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Impact of Dialysis Time on Long-term Outcomes in HLA-identical Living Donor Kidney Transplant Recipients

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Background. Dialysis vintage is associated with worse outcomes after kidney transplantation. The reasons behind this observation include immunological and nonimmunological risk factors. To mitigate the influence of immunological factors, we examined the association between time on dialysis and clinical outcomes in a cohort of HLA-identical kidney transplant recipients. **Methods.** This retrospective study included 13321 kidney transplant recipients between 1999 and 2016, of whom 589 were HLA identical followed for at least 5 y. Patient and graft survivals were compared according to dialysis time (<12 or >12 mo) using the log-rank test and Cox regression analysis. We compared surgical complications, cytomegalovirus infection, acute rejection, disease recurrence, and the trajectories of estimated glomerular filtration rate (eGFR). **Results.** Median time on dialysis was 15 mo; 9.2% of patients received preemptive transplants, and 55.3% of patients were on dialysis for >12 mo. After a median follow-up time of 154 mo, there were no differences in unadjusted and adjusted patient and graft survivals (1, 5, 10, and 15 y) between the 2 groups. There were no differences in the incidence of surgical complications (6.2% versus 3.1%), acute rejection (6.1% versus 7.7%), cytomegalovirus infection (7.6% versus 4.0%), and disease recurrence (4.2% versus 4.0%), respectively. There were no differences in mean eGFR during 5 y or in the proportion of patients with an eGFR <30 mL/min at 5 y (9.9% versus 9.2%). **Conclusions.** In this low immunological risk cohort of HLA-identical kidney transplant recipients, we did not observe any association between dialysis vintage on patient survival and graft survival.

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Following the improvements in HLA matching, the availability of multi-target immunosuppressive schemas, management of viral infections and cancer, and kidney and patient graft survival have evolved.[1] However, in specific subgroups, we remain to find the impact of reduced survival after kidney transplantation, such as older recipients, patients with diabetes, and those who experienced delayed graft function and acute rejection episodes.[2,3] Factors influencing graft and patient survival can be divided into donor-related (eg, age, living or deceased), recipient-related (eg, age, dialysis time, comorbidities), transplant process (eg, cold ischemia time), and posttransplant care and complications (eg, delayed graft function, infections, transplant care protocols).[2] In the long term, significant efforts have been focused on targeting the management of modifiable factors, objecting to maintaining a viable graft and a healthier recipient.[4]

Dialysis vintage, that is, time on dialysis before kidney transplantation, is one of these potentially modifiable factors that has been associated with worse outcomes and lower patient and graft survival.[5-7] The accumulation of morbidities, cardiovascular burden because of endothelial dysfunction, and augmented atherosclerotic disease linked to chronic kidney disease are potential causes for increased mortality.[5,6,8] Limited evidence suggest that increased T-cell alloreactivity in more prolonged dialysis exposure provides a basis for an explanation for reduced graft survival.[9] The detrimental effect of dialysis vintage occurs in a dose-dependent manner, even with short periods of 6 mo, despite the type of donor and transplant era.[10-13]

It is consensus that transplantation performed between pairs who share the same HLA antigens, called HLA-identical graft from a sibling, carries the lowest immunological risk compared with HLA-mismatched donors.[14] A less immunogenic

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graft leads to a 20-y survival of 67% and an estimated lifetime of 18–35 y.[15,16] HLA-identical transplants are uncommon, representing 8.9% to 16.2% of all living transplants and <3% of all kidney grafts in large series.[15-17] However, this scenario of less alloactivation is a unique opportunity to explore the relationship of theoretical antigen-unrelated graft survival, such as dialysis vintage. Thus, this study aimed to evaluate the dialysis vintage impact on long-term outcomes in recipients of HLA-identical living kidney transplantation, including patient survival and graft survival, and intermediate outcomes, such as glomerular filtration rate, acute rejection incidence, surgical complications, cytomegalovirus (CMV) infection, and recurrence.

MATERIALS AND METHODS

Study Design and Participants

This was a retrospective cohort study. We studied patients transplanted in a single transplant center, Hospital do Rim, São Paulo, Brazil, from January 1999 to December 2016, with the last follow-up date in July 2023. During this period, we performed 13 321 kidney transplants, 686 patients received grafts from HLA-identical living donors, and 97 were followed in other centers, resulting in a sample of 589 patients (Figure 1). Data were collected from institutional databases and electronic medical records. The study protocol was submitted and approved by the Ethics Committee of the Federal University of São Paulo (protocol No. 52908421.9.0000.5505, approval number 5.114.320). The informed consent form was waived.

The inclusion criteria included adults who received grafts from HLA-identical siblings, transplanted, and followed at the institution. We excluded those with incomplete follow-up records. To better evaluate the impact of dialysis vintage, we divided the cohort according to time on dialysis into 2 groups: up to 12 mo and >12 mo.[10,11,18]

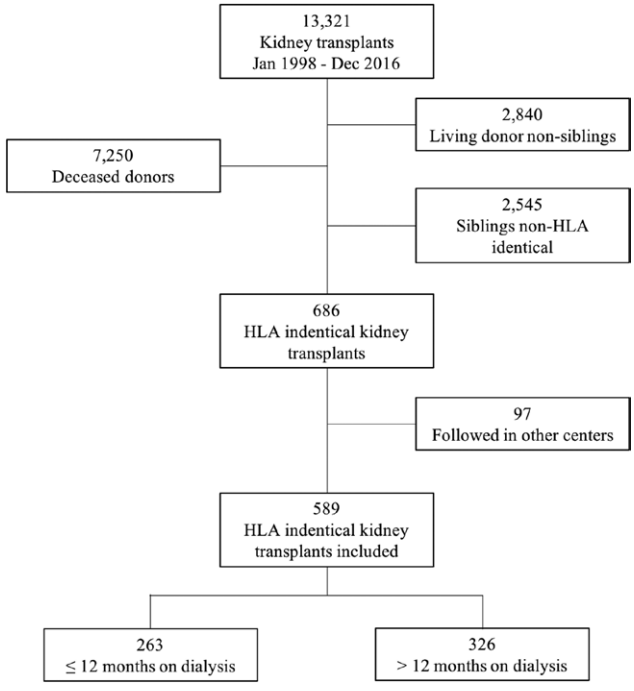

FIGURE 1. Sample disposition. A total of 589 HLA-identical kidney transplant recipients were included, comprising 263 individuals with ≥12 mo on dialysis and 326 individuals with >12 mo.

Outcomes and Variables of Interest

The main outcome was composed of death and graft loss. As intermediate outcomes, we assessed graft function by estimating the glomerular filtration rate (mL/min/1.73 m^2) using the Chronic Kidney Disease Epidemiology Collaboration equation[19,20] yearly till 5 y posttransplantation. The incidence of acute rejection episodes (biopsy-proven), surgical complications, CMV infection, and recurrence of CKD cause were also registered.

We collected demographic and clinical data as follows: age, sex, race (Caucasian, African American, and mixed), body mass index (kg/m^2), obesity (body mass index ≥30 kg/m^2), comorbidities (hypertension and diabetes, defined when the information was present in the medical record during the pretransplant clinical evaluation or in cases the patients underwent specific pharmacological), cause of CKD (undetermined, chronic glomerulopathy, diabetes, and polycystic kidney disease), CMV serologic status (positive versus negative), time on dialysis, type of renal replacement therapy (RRT), and immunosuppression schema (prednisone, cyclosporine A (CyA), tacrolimus, azathioprine (AZA), mycophenolate, and proliferator signals inhibitors [sirolimus and everolimus]).

HLA Typing

The HLA typing changed during the time considered for the study. From 1999 to 2000, recipients and donors were typed for HLA-A and HLA-B by serology using First HLA Class I (LM172), One Lambda. From 2001 to 2007, recipients were typed for HLA-A, -B, and -DRB1 by polymerase chain reaction with sequence-specific primer using Micro SSP typing trays, One Lambda, whereas donors were typed for HLA-A and HLA-B by serology (First HLA Class I [LM172], One Lambda) and for HLA-DRB1 by SSP using Micro SSP typing trays, One Lambda. Lastly, from 2008 to 2016, recipients and donors were typed for HLA-A, -B, and -DRB1 by PCR-rSSO using LABType, One Lambda.

Immunosuppression and Prophylaxis

The immunosuppression used in the service for HLA-identical living donor kidney transplant recipients remained unchanged throughout the period considered for patient inclusion. The clinical routines included a dose of 1g of methylprednisolone intraoperatively and sequential immunosuppression with prednisone, a calcineurin inhibitor, generally CyA, and an antimetabolite, typically AZA, with possible variations according to clinical indications. The strategy for reducing the risk of CMV-related events was the preemptive strategy, as previously published. The criteria for entry into the preemptive strategy applicable to this population were CMV IgG-negative recipients from IgG-positive donors, use of mycophenolate, or a history of acute rejection treatment. CMV-associated disease was diagnosed in the presence of attributable symptoms or clinical signs associated with a positive viremia, as requested by clinical indication. Both infection episodes, meaning patients eventually treated with positive viremia but without symptoms, and those diagnosed with the disease were included in this study. Other protocol prophylaxes included using albendazole before and sulfamethoxazole-trimethoprim for at least 6 mo after transplantation.

Statistical Analysis

Descriptive statistics are presented as medians and interquartile ranges according to distribution assessed by Kolmogorov-Smirnov or as percentages for categorical variables. For all associations, we tested the impact of the dialysis vintage, comparing the 2 groups, up to 12 mo and >12 mo on dialysis, using the Mann-Whitney *U* test, Qui square, or Fisher exact tests whenever appropriate. We chose 12 mo as the threshold for dialysis vintage as previously reported as the point at which the impact could be seen,[10,11,18] and also because of the distribution of this variable in our sample (median of 15 mo), also reported by others.[16]

The frequency of the main outcome was compared between groups and compared using the χ^2 test. Patient, graft, and death-censored graft survival were compared using Kaplan-Meier survival curves followed by the log-rank test. Multivariate analysis for graft loss was performed by Cox regression (backward variable selection), including donor and recipient variables already present before the transplantation, with an association of $P < 0.20$ in univariate analysis (age, diabetes, chronic glomerulopathy, CyA/AZA immunosuppression, and donor age) and time on dialysis. The frequency of intermediate outcomes (including the frequency of recipients who had a 5-y estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2) was also compared using χ^2 test, and additionally, we compared the graft function of the 2 studied groups at 1, 2, 3, 4, and 5 y by generalized estimating equations, adjusted by Bonferroni test. Analyses were performed using IBM SPSS Statistics for Windows (version 29.0. IBM Corp, Armonk, NY), and a *P* value of <0.05 was considered significant.

RESULTS

Demographic and Clinical Profile

Of 13 321 patients transplanted in our center in the study period, 589 (4.4%) were included in this analysis (Figure 1). Most were young men (median 40 y), with hypertension (76.6%), reported CKD of undetermined cause (45.7%), and were on hemodialysis (84.6%) before transplant. The median time on dialysis was 15 mo (8.0–28.0), <10% did not receive any RRT, and 55.3% were >1 y on dialysis (Figure 2). The 97 patients not included because of lack of data did not differ from the analyzed cohort regarding age, sex, and dialysis vintage in months (**Table S1, SDC,** http://links.lww.com/TXD/A692), but among those included, the frequency of patients with <12 mo on dialysis was lower (44.7% versus 61.8%; $P = 0.003$). The demographic and clinical characteristics of recipients and donors were compared and shown in Table 1. Recipients from the group with less time on dialysis were more of Caucasian race (65.8% versus 51.2%), with a lower frequency of hemodialysis as RRT (74.5 versus 92.6; $P < 0.001$); 9.2% of recipients received the graft preemptively from older donors (41.0 versus 39.5; $P = 0.07$) and were less on CyA with AZA maintenance immunosuppression regimen (85.9 versus 92.0; $P = 0.003$) than patients in the group with >12 mo on dialysis.

Main Outcome

In the median follow-up time of 154.6 (98.7–205.7) mo, 168 individuals (28.5%) experienced graft loss (n = 69; 11.7%) or death (n = 99; 16.8%), with no difference observed on the basis of the dialysis vintage (Table 2). This was similar for the composite outcome (27.0% versus 29.8%; $P = 0.46$), as well as for death (14.8% versus 18.4%; $P = 0.25$) and graft loss (12.2% versus 11.3%; $P = 0.76$) when evaluated individually, for durations of ≤12 or >12 mo, respectively. The time between the transplant and the graft loss was 103.1 (31.2–153.7) mo, and the causes were vascular thrombosis (n = 2), immunological interstitial fibrosis and tubular atrophy (n = 25), nonimmunological interstitial fibrosis and tubular atrophy (n = 28), glomerular disease (recurrent or de novo, n = 9), and others (n = 9). In contrast, the time between death was 128.0 (73.9–182.2) mo, and the causes were infection (n = 49), cancer (n = 24), cardiovascular (n = 13), unknown (n = 7), and others (n = 6). Despite the low frequency in the entire cohort, the frequency of fatal cardiovascular events was significantly higher in patients who had been on dialysis for ≥12 mo compared with those on dialysis for <12 mo (3.7% versus 0.4%; $P = 0.007$). Moreover, both groups had similar patient, graft, and death-censored graft survivals (Figure 3). The 5-, 10-, and 15-y death noncensored graft survivals were 92.6%, 86.1%, and 74.3% for recipients with ≤12 mo on dialysis, and 90.7%, 82.7%, and 71.4% for those with

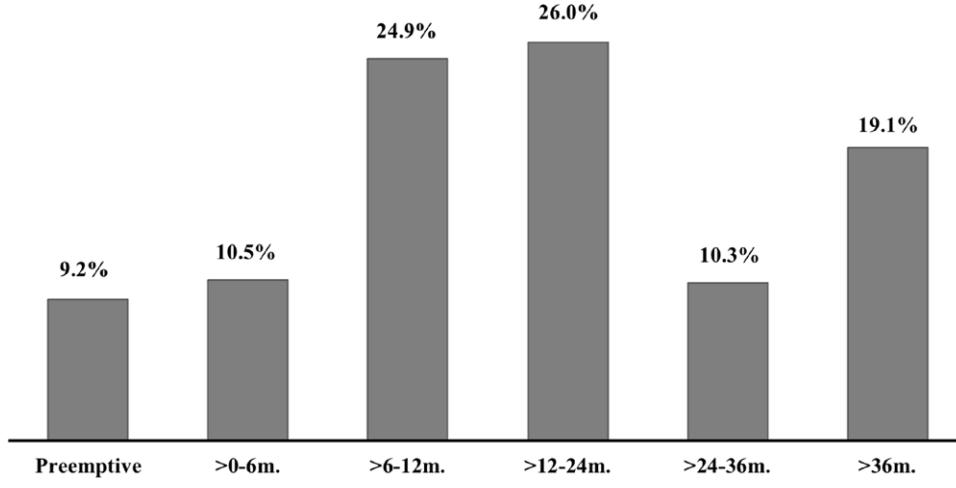

FIGURE 2. Distribution of time on dialysis. Only 9.2% of recipients were preemptively transplanted.

TABLE 1.

Demographic and clinical characteristics of the cohort, according to time on dialysis

Variable	Total (N = 589)	Time on dialysis		P
		≤12 mo (N = 263)	>12 mo (N = 326)	
Recipients				
Age, y	41.0 (34.0–48.0)	41.0 (34.0–48.0)	41.0 (34.0–48.0)	0.87
Male, n (%)	350 (59.4)	165 (62.7)	185 (56.7)	0.14
Race, n (%)				<0.001
Caucasian	340 (57.7)	173 (65.8)	167 (51.2)	
Mixed	130 (22.1)	57 (21.7)	73 (22.4)	
African American	119 (20.2)	33 (12.5)	86 (26.4)	
BMI,[a] kg/m^2	22,8 (20.7–26.4)	22.5 (20.7–26.4)	23.3 (20.7–26.6)	0.50
Obesity,[a] n (%)	38 (7.4)	22 (7.9)	16 (6.8)	0.63
Hypertension, n (%)	451 (76.6)	198 (75.3)	253 (77.6)	0.51
Diabetes, n (%)	48 (8.1)	23 (8.7)	25 (7.7)	0.63
CKD cause, n (%)				0.59
Undetermined	280 (45.7)	131 (49.8)	149 (45.7)	
Glomerulopathy	177 (30.1)	72 (27.4)	105 (32.2)	
Diabetes	44 (7.5)	21 (8.0)	23 (7.1)	
PKD	29 (4.9)	15 (5.7)	14 (4.3)	
Other	59 (10.0)	24 (9.1)	35 (10.7)	
CMV positive (IgG),[a] n (%)	515 (91.8)	228 (90.1)	287 (93.2)	0.19
Time on RRT, mo	15.0 (8.0–28.0)	7.0 (3.0–10.0)	26.0 (18.0–48.0)	<0.001
RRT modality, n (%)				<0.001
Hemodialysis	498 (84.6)	196 (74.5)	302 (92.6)	
Preemptive	54 (9.2)	54 (20.9)	–	
Peritoneal dialysis	37 (6.3)	13 (4.9)	24 (7.3)	
Prednisone	588 (99.8)	263 (100)	325 (99.7)	0.99
Other immunosuppressive				0.003
CyA + AZA	526 (89.3)	226 (85.9)	300 (92.0)	
CyA/TAC + imTOR	28 (4.8)	22 (8.4)	6 (1.8)	
Tac + AZA/MPS	19 (3,2)	7 (2,7)	12 (3,7)	
Other	16 (2.7)	8 (3.0)	8 (2.5)	
Donors				
Age, y	40.0 (34.0–48.0)	41.0 (35.0–48.0)	39. 5 (33.0–47.0)	0.07
Male, n (%)	269 (45.7)	124 (47.1)	145 (44.5)	0.52
Race, n (%)				<0.001
Caucasian	327 (58.1)	167 (67.9)	160 (50.5)	
Mixed	109 (19.4)	42 (17.1)	67 (21.1)	
African American	127 (22.6)	37 (15.0)	90 (28.4)	

Continuous variables were compared by the Mann-Whitney *U* test and frequencies by the chi-square test or the Fisher exact test.

[a]Variables with missing data: BMI, 72; obesity, 72; CMV positive (IgG), 28.

AZA, azathioprine; BMI, body mass index; CKD, chronic kidney disease; CMV, cytomegalovirus; CyA, cyclosporine A; imTOR, proliferator signals inhibitor; MPS, mycophenolate; PKD, polycystic kidney disease; RRT, renal replacement therapy; Tac, tacrolimus.

>12 mo on dialysis, with no difference between the groups (Figure 3B; log-rank = 0.57).

In the univariate analysis using Cox regression (Table 3), the variables associated with the main outcome (death and graft loss) were recipient and donor age and diabetes as comorbidity among the recipients; there was a trend of reduced risk for recipients receiving CyA + AZA as the baseline maintenance immunosuppressive regimen compared with others ($P = 0.06$). In a sensitivity analysis, where dialysis vintage was evaluated as a continuous variable (in months) or categorized (preemptive, 0–6, 6–12, >12 mo), or as preemptive (yes versus no), no significant effects were observed (**Table S2, SDC,** http://links.lww.com/TXD/A692). On selecting variables with a P value of <0.20 from the univariate analysis for inclusion in the multivariate analysis, the following were included in the model: recipient age, diabetes as comorbidity, chronic kidney etiology (categorized into glomerulopathy or not), the baseline maintenance immunosuppressive regimen (CyA + AZA versus others), and donor age. Additionally, irrespective of the univariate analysis results, time on dialysis (≤12 versus >12 mo) was incorporated into the model. Following backward selection, the variables significantly associated with the main outcome were recipient age (hazard ratio for each age = 1.04; 95% confidence interval [CI], 1.02-1.06; $P < 0.001$) and diabetes as a comorbidity (hazard ratio for yes versus no = 2.33; 95% CI, 1.53-3.55; $P < 0.001$).

Intermediate Outcomes

A trend indicating more frequent surgical complications and CMV-related events was observed in the group with lower dialysis vintage (Table 2). Specifically, the rate of surgical complications stood at 6.2% for recipients with ≤12 mo on dialysis, compared with 3.1% for those with >12 mo ($P = 0.07$). Similarly, the frequency of CMV-related events

TABLE 2.

Main and intermediate outcomes

Variables	Total	Time on dialysis ≤12 mo (N = 263)	Time on dialysis >12 mo (N = 326)	*P*
Main outcome, n (%)	168 (28.5)	71 (27.0)	97 (29.8)	0.46
Graft loss	69 (11.7)	32 (12.2)	37 (11.3)	0.76
Death	99 (16.8)	39 (14.8)	60 (18.4)	0.25
Loss of follow-up, n (%)	59 (10)	21 (8.0)	38 (11.7)	0.14
Intermediate outcomes				
Surgical complications, n (%)	26 (4.5)	16 (6.2)	10 (3.1)	0.07
Acute rejection, n (%)	41 (7.0)	16 (6.1)	25 (7.7)	0.45
CMV infection, n (%)	33 (5.6)	20 (7.6)	13 (4.0)	0.06
Glomerulopathies,[a] n (%)	24 (4.1)	11 (4.2)	13 (4.0)	0.90
eGFR <30 mL/min/1.73 m² at 5 y, n (%)	56 (9.5)	26 (9.9)	30 (9.2)	0.78

Frequencies were compared using the chi-square test.
[a]Recurrence or de novo glomerulonephritis.
CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate.

was 7.6% versus 4.0% ($P = 0.06$), respectively. However, no significant differences concerning dialysis vintage were observed in the frequency of acute rejection, posttransplant glomerular diseases (recurrence and de novo), or eGFR of <30 mL/min/1.73 m² 5 y posttransplantation. A total of 41 patients experienced acute rejection at a median of 237 d (48.2–548.7) posttransplantation. Among them, 25 patients encountered rejection within the first year: 6 within the initial 30 d, 9 between 30 and 90 d, and 4 between 90 and 180 d posttransplantation. Histologically, 15 patients presented with Banff IA, 8 with IB, 4 with IIA, and 1 with IIB classifications. In 5 patients, rejection was suspected clinically because of deteriorating creatinine levels, and 8 patients showed borderline changes, but in both groups, graft function improved after rejection treatment. Treatment included high-dose steroids for 36 patients and thymoglobulin for 5 patients.

Analyzing the eGFR achieved at 1 y as the reference point, a significant reduction over time was evident ($P < 0.001$), which persisted even after Bonferroni test adjustment (Figure 4; described as mean and 95% CI, −1.43 [−2.30 to −0.48] at 2 y [$P = 0.03$]; −2.57 [−3.74 to −1.40] at 3 y [$P < 0.001$]; −3.21 [−4.50 to −1.92] at 4 y [$P < 0.001$]; and −4.06 [−5.45 to −2.68] at 5 y [$P < 0.001$]). This trend of eGFR reduction was similar between the groups stratified by the dialysis vintage ($P = 0.45$ adjusted for the Bonferroni test).

DISCUSSION

In this study, which focuses on HLA-matched kidney transplant recipients with the lowest immunological risk, we found that a 12-mo dialysis vintage had no discernible impact on posttransplant survival in the short and long term. Furthermore, we present a comprehensive epidemiological profile of this transplantation type within a large single-center cohort, particularly emphasizing long-term follow-up.

The influence of dialysis vintage on clinical outcomes in HLA-identical recipients has not been previously explored. Previous studies have indeed demonstrated the impact of dialysis vintage on posttransplant outcomes, particularly in terms of graft survival not censored for death, and this association is stronger for recipients of living donors. Studies predating the year 2000 have consistently shown that preemptive transplantation[21] or shorter dialysis vintage results in better graft and patient survival, as seen in comparisons of <6 mo versus >2 y,[12] as well as durations <1.5 or >1.5 y.[11] More recently, a meta-analysis of 87 studies examining clinical outcomes of preemptive kidney transplantation, involving analysis of 859 715 patients from older and recent cohorts, indicated a lower risk of death only in preemptive patients who received grafts from living donors, with no impact on patient survival among recipients of deceased donors.[22] Similar results were observed on the French database after adjusting for diabetes and cardiovascular comorbidities, where preemptive patients still exhibited better graft survival than those who underwent any duration of dialysis.[13]

One proposed factor contributing to lower patient survival associated with longer dialysis vintage is the increased risk of cardiovascular mortality stemming from prolonged exposure to dialysis and subsequent cardiovascular damage caused by systemic inflammation and its consequences.[23] To mitigate the risks associated with dialysis treatment, such as catheter infections and increased morbidities, preemptive transplants enable an overall decreased graft loss of 18%–20%, compared with living and deceased donors, respectively.[22] In our study (**Table S2, SDC,** http://links.lww.com/TXD/A692), we did not observe differences in the comparison between preemptive and nonpreemptive transplantation; however, it is worth noting that <10% of the patients

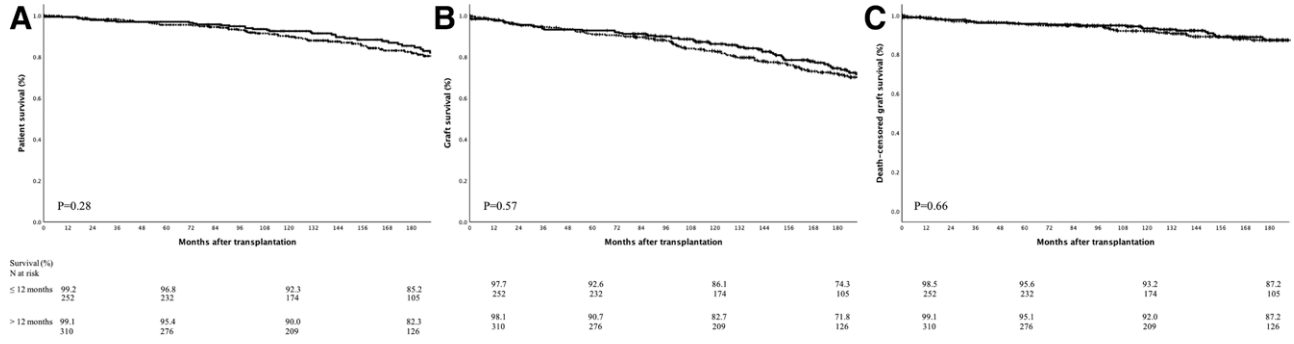

FIGURE 3. Patient survival (A), graft survival (B), and death-censored graft survival (C) according to time on dialysis. The patients with ≥12 mo on dialysis are shown in solid lines and with >12 mo on dialysis in dashed lines.

TABLE 3.

Univariate and multivariate analyses for the main outcomes: graft loss and death

	Univariate			Multivariate		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age (for each year)	1.04	1.03-1.06	<0.001	1.04	1.02-1.06	<0.001
Male (yes vs no)	0.98	0.72-1.33	0.88	–	–	–
Race, Caucasian	Reference	–	–	–	–	–
Mixed	0.89	0.59-1.35	0.59	–	–	–
African American	1.12	0.77-1.64	0.55	–	–	–
Hypertension (yes vs no)	0.78	0.56-1.08	0.14	–	–	–
Diabetes (yes vs no)	2.44	1.60-3.70	<0.001	2.33	1.53-3.55	<0.001
Obesity (yes vs no)	1.15	0.88-1.50	0.30	–	–	–
BMI (for each kg/m^2)	1.02	0.98-1.07	0.31	–	–	–
CKD etiology (GP vs other)	0.72	0.51-1.02	0.06	–	–	–
CMV IgG-positive (yes vs no)	0.88	0.52-1.48	0.63	–	–	–
Time on dialysis (≤12 vs >12 mo)	0.92	0.67-.125	0.55	–	–	–
Type of RRT (HD vs others)	1.23	0.79-2.14	0.31	–	–	–
CyA + AZA (vs others)	0.63	0.38-1.03	0.06	0.62	0.37-1.01	0.06
Donor age (for each year)	1.03	1.01-1.05	<0.01	–	–	–
Male donor (yes vs no)	0.99	0.73-1.35	0.97	–	–	–
Donor race, Caucasian	Reference	–	–	–	–	–
Mixed	0.77	0.47-1.26	0.29	–	–	–
African American	1.11	0.77-1.61	0.55	–	–	–

For multivariate analysis, we selected variables with an association of $P < 0.20$ in univariate analysis (age, diabetes as comorbidity, CKD cause, CyA + AZA immunosuppression, and donor age), and time on dialysis.

AZA, azathioprine; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CMV, cytomegalovirus; CyA, cyclosporine; GP, glomerulopathy; HD, hemodialysis; HR, hazard ratio; RRT, renal replacement therapy.

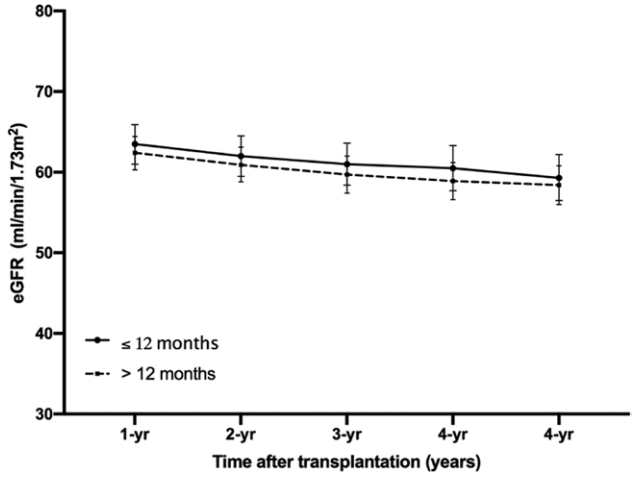

FIGURE 4. Graft function in groups according to time on dialysis. The patients with ≥12 mo are shown in solid lines and with >12 mo in dashed lines. eGFR, estimated glomerular filtration rate.

(n = 54) underwent preemptive transplants. Yet, the comparison of preemptive transplantation frequency is difficult to set because reports vary a lot, from 2.9% to 24.5%.[24-26]

In terms of HLA-identical recipients outcomes, there have been several reports about acute rejection,[25,27] immunological risk by the panel-reactive antibodies[28,29] or innate immunity-related molecules,[30] and immunosuppression schema[31] as risk factors for adverse outcomes. Ours observed early and long-term graft survival rates align with those found in both large[15,16] and small cohorts[24-29,32] investigating the HLA-identical recipients. In contrast, regarding a dialysis vintage of 12 mo, in our study, survival rates were similar, and we also saw an absence of impact of this variable on Cox regression for graft loss and death. Thus, in the setting of the lowest HLA mismatch, the deleterious effect of prolonged time in RRT was no longer relevant.

Some peculiar characteristics of our population could explain the reasons why we did not identify the effect of time on dialysis on the outcomes of HLA-identical donor transplant recipients. The first one is a potential bias of immortality time.[33,34] That is to say, it is possible that those patients who had more time on dialysis before the transplant were the ones who survived the first months (or years) on dialysis and, therefore, underwent a bias of natural selection. This is especially relevant when considering the characteristics of the public health reality in Brazil. In a Brazilian study that evaluated 4945 incident dialysis cases between 2012 and 2017, 60.2% started dialysis in an unplanned situation, 56.6% did so through a short-term catheter, and 45.2% had evidence of volume overload, leading to a 1-y mortality rate of around 20%.[35]

Another relevant reason is the number of patients included in our study. It is worth noting that recipients of HLA-identical kidney transplants naturally exhibit a good progression, with low rates of death and graft loss, even with long-term follow-up.[15,16] Although this is the largest single center and the third HLA-identical kidney transplant recipient cohort ever studied,[16,31] comprising 589 individuals, the number of patients included and the duration of observation may not have been sufficient to assess the effect of time on dialysis as an independent variable in few frequent events.

Although our study is one of the largest cohorts investigating the long-term outcome for HLA-identical kidney transplant recipients, our study has some limitations. The

inference is limited in observational studies; however, the need to make treatment decisions about issues for which randomized controlled studies are unavailable highlights the importance of such kinds of results, bringing results from a relevant real-world evidence study. Given the possibilities of confounding factors inherent to dialysis vintage, some aspects of the epidemiologic profile of our sample could limit extrapolations about survival rates. Differences in waitlist criteria, donation legislation, and quality of dialysis are examples of confounding factors reported by others.[7] Nevertheless, the large size of our sample adds data on unanswered questions considering the unique environment of lower immunological disparity.

In the context of lower immunological HLA mismatching of HLA-identical recipients, which allows a better exploration of antigen-independent factors, graft survival and patient survival were similar regarding a 12-mo dialysis vintage, reinforcing the efforts to pursue a better HLA matching.

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REFERENCES

1. Hariharan S, Israni AK, Danovitch G. Long-term survival after kidney transplantation. *N Engl J Med*. 2021;385:729–743.
2. Foroutan F, Friesen EL, Clark KE, et al. Risk factors for 1-year graft loss after kidney transplantation: systematic review and meta-analysis. *Clin J Am Soc Nephrol*. 2019;14:1642–1650.
3. Ponticelli C, Reggiani F, Moroni G. Delayed graft function in kidney transplant: risk factors, consequences and prevention strategies. *J Pers Med*. 2022;12:1557.
4. Neuberger JM, Bechstein WO, Kuypers DR, et al. Practical recommendations for long-term management of modifiable risks in kidney and liver transplant recipients: a guidance report and clinical checklist by the consensus on managing modifiable risk in transplantation (COMMIT) group. *Transplantation*. 2017;101(4S Suppl 2):S1–S56.
5. Abramowicz D, Hazzan M, Maggiore U, et al; Descartes Working Group and the European Renal Best Practice (ERBP) Advisory Board. Does pre-emptive transplantation versus post start of dialysis transplantation with a kidney from a living donor improve outcomes after transplantation? A systematic literature review and position statement by the descartes working group and ERBP. *Nephrol Dial Transplant*. 2016;31:691–697.
6. Azegami T, Kounoue N, Sofue T, et al. Efficacy of pre-emptive kidney transplantation for adults with end-stage kidney disease: a systematic review and meta-analysis. *Ren Fail*. 2023;45:2169618.
7. Haller MC, Kammer M, Oberbauer R. Dialysis vintage and outcomes in renal transplantation. *Nephrol Dial Transplant*. 2019;34:555–560.
8. Helantera I, Salmela K, Kyllonen L, et al. Pretransplant dialysis duration and risk of death after kidney transplantation in the current era. *Transplantation*. 2014;98:458–464.
9. Augustine JJ, Poggio ED, Clemente M, et al. Hemodialysis vintage, black ethnicity, and pretransplantation antidonor cellular immunity in kidney transplant recipients. *J Am Soc Nephrol*. 2007;18:1602–1606.
10. Goldfarb-Rumyantzev A, Hurdle JF, Scandling J, et al. Duration of end-stage renal disease and kidney transplant outcome. *Nephrol Dial Transplant*. 2005;20:167–175.
11. Haller MC, Kainz A, Baer H, et al. Dialysis vintage and outcomes after kidney transplantation: a retrospective cohort study. *Clin J Am Soc Nephrol*. 2017;12:122–130.
12. Meier-Kriesche HU, Kaplan B. Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes: a paired donor kidney analysis. *Transplantation*. 2002;74:1377–1381.
13. Prezelin-Reydit M, Combe C, Harambat J, et al. Prolonged dialysis duration is associated with graft failure and mortality after kidney transplantation: results from the French transplant database. *Nephrol Dial Transplant*. 2019;34:538–545.
14. Bestard O, Thaunat O, Bellini MI, et al. Alloimmune risk stratification for kidney transplant rejection. *Transpl Int*. 2022;35:10138.
15. CTS. *Collaborative transplant study*. Available at https://www.ctstransplant.org/public/graphics/sample.shtml. Accessed April 1, 2024
16. Williams RC, Opelz G, Weil EJ, et al. The risk of transplant failure with HLA mismatch in first adult kidney allografts 2: living donors, summary, guide. *Transplant Direct*. 2017;3:e152.
17. Williams RC, Opelz G, McGarvey CJ, et al. The risk of transplant failure with HLA mismatch in first adult kidney allografts from deceased donors. *Transplantation*. 2016;100:1094–1102.
18. Meier-Kriesche HU, Port FK, Ojo AO, et al. Effect of waiting time on renal transplant outcome. *Kidney Int*. 2000;58:1311–1317.
19. Delgado C, Baweja M, Crews DC, et al. A unifying approach for gfr estimation: recommendations of the NKF-ASN task force on reassessing the inclusion of race in diagnosing kidney disease. *Am J Kidney Dis*. 2022;79:268–288.e1.
20. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
21. Kasiske BL, Snyder JJ, Matas AJ, et al. Preemptive kidney transplantation: the advantage and the advantaged. *J Am Soc Nephrol*. 2002;13:1358–1364.
22. Rana Magar R, Knight SR, Maggiore U, et al. What are the benefits of preemptive versus non-preemptive kidney transplantation? A systematic review and meta-analysis. *Transplant Rev (Orlando)*. 2023;37:100798.
23. Zimmermann J, Herrlinger S, Pruy A, et al. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int*. 1999;55:648–658.
24. Bentata Y, ElKabbaj D, Bahadi A, et al. HLA-identical living related kidney transplantation: outcomes of a national multicenter study. *Int J Urol*. 2022;29:519–524.
25. Ossman R, Jamme M, Moulin B, et al; RADOVFULL Study Group. Immunosuppression and graft rejection in living-related HLA-identical renal transplantation: the RADOVFULL study. *Transplantation*. 2020;104:1256–1262.
26. Shaw BI, Villani V, Kesseli SJ, et al. A historical cohort in kidney transplantation: 55-year follow-up of 72 HLA-identical, donor-recipient pairs. *J Clin Med*. 2021;10:5505.
27. Keitel E, Santos AF, Alves MA, et al. Immunosuppression protocols for HLA identical renal transplant recipients. *Transplant Proc*. 2003;35:1074–1075.
28. Opelz G; Collaborative Transplant Study. Non-HLA transplantation immunity revealed by lymphocytotoxic antibodies. *Lancet*. 2005;365:1570–1576.
29. Verghese PS, Dunn TB, Chinnakotla S, et al. Calcineurin inhibitors in HLA-identical living related donor kidney transplantation. *Nephrol Dial Transplant*. 2014;29:209–218.
30. Garcia-Sanchez C, Casillas-Abundis MA, Pinelli DF, et al. Impact of SIRPalpha polymorphism on transplant outcomes in HLA-identical living donor kidney transplantation. *Clin Transplant*. 2021;35:e14406.
31. Perez-Saez MJ, Montero N, Oliveras L, et al; ERA-EDTA-Descartes Working Group. Immunosuppression of HLA identical living-donor kidney transplant recipients: a systematic review. *Transplant Rev (Orlando)*. 2023;37:100787.
32. D'Costa MR, Bentall A, Denic A, et al. Chronic histologic changes are present regardless of HLA mismatches: evidence from HLA-identical living donor kidney transplants. *Transplantation*. 2021;105:e244–e256.
33. Levesque LE, Hanley JA, Kezouh A, et al. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ*. 2010;340:b5087.
34. Suissa S. Immortal time bias in observational studies of drug effects. *Pharmacoepidemiol Drug Saf*. 2007;16:241–249.
35. Barra ABL, Silva A, Canziani MEF, et al. Survival in hemodialysis in Brazil according to the source of payment for the treatment: public healthcare system (SUS) versus private insurance. *J Bras Nefrol*. 2023;45:302–309.