NEPHROLOGY - ORIGINAL PAPER

Pretransplant peritoneal dialysis relative to hemodialysis improves long-term survival of kidney transplant patients: a single-center observational study

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Abstract

Background Kidney transplantation is the best option for the treatment of end-stage renal disease in terms of survival and quality of life. These results can be influenced by the pretransplant dialysis modality. The aim of this study was to evaluate whether the pretransplantation dialysis modality influences patient and allograft survival beyond 10 years and examine the potential risk factors associated with the outcomes.

Methods We conducted an observational, retrospective, single-center clinical study that included 236 patients [118 undergoing peritoneal dialysis (PD) and 118 undergoing

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hemodialysis (HD)] who proceeded to transplantation during the period December 1990–2002. Donor and recipient data were collected from our hospital's clinical registries. The follow-up period extended to the patient's death, the loss of the allograft, or loss to follow-up. The end date of the study was set at March 2012.

Results In the multivariate analysis, the long-term patient survival rate was higher for the PD group than for the HD group [HR = 2.62 (1.01-6.8); p = 0.04]; however, the allograft survival rate was not significantly different between the two groups [HR = 0.68 (0.41-1.10); p = 0.12].

Conclusion Pretransplantation dialysis modality is associated with long-term patient survival, with outcomes favoring peritoneal dialysis over hemodialysis. However, the pretransplant dialysis modality does not influence long-term graft loss risk.

Keywords Peritoneal dialysis · Hemodialysis · Kidney transplantation · Outcomes

Introduction

End-stage renal disease (ESRD) is a life-threatening disease that requires the appropriate and sequential selection and ordering of available therapies, dialysis, and transplantation to accomplish the general objective of prolonging the patient's life. Although kidney transplantation is the best option in terms of positive outcomes (survival and quality of life) [1], the overall results could be influenced by the interaction between previous treatments and the transplantation. The various dialysis modalities, which differ in practical terms, can differentially influence the outcomes for transplanted patients [2–11].



The long-term effects of the interaction among the three modalities have been explored in a number of studies, with conflicting results. A number of authors have demonstrated that the dialysis modality does not affect the outcome [3–6, 8, 9, 12]. Other authors have shown increased survival for patients and grafts treated by peritoneal dialysis (PD) [7, 10, 13, 14] or on the contrary increased graft survival by hemodialysis (HD) [6]. A common element of these studies was the use of a medium-term survival analysis, which did not extend the analysis of the patient outcome to 10 years. The importance of considering the long term when evaluating the true success of kidney transplantation is unquestionable. A long-term perspective could provide additional information to the already available data by confirming or disproving the interpretation of the synergies and antagonisms among the various ESRD treatments.

The objective of the present study was to evaluate whether the pretransplantation dialysis modality influences allograft and patient survival beyond 10 years and examine the potential risk factors associated with the outcomes. The study was conducted on a large series of patients from a university hospital kidney transplantation program from December 1990 to 2002.

Patients and methods

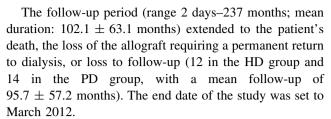
The study was conducted according to the strengthening the reporting of observational studies in epidemiology (STROBE) methodology [15].

Study design

This was an observational, retrospective, single-center, record-based clinical study. We created two cohorts based on the immediate pretransplantation dialysis modality. The first cohort consisted of patients treated with PD, and the second cohort consisted of patients treated with HD.

Patients

We included all 118 patients who were treated with PD at our center and who proceeded to kidney transplantation during the period from December 1990 to 2002 (PD group). This period was selected for reasons related to the beginning of the cyclosporine (CyA) era. The control group (HD group) included 118 patients treated with HD who received a kidney allograft from the same donor (58 cases matched by donor) or, in cases where no matching donor was available, the HD recipient who closely preceded or followed each PD case. For both groups, we only included the first allograft received during the study period.



Donor and recipient data were collected from our hospital's clinical registries. Donor selection and acceptance was performed with similar criteria based on kidney function, absence of clinical kidney abnormalities, and macroscopic examination of grafts, all of which occurred over the 12-year period. Pretransplant kidney biopsies were not performed in this study group.

Immunosuppression regimen

The immunosuppression protocol was based on steroids, cyclosporine (CyA) or tacrolimus (Tac), and azathioprine (Aza). Aza has been substituted by mycophenolate mofetil (MMF) since 1995. Induction therapy with OKT3 was added in high immunological risk patients (panel reactive antibody >50 %).

Demographic and clinical variables

We included recipient variables (age, gender, body mass index, pretransplantation time on dialysis, and cause of kidney disease), donor variables (age, gender, donor type, and cause of death in cadaver donors), and transplantation variables (length of stay of the initial hospitalization, HLA-DR mismatches, cold ischemia time, and immediate use of calcineurin inhibitors vs. administration of OKT3).

Other variables related to the intermediate outcome were also included: surgical complications over the first 6 months, incidence of acute rejection, immediate graft function (defined as immediate diuresis with a decrease of at least 30 % in serum creatinine levels 6 h after surgery), and delayed graft function (DGF), defined as the requirement for post-transplantation dialysis during the first week. Laboratory measurements included kidney function evaluated by serum creatinine and 24-h proteinuria levels and lipid profiles.

Survival analysis

We performed an overall patient and graft survival analysis that considered causes of death and graft loss. We also performed a specific analysis of graft survival rates comparing patients in the PD and HD groups who shared the same donor to examine the effects of truly paired kidneys by origin.



Statistical analysis

The statistical analysis was performed using SPSS and the R, cmprsk statistical package. Qualitative data are expressed in absolute and relative frequencies [percentage (%)]. Quantitative data are described as mean \pm standard deviation or median and interquartile range (IQR, pp 25–75).

We used a χ^2 test or Fisher's exact test to study the association between qualitative variables. To compare the means of two independent samples, we used Student's t test.

To study patient and graft survival, we calculated the cumulative incidence of mortality and graft loss in the presence of competitive events. We considered graft loss to be a competing event of death, given that graft loss was the condition being tracked. Death was also considered a competing event of graft loss. We considered censored patients all those who dropped out of the study without reaching the primary outcome.

A univariate analysis was performed to study the possible risk factors associated with mortality and graft loss. Variables with clinical effects and a value of p < 0.2 in the univariate analysis were included in a multivariate model to estimate the effect of treatment adjusted for other risk factors. The univariate analysis was performed with the proportional hazards regression models described by Fine and Gray (1999) for quantitative variables and Gray's test to compare cumulative incidences between groups. The multivariate model was adjusted by the same method.

We considered p values <0.05 to be statistically significant. All statistical tests were two-tailed.

Results

Table 1 shows the demographic characteristics of all patients included in this study. Patients in the PD group were younger, spent a shorter time on pretransplantation dialysis, and had a lower frequency of prior failed allografts. However, other general risk factors such as diabetes as the cause of kidney disease and significantly higher BMI (BMI data were available for 55 % of the patients) were more frequent among PD patients. The other analyzed variables showed no significant differences between the two groups.

Of the 236 patients, 226 patients received a cadaver donor allograft, 2 received a non-heart beating donor allograft, and 8 received a living donor allograft. These proportions and other donor characteristics (age, gender, and cause of death) were similar in both groups. There were no differences in cold ischemia times and the number of HLA-DR mismatches.

The initial immunosuppression regimen was similar in both groups. Patients in the HD group received OKT3 more frequently, although the differences were not significant.

Immediate post-transplantation period

Patients in the PD group showed earlier kidney function recovery with less need for dialysis during the first week. The acute rejection rates were similar for both groups, as was the frequency of surgical complications during the first 6 months (Table 2).

Table 1 Demographic and baseline clinical characteristics of recipients and donors

	PD (<i>n</i> = 118)	HD $(n = 118)$	p
Recipients			
Age, years	43.5 ± 12.4	47.5 ± 13.1	0.01
Male gender, $(\%)$ [n]	52.5 (62)	60.2 (71)	0.23
Primary kidney disease, (%) [n]			
Diabetes mellitus	11 (13)	1.6 (2)	0.003
Chronic glomerulonephritis	31.4 (37)	33.1 (39)	0.78
Nephrosclerosis	5.1 (6)	8.5 (10)	0.3
Polycystic kidney disease	14.4 (17)	10.2 (12)	0.32
Tubulointerstitial disease	15.3 (18)	18.6 (22)	0.48
Systemic disease	11 (13)	4.2 (5)	0.05
Unknown	8.5 (10)	18.6 (22)	0.02
Other	3.4(4)	5.1 (6)	0.51
Previous kidney transplant, (%) [n]	2.5 (3)	12.7 (15)	0.003
BMI	25.5 ± 4.39	23.8 ± 3.83	0.01
Mean duration of hospitalization, days	22.7 ± 14.4	22.9 ± 13.6	0.9
Mean time on dialysis, months	27.9 ± 27.9	50.7 ± 67.5	0.001
Donors			
Age, years	45.8 ± 16.2	44.7 ± 14.9	0.6
Male gender, $(\%)$ [n]	65.2 (73)	65.5 (74)	0.9
Donor type			
Cadaver donor, $(\%)$ $[n]$	95.8 (113)	95.8 (113)	1
Non-heart beating donor, $(\%)$ $[n]$	0.8 (1)	0.8 (1)	
Living donor, $(\%)$ [n]	3.4 (4)	3.4 (4)	
Cause of death in cadaver donors	s		
Vascular, (%) [n]	61.5 (48)	61.6 (45)	0.9
Traumatism, (%) [n]	38.5 (30)	38.4 (28)	
Pretransplant characteristics			
% HLA-DR mismatch: 0/1/2	35/57/8	34/58/8	NS
Cold ischemia time (h)	18 ± 6.5	17.7 ± 6.4	0.71

Data are summarized using percentage and means \pm SD BMI body mass index, PD peritoneal dialysis, HD hemodialysis



Table 2 Immediate post-transplant period and causes of death and graft loss

	PD $(n = 118)$	HD $(n = 118)$	p
Immunosuppression, (%) [n]			
Tacrolimus	43.1 (50)	43.6 (51)	0.9
Cyclosporine	56.9 (66)	` ′	0.9
OKT3	22.2 (26)	31.9 (37)	0.09
Immediate graft function, $(\%)$ $[n]$	77.1 (91)	63.6 (75)	0.01
DGF, (%) [n]	13.9 (16)	23.1 (27)	0.07
Acute rejection, (%) [n]	28.2 (33)	29.1 (34)	0.88
Surgical complications, (%) [n]	29.3 (34)	33.1 (39)	0.53
Deaths, (%) [n]	14.4 (17)	25.4 (30)	0.07
Vascular	2.5 (3)	8.5 (10)	
Infections	6.7 (8)	5.9 (7)	
Neoplasia	1.7 (2)	7.6 (9)	
Chronic hepatic disease	0.8 (1)	0	
Unknown	2.5 (3)	3.4 (4)	
Graft loss, (%) (n)	36.4 (43)	27.1 (32)	0.07
Acute rejection	3.4 (4)	1.7 (2)	
Chronic nephropathy	23.5 (28)	17.8 (21)	
Primary graft thrombosis	3.4 (4)	0.8 (1)	
Others	0.8 (1)	6.8 (8)	
Kidney disease recurrence	5 (6)	0	

Bold values indicate the significant data

DGF delayed graft function (defined as the need for hemodialysis in the first week after transplantation), PD peritoneal dialysis, HD hemodialysis

Medium- and long-term kidney function outcomes

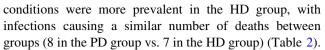
The overall results for serum creatinine and 24-h proteinuria levels showed no significant differences between the two groups throughout the follow-up; however, 24-h proteinuria levels were significantly higher in the PD group at 12 months (PD: 0.8 ± 2.3 vs. HD: 0.3 ± 0.3 ; p = 0.03). A higher kidney disease recurrence was confirmed as the cause of graft loss in the PD group.

Lipid profile

The serum cholesterol levels were similar throughout the study, but the serum triglyceride levels at 12 months were significantly higher in the PD group (PD: 175.3 ± 974 vs. HD: 147.8 ± 62.9 ; p = 0.02).

Causes of death and patient survival

A total of 47 deaths (17 in the PD group and 30 in the HD group, p = 0.07) were registered. Deaths resulting from vascular (3 in the PD group vs. 10 in the HD group) and neoplastic (2 in the PD group vs. 9 in the HD group)



The long-term patient survival rate was higher for the PD group than for the HD group (Fig. 1), both overall (Table 4) and when adjusted for significant univariate variables (Table 3) [PD vs. HD; HR = 2.62 (1.01–6.8); p = 0.04]. Recipient age was another independent variable inversely correlated with survival [HR = 1.09 (1.00–1.17); p = 0.02]. Pretransplantation BMI was also significantly and inversely correlated with survival [HR = 1.12 (1.12–1.23), p = 0.019]. The type of calcineurin inhibitor was also a protective factor for patient survival, which favored tacrolimus over CyA [HR = 2.64 (1.12–6.23); p = 0.02].

Causes of graft loss and allograft survival

Seventy-five (75) cases experienced allograft loss over the course of the follow-up, 43 in the PD group and 32 in the HD group (p=0.07). The causes of loss varied and included vascular thrombosis (4 in the PD group and 1 in the HD group, p=0.17) and kidney disease recurrence (6 in the PD group and 0 in the HD group). The detailed causes of loss are shown in Table 2. Patients in the PD group had a higher frequency of graft loss during the first 3 months due to various reasons that included vascular thrombosis (4 cases), kidney disease recurrence (3 cases), and acute rejection (3 cases). In the HD group, the causes included vascular thrombosis (1 case), acute rejection

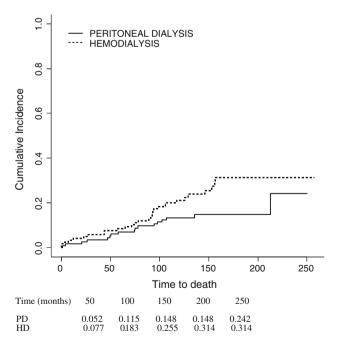


Fig. 1 Cumulative incidence of mortality by pretransplant dialysis modality



Table 3 Univariate analysis for mortality and graft loss risks (values of *p* and HR)

	Death		Graft lo	oss
	p	HR	p	HR
Recipient age	< 0.001	1.08 (1.04–1.1)	0.02	0.98 (0.96-0.99)
BMI	0.001	1.15 (1.06–1.26)	0.54	1.02 (0.94-1.11)
Tacrolimus (vs. cyclosporine) use	0.01	2.41 (1.22-4.75)	0.15	1.43 (0.88-2.34)
Pretransplant dialysis modality (HD vs. PD)	0.04	1.83 (1.01–3.3)	0.10	0.68 (0.43–1.07)
Donor age	0.18	0.98 (0.96-1)	0.01	1.02 (1.01-1.04)
Surgical complications	0.54	0.82 (0.43-1.56)	0.01	1.73 (1.1-2.73)
OKT3 use	0.70	0.88 (0.46-1.69)	0.04	1.67 (1.02-2.74)
Diabetic nephropathy	0.57	1.32 (0.49-3.52)	0.29	1.47 (0.71-3.03)
Time on dialysis	0.20	1 (0.99–1.01)	0.34	1 (0.99-1.01)
Previous kidney transplant	0.85	1.09 (0.4-3)	0.45	1.37 (0.59-3.16)
Type of donor	0.42	0.66 (0.24-1.85)	0.89	1.03 (0.63-1.71)
Cold ischemia time	0.20	1.03 (0.98-1.08)	0.45	0.98 (0.95-1.02)
Immediate graft function	0.60	1.19 (0.62-2.27)	0.41	0.81 (0.49-1.33)
DGF	0.30	0.64 (0.27-1.49)	0.08	1.6 (0.93-2.75)
Acute rejection	0.17	1.51 (0.83-2.7)	0.47	1.19 (0.73-1.94)

Bold values indicate the significant data *BMI* body mass index, *DGF* delayed graft function (defined as the need for hemodialysis in the first week after transplantation), *PD* peritoneal

dialysis, HD hemodialysis

(2 cases), and other causes (3 cases). Death with functioning graft was not included among the causes of graft loss, although it was the principal cause of graft loss among HD patients.

Figure 2 shows the cumulative incidence of graft loss, which was higher in the PD group due to the higher premature loss rate. However, the allograft survival rate was not significantly different between the two groups in the univariate [HR = 0.7 (0.43–1.1); p = 0.1] and multivariate analysis [HR = 0.68 (0.41–1.10); p = 0.12] of the pretransplant dialysis modality.

Recipient age [younger: HR = 0.98 (0.96–0.99); p = 0.02] and donor age [older: HR = 1.02 (1–1.04); p = 0.01] were associated with a higher allograft loss rate in the multivariate analysis model. The time spent on dialysis was not statistical significant (Table 4).

Discussion

The main result from our study is the higher 10-year patient survival rate after transplantation for patients treated with PD than for patients treated with HD. The practice of performing PD before transplantation could add years of life to the transplant and suggests that there could be a connection between these two therapies. We believe that a high degree of self-care, a fundamental property on which PD is based, could have contributed to this result. Patients treated with this technique before transplantation can extend their self-care skills into the post-transplantation period.

Our results are in line with earlier studies, such as the US Renal Data System study (n = 92,844) (Goldfarb-

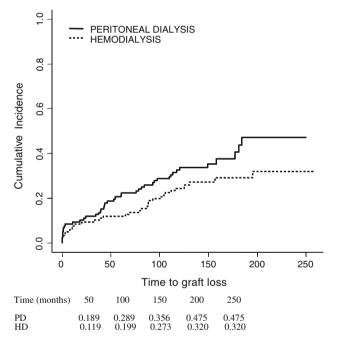


Fig. 2 Cumulative incidence of graft loss by pretransplant dialysis modality

Rumyantzev et al. [13]) that found greater patient survival $[HR = 0.94 \ (0.91-0.97)]$ for transplant recipients who received PD immediately before transplantation; the study by Molnar et al. [10] (n = 14,508) that demonstrated a patient survival benefit for patients with the pretransplant PD modality, with a 43 % $[HR = 0.57 \ (0.38-0.87)]$ lower death risk; and the study by Schwenger et al. [14] (n = 57,315) that showed greater all-cause 5-year patient survival in patients treated with PD [HR = 1.10]



Table 4 Multivariate analysis for mortality and graft loss

Mortality risk	p	HR	HR CI
Recipient BMI	0.019	1.123	1.123-1.239
CyA vs. Tac use	0.02	2.647	1.124-6.232
Recipient age	0.02	1.09	1.009-1.178
Pretransplant dialysis modality (HD vs. PD)	0.04	2.62	1.014-6.804

Graft loss risk	p	HR	HR CI
Recipient age	0.02	0.98	0.96-0.99
Donor age	0.01	1.02	1.00-1.04
Time on dialysis	0.13	1.00	0.99-1.00
Pretransplant dialysis modality (HD vs. PD)	0.12	0.68	0.41-1.11

Bold values indicate the significant data

HR hazard ratio, CI confidence interval, CyA cyclosporine, Tac tacrolimus, PD peritoneal dialysis, HD hemodialysis, BMI body mass index

(1.02–1.18)]. A large US study (n = 22,776) by Snyder et al. [6], however, reported that patients treated with PD had mortality rates similar to those of patients treated with HD [PD: HR = 0.95 (0.85–1.06)].

However, as in other studies, the different baseline characteristics between our two groups could explain the different results. As we can see in Table 1, patients on PD spent less time on dialysis before transplantation, had fewer second transplants, and were younger. Nevertheless, the univariate and multivariate analyses confirmed that recipient age, pretransplant PD (vs. HD), pretransplant BMI (independent of dialysis modality), and tacrolimus use (vs. CyA) were independent risk factors in terms of long-term patient survival. Time on dialysis before transplantation and retransplantation did not influence patient survival.

The patients in our PD group had a higher mean pretransplant BMI than the patients in the HD group, and BMI was an independent risk factor for long-term patient survival [HR = 1.12 (1.12–1.23)] but not for graft survival. The mortality risk for patients treated with HD is inversely related to body size; however, the results for patients treated with PD are less consistent. Analyses of data from the Australia and New Zealand registry (ANZDATA) (n = 27,015) have consistently shown a higher mortality risk for obese patients treated with PD [16], which is in line with our results. Other studies such as the study by Lievense et al. [17] (n = 8,016), however, have shown similar survival for obese patients treated with PD and for those treated with HD.

Another predictor of graft and patient survival evaluated in our analysis was diabetic nephropathy, which did not influence patient or graft survival [HR = 1.32 (0.49–3.52); p = 0.57 and HR = 1.47 (0.71–3.03); p = 0.29,

respectively], which was in line with the study by Goldfarb-Rumyantzev (HR = 1.11; p = 0.107 and HR = 0.96; p = 0.48, respectively) [13].

Furthermore, the improved survival rate among PD patients when compared with HD patients was independent of higher allograft loss, which was caused primarily by chronic allograft nephropathy.

We also found greater long-term survival among patients who were treated with tacrolimus than among those treated with CyA. Given that our study was not designed to assess this difference, this issue needs to be directly addressed in future studies in order to be confirmed.

Our long-term graft survival results did not differ between patients treated with pretransplant HD and PD, which was in line with the adjusted results of Molnar et al. [10] [PD HR = 0.95 (0.74–1.23)] and those of other studies [4-6, 9]. These results, however, differed from those of Goldfarb-Rumyantzev et al. [13], who reported higher graft survival for PD patients [HR = 0.97 (0.94–1.00)], and those of Snyder et al. [6], who observed a lower death-censored graft survival for PD patients [HR = 1.15 (1.04-1.26)] restricted to the first 3 months of follow-up. In our study, patients in the PD group experienced graft loss more frequently and earlier than patients in the HD group (as seen in the study by Snyder et al. [6]), although this difference was not statistically significant. Chronic allograft nephropathy was the main cause of graft loss in both groups. Graft loss due to primary graft thrombosis and kidney disease recurrence was more frequent in the PD group, and it is likely that both causes contributed to the higher rate of early graft failure in the PD group. Four patients in the PD group and 1 patient in the HD group lost their graft due to vascular thrombosis; however, these differences were not significant (p = 0.17) and were not confirmed when examining paired donation allografts (data not shown). Our results were in line with those of a preliminary survey by Escuin et al. [18] (n = 1,030, incidence of graft thrombosis PD vs. HD: 2.17vs. 3.47 %, NS) and those of the study by Pérez-Fontán et al. [19] (n = 827, incidence of graft thrombosis PD vs. HD: 4.7 vs. 6.1 %, NS) who specifically examined this question and did not confirm an increased risk of primary graft thrombosis in patients treated with PD. On the other hand, Snyder et al. [6] and Murphy et al. [20] (n = 202)have reported that graft thrombosis is more common in patients treated with PD than in those treated with HD [Snyder et al.: HR = 1.59 (1.08–2.36); Murphy et al.: prevalence of graft thrombosis PD vs. HD: 9.27 vs. 0 %]. Their results, however, should be interpreted cautiously because the study by Snyder et al. had a large proportion of missing data on the cause of graft failure, and the study by Murphy et al. was conducted on a small population with no multivariate analysis, thereby limiting their conclusions.



Overall, older donors and younger recipients were associated with shorter long-term graft survival. However, at the time of our study, our donors and recipients were younger than current donors and recipients. Seventy-two percent of the donors and recipients were younger than 55 years of age, which suggests that this result is irrelevant. However, older recipients showed better graft survival, although the main reason for loss was chronic allograft nephropathy at any age. These findings were independent of those related to dialysis modality.

The overall incidence of acute rejection was also similar between the two groups despite the higher number of graft losses for acute rejection in the PD group. Patients treated with PD have been reported to have better immune responses to various agents [21], which can induce a higher rejection severity.

Pérez-Fontán [3] was one of the first authors to show that patients treated with PD had a lower risk of DGF than patients on HD. Other studies, including ours, have confirmed this finding [5, 9–11]. In our case, the immediately improved function did not influence long-term graft survival. The reasons for late losses were independent of the kidney function recovery rate and were related to specific delayed complications.

Our study is limited primarily by its single-center nature, which could favor uniformity in various actions but limits the extrapolation of results. However, this does not lessen the validity of the results, although their interpretation requires consideration of local conditions and circumstances. The retrospective nature of this study was unavoidable because randomization of the dialysis modality is difficult and data from randomized trials are currently not available. However, the use of the STROBE methodology in this study can help overcome this difficulty.

The strengths of our study include the homogeneity of the clinical practice; our hemodialysis, peritoneal dialysis, and transplantation programs have been conducted by the same nephrologists, and the daily practice and protocols have remained essentially unchanged, although they have been regularly updated. Another strength of the study was the long-term observation, which lasted 22 years. A final strength of our study was the use of competing risk methods to evaluate the differences in transplant outcomes between both dialysis modalities; a competitive event survival analysis precludes interferences [22].

In conclusion, our data show that the pretransplantation dialysis modality is associated with long-term patient survival, with the results favoring peritoneal dialysis over hemodialysis, independently of other conditions (younger age, lower BMI, and immunosuppression based on tacrolimus). However, pretransplant dialysis modality did not influence long-term allograft survival.

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Conflict of interest The authors declare that they have no conflicts of interest.

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