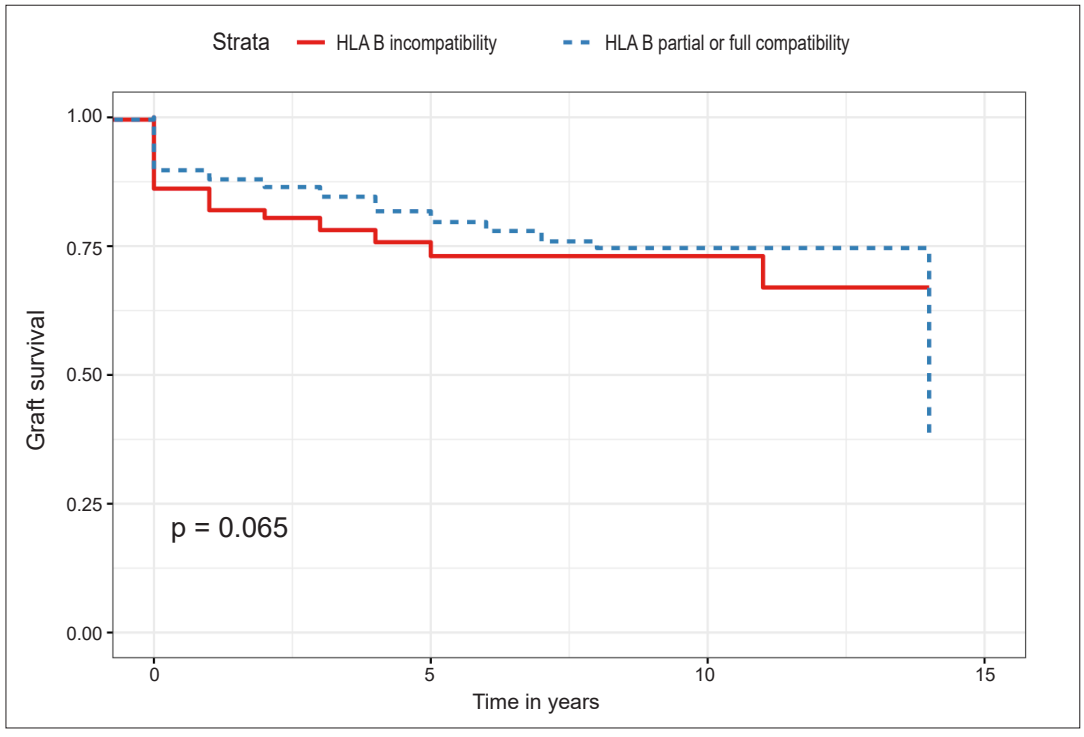

Figure 2. Kaplan Meier curve for graft survival in patients with HLA B compatibility/incompatibility.
Source: Authors' own elaboration.

When comparing the survival of the kidney graft, a one-year survival rate of 87.6% (95%CI 83.7-91.7%) and a five-year survival rate of 79.4% (95% CI 73.6-85) were found for patients with compatibility and 80.9% (95%CI 76.2-85.8%) and 71.4% (95%CI 65.2-78.2%) for patients with HLA incompatibility DR (Figure 3). When performing the log rank test, a statistically significant difference was observed (p=0.042), and in the Cox regression, an HR of 0.67 (95%CI 0.46-0.98; p=0.04).

Discussion

Among the most relevant findings of this research, it was found that when adjusting the comparison groups by PSM, only HLA DR compatibility had a statistically significant association with graft survival. When adjusting for covariates, HLA A and B compatibility did not have a significant association with graft loss in transplant recipients from cadaveric donors. This same phenomenon was described in 2018 in a meta-analysis [17] of 23 studies and 486,000 kidney transplant recipients, which included four studies and 146,000 patients that evaluated the relationship of HLA B with graft loss, finding a non-significant HR of 1.01 (95%CI 0.9-1.15; p=0.83). Similarly, to study the association of HLA A, they included three studies with more than 40,000 recipients, again reporting a non-significant HR of 1.06 (95%CI 0.9-1.15; p=0.83). The HLA A and B results were confirmed in subsequent sensitivity analyses.

Some authors suggest that the decreased relevance of HLA in kidney transplant outcomes may be due to advances in immunosuppression, as well as the prioritization of other factors such as donor age and living donor transplantation [26,27]. International multicenter cohorts, such as those from the collaborative transplant study, have demonstrated on multiple occasions and populations that patients with HLA A, B, and DR incompatibility have lower graft survival [10-12,15]. Other recently published studies demonstrated the relevance of HLA

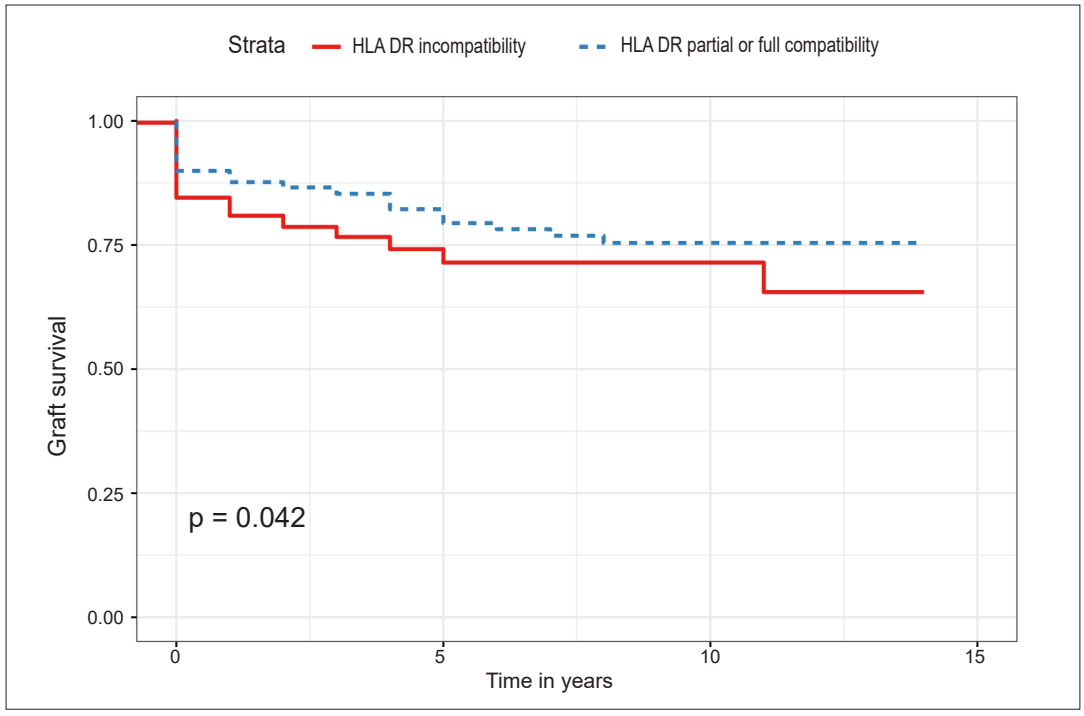

Figure 3. Kaplan Meier curve for graft survival in patients with HLA DR compatibility/incompatibility.
Source: Authors' own elaboration.

compatibility in transplantation with a cadaveric donor and expanded criteria [13]. Lim et al. [27] in a cohort of 8036 kidney transplants studied HLA A, B and DR incompatibility in a subgroup of cadaveric donors, reporting an adjusted HR of 1.58 (95%CI 1.07-2.34). Additionally, they reported an HR of 1.41 (95%CI 1.11-1.79) for patients with HLA A and B incompatibilities and 1.22 (95%CI 1.05-1.42) for complete HLA DR incompatibility.

Seen this phenomenon from a public health perspective, the association of HLA with the outcomes of kidney transplantation has determined the allocation of organs in different countries around the world. In countries like the United States, HLA A and B are no longer taken into account in the assignment score, considering their lower relevance in transplant outcomes and a high difficulty for their compatibility in ethnic minorities [18,19]. Similarly, in the United Kingdom, a cohort of 7350 kidney transplant recipients was studied, finding that HLA A had no effect on transplant outcomes, but that B and DR did impact graft loss [28,29]. Therefore, in the United Kingdom organ allocation system for cadaveric donor kidney transplantation, the HLA A compatibility criterion was eliminated [29].

On the contrary, countries and associations such as Australia, New Zealand, Canada, EuroTransplant (Austria, Belgium, Germany, Luxembourg, Netherlands, and Slovenia), and ScandiaTransplant (Denmark, Finland, Norway, Sweden, and Iceland) continue to consider HLA A-B-DR within of their organ allocation systems [30-33]. It is important to highlight that these organ allocation policies are mostly supported by data from national cohorts that allow us to understand the factors associated with the outcomes of kidney transplantation and the particularities of the system's functioning.

Understanding the gap between the supply and demand of organs in Colombia, especially in kidney transplantation, where 76% of patients on the waiting list did not receive a transplant in 2022 [3], some authors have proposed expanding the legal presumption of organ donation, as well as the creation of a kidney exchange program [34]. Likewise, the understanding and study of the role of HLA, especially A and B, in the country's organ allocation process is relevant.

In Colombia, the organ allocation system in kidney transplantation is carried out through a score that includes eight aspects [4]:

1. The geographic level, where a local assignment is prioritized, if it is not found, it is passed to a regional recipient and finally National.
2. The blood group, which confers between 0-15 points in case of compatibility.
3. The relationship between the age group of the recipient and the donor: if the donor is under 30 years of age and the recipient is under 60, 2 points are added; if the donor and recipient are over 60 years of age, 2 points are awarded and if they are under 18 years old 4 points.
4. Pediatric patients with donors under 35 years of age can receive between 6-9 points.
5. The history of being a living donor adds 4 points or having expressed a positive will in the national donor registry adds 1 point.
6. Time on the waiting list adds one point for each year listed.
7. The compassionate state that applies at the local level for patients at risk of loss of vascular access or without the possibility of peritoneal dialysis.
8. HLA compatibility, where the fully compatible HLA DR generates 12 points and partially 6 points, the complete compatibility by A and B generates 4 points, and the complete compatibility of HLA A-B-DR contributes 10 more points. In total, a patient with complete HLA DR matching would have 12 points, a patient with complete HLA A-B matching would have 4 points and a patient with complete HLA A-B-DR matching would have 26 points.

Therefore, in our country the compatibility of HLA A and B can make the difference between whether or not a patient receives a kidney transplant, which should be studied in light of the current evidence presented on the role of HLA A and B in graft loss.

The results presented here have to be understood within the limitations of the research. First, the retrospective nature of the study decreases the quality of the information collected. Second, being an observational study, it has an increased risk of bias and confusion factors, which were reduced through the use of propensity score matching. Third, the PSM mainly considered recipient and transplant factors, lacking stratification by donor conditions. Fourth, the results presented, although they have a considerable sample size, are from a single center, which limits the generalization of the results at the national level.

Conclusion

In conclusion, this study reported that HLA A and B compatibility does not have a significant relationship with graft loss when adjusting the covariates by propensity score matching, while HLA DR compatibility improves kidney graft survival in a statistically significant manner. These results could be a basis for the evaluation by decision makers of the relevance and scoring within organ allocation. It is emphasized that multicenter studies are required, with a larger sample in the country, to validate these results at the national level.

Compliance with ethical standards

Informed consent: According to resolution 8430 of 1993, this is a risk-free study that did not require informed consent from the patients given its retrospective nature, in which absolute confidentiality of the identification data was kept. All transplants performed complied with the Istanbul declaration for organ donation [35], as well as international guidelines for research in human beings. The study was endorsed with No. 00715 by the Dexa Diab ethics committee.

Conflict of interest: The authors declare no conflicts of interest.

Use of artificial intelligence: The authors declared that they did not use artificial intelligence (AI)-assisted technologies (such as large language models, chatbots, or image creators) in the production of this work.

Funding: Funded by the authors.

Author's contributions

- Conception and design of the study: Nicolás Lozano-Suárez, Andrea García-López, Andrea Gómez-Montero, Fernando Girón-Luque.
- Acquisition of data: Nicolás Lozano-Suárez.
- Data analysis and interpretation: Nicolás Lozano-Suárez, Andrea García-López, Andrea Gómez-Montero, Fernando Girón-Luque.
- Drafting the manuscript: Nicolás Lozano-Suárez.
- Critical review: Nicolás Lozano-Suárez, Andrea García-López, Andrea Gómez-Montero, Fernando Girón-Luque.

References

1. Ghanta M, Jim B. Renal transplantation in advanced chronic kidney disease patients. Med Clin Nort Am. 2016;100:465-76. https://doi.org/10.1016/j.mcna.2015.12.003
2. Espitia D, García-López A, Patino-Jaramillo N, Girón-Luque F. Desenlaces a largo plazo en pacientes trasplantados renales con donantes de criterios expandidos: experiencia de 10 años. Rev Colomb Cir. 2022;37:214-25. https://doi.org/10.30944/20117582.1052
3. Instituto Nacional de Salud, Ministerio de Salud y Protección Social. Informe ejecutivo Red de Donación y Trasplantes 2022. Bogotá, D.C., Colombia;2022. Fecha de consulta: 12 de septiembre de 2023 Disponible en: https://www.ins.gov.co/Direcciones/RedesSaludPublica/DonacionOrganosYTejidos
4. Ministerio de Salud, Instituto Nacional de Salud, Red de donación y trasplantes. Criterios de asignación para trasplante renal en Colombia. Bogotá, D.C., Colombia; 2018. Fecha de consulta: 9 de septiembre de 2023. Disponible en: https://www.ins.gov.co/direcciones/redessaludpublica/donacionorganosytejidos/documentostecnicos/forms/allitems.aspx
5. Alelign T, Ahmed MM, Bobosha K, Tadesse Y, Howe R, Petros B. Kidney transplantation: The challenge of human leukocyte antigen and its therapeutic strategies. J Immunol Res. 2018;e5986740. https://doi.org/10.1155/2018/5986740
6. Montgomery RA, Tatapudi VS, Leffell MS, Zachary AA. HLA in transplantation. Nat Rev Nephrol. 2018;14:558-70. https://doi.org/10.1038/s41581-018-0039-x
7. Trivedi VB, Dave AP, Dave JM, Patel BC. Human leukocyte antigen and its role in transplantation biology. Transplant Proc. 2007;39:688-93. https://doi.org/10.1016/j.transproceed.2007.01.066
8. Süsal C, Roelen DL, Fischer G, Campos EF, Gerbase-DeLima M, Hönger G, et al. Algorithms for the determination of unacceptable HLA antigen mismatches

in kidney transplant recipients. Tissue Antigens. 2013;82:83-92. https://doi.org/10.1111/tan.12137

9. Süsal C, Fichtner A, Tönshoff B, Mehrabi A, Zeier M, Morath C. Clinical relevance of HLA antibodies in kidney transplantation: recent data from the Heidelberg Transplant Center and the Collaborative Transplant Study. J Immunol Res. 2017:e5619402. https://doi.org/10.1155/2017/5619402
10. Williams RC, West LJ, Opelz G. The risk of failure with HLA mismatch and recipient age in first pediatric (< 18 years) kidney transplants. Transplant Direct. 2018;4:e365. https://doi.org/10.1097/TXD.0000000000000801
11. Opelz G, Döhler B, Middleton D, Süsal C. HLA matching in pediatric kidney transplantation. HLA poorly matched living donor transplants versus HLA well-matched deceased donor transplants. Transplantation. 2017;101:2789-92. https://doi.org/10.1097/TP.0000000000001811
12. Williams RC, Opelz G, McGarvey CJ, Weil EJ, Chakkera HA. The risk of transplant failure with HLA mismatch in first adult kidney allografts from deceased donors. Transplantation. 2016;100:1094-102. https://doi.org/10.1097/TP.0000000000001115
13. Echterdiek F, Latus J, Döhler B, Schwenger V, Süsal C. Impact of HLA compatibility in recipients of kidneys from expanded criteria donors: A Collaborative Transplant Study Report Int J Immunogenet. 2021;48:201-10. https://doi.org/10.1111/iji.12512
14. Engels G, Döhler B, Tönshoff B, Oh J, Kruchen A, Müller I, et al. Maternal versus paternal living kidney transplant donation is associated with lower rejection in young pediatric recipients: A Collaborative Transplant Study report. Pediatr Transplant. 2022;26:e14154. https://doi.org/10.1111/petr.14154
15. Williams RC, Opelz G, Weil EJ, McGarvey CJ, Chakkera HA. The risk of transplant failure with HLA mismatch in first adult kidney allografts 2: living donors, summary, guide. Transplant Direct. 2017;3:e152. https://doi.org/10.1097/TXD.0000000000000664
16. Cecka JM. HLA matching for organ transplantation... Why not? Int J Immunog. 2010;37:323-7. https://doi.org/10.1111/j.1744-313X.2010.00957.x
17. Shi X, Lv J, Han W, Zhong X, Xie X, Su B, et al. What is the impact of human leukocyte antigen mismatching on graft survival and mortality in renal transplantation? A meta-analysis of 23 cohort studies involving 486,608 recipients. BMC Nephrol. 2018;19:116. https://doi.org/10.1186/s12882-018-0908-3
18. Leffell MS, Zachary AA. The national impact of the 1995 changes to the UNOS renal allocation system. Clin Transplant. 1999;13:287-95. https://doi.org/10.1034/j.1399-0012.1999.130402.x
19. Ashby VB, Port FK, Wolfe RA, Wynn JJ, Williams WW, Roberts JP, et al. Transplanting kidneys without points for HLA-B matching: consequences of the policy change. Am J Transplant. 2011;11:1712-8. https://doi.org/10.1111/j.1600-6143.2011.03606.x
20. Tein JY, Mazza GL, Gunn HJ, Kim H, Stuart EA, Sandler IN, et al. Multigroup Propensity Score Approach to evaluating an effectiveness trial of the new beginnings program. Eval Health Prof. 2018;41:290-320. https://doi.org/10.1177/0163278718763499
21. Austin PC. An Introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011;46:399-424. https://doi.org/10.1080/00273171.2011.568786
22. Zhao QY, Luo JC, Su Y, Zhang YJ, Tu GW, Luo Z. Propensity score matching with R: conventional methods and new features. Ann Transl Med. 2021;9:812. https://doi.org/10.21037/atm-20-3998
23. Zhang Z. Multiple imputation with multivariate imputation by chained equation (MICE) package. Ann Transl Med. 2016;4:30.
24. Rubin DB. Using Propensity Scores to help design observational studies: application to the tobacco litigation. Health Serv Outcomes Res Methodol. 2001;2:169-88. https://doi.org/10.1023/A:1020363010465
25. Stuart EA. Matching methods for causal inference: A review and a look forward. Stat Sci. 2010;25:1–21. https://doi.org/10.1214/09-STS313
26. Kim JJ, Fuggle S V, Marks SD. Does HLA matching matter in the modern era of renal transplantation? Pediatr Nephrol. 2021;36:31-40. https://doi.org/10.1007/s00467-019-04393-6
27. Lim WH, Chadban SJ, Clayton P, Budgeon CA, Murray K, Campbell SB, et al. Human leukocyte antigen mismatches associated with increased risk of rejection, graft failure, and death independent of initial immunosuppression in renal transplant recipients. Clin Transplant. 2012;26:428-37. https://doi.org/10.1111/j.1399-0012.2012.01654.x
28. Johnson RJ, Fuggle SV, O'Neill J, Start S, Bradley JA, Forsythe JLR, et al. Factors influencing outcome after deceased heart beating donor kidney transplantation in the united kingdom: an evidence base for a new national kidney allocation policy. Transplantation. 2010;89:379-86. https://doi.org/10.1097/TP.0b013e3181c90287
29. Johnson RJ, Fuggle SV, Mumford L, Bradley JA, Forsythe JLR, Rudge CJ. A New UK 2006 National Kidney Allocation Scheme for deceased heart-beating donor kidneys. Transplantation. 2010;89:387-94. https://doi.org/10.1097/TP.0b013e3181c9029d
30. ScandiaTransplant. Scandiatransplant Acceptable Mismatch Program (STAMP) and Local Acceptable Mismatch Program (LAMP). Fecha de consulta: 12 de septiembre de 2023. Disponible en: http://www.scandiatransplant.org/organ-allocation/Manual_STAMP_9.1.pdf

31. The Canadian Council for Donation and Transplantation. Kidney Allocation in Canada: A Canadian Forum. Toronto; 2006. Fecha de consulta: 15 de septiembre de 2023 Disponible en: https://professionaleducation.blood.ca/sites/default/files/Kidney_Allocation_FINAL.pdf
32. Mayer G, Persijn GG. Eurotransplant kidney allocation system (ETKAS): rationale and implementation. Nephrolo Dial Transplant. 2006;21:2-3. https://doi.org/10.1093/ndt/gfi269
33. The Transplantation Society of Australia and New Zealand. Clinical Guidelines for Organ Transplantation from Deceased Donors 2023. Fecha de consulta: 22 de septiembre de 2023. Disponible en: https://tsanz.com.au/storage/documents/TSANZ_Clinical_Guidelines_Version-111_13062023Final-Version.pdf
34. Cruz JP, Guerrero-Rueda WJ, Pérez ER, Lizarazo-Walteros DL, Rico-Ardila PC, Castillo AM, et al. Sistema de obtención de riñones en Colombia: un enfoque basado en la dinámica de sistemas. Revista de Gerencia y Políticas de Salud. 2019;18:1–26. https://doi.org/10.11144/Javeriana.rgps18-36.kpsc
35. Abboud O, Abbud-Filho M, Abdramanov K, Abdulla S, Abraham G, Abueva AV, et al. The Declaration of Istanbul on organ trafficking and transplant tourism. Clin J Am Soc Nephrol. 2008;3:1227-31. https://doi.org/10.2215/CJN.03320708