

ORIGINAL ARTICLE

Duration of dialysis pretransplantation is an important risk factor for delayed recovery of renal function following deceased donor kidney transplantation

Douglas S. Keith,^{1*} Marcelo Cantarovich,¹ Steven Paraskevas² and Jean Tchervenkov²

¹ Department of Medicine, Multi-organ Transplant Program, McGill University Health Center, Montreal, PQ, Canada

² Department of Surgery, Multi-organ Transplant Program, McGill University Health Center, Montreal, PQ, Canada

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Correspondence

Douglas S. Keith MD, McGill University Health Center, Royal Victoria Hospital, Department of Nephrology, 687 Ave. Des Pins, Montreal, PQ H3A 1A1, Canada. Tel.: +1 514 328 8170; fax: +1 514 843 2815; e-mail: douglas.keith@muhc.mcgill.ca

*Douglas S. Keith, MD, performed the statistical analysis of data. The author is affiliated with McGill University.

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Summary

Delayed graft function (DGF) is a common problem in kidney transplantation and is associated with adverse graft outcomes and increased cost of care. The purpose of this study was to determine if the duration of dialysis increases the risk of DGF. All primary deceased donor renal transplants between January 2000 and December 2003 were identified in the Organ Procurement and Transplant Network database. Two separate definitions of DGF were used: dialysis in the first week post-transplant (DPT) and creatinine drop of < 25% in the first 24 h or slow graft function (SGF). The rate of DPT and SGF increased from 5.7% and 34.4%, respectively, for pre-emptively transplanted patients, to 32% and 49.9% for patients who had been on dialysis for 6 or more years. When compared to pre-emptive transplantation, increasing duration of dialysis increased the adjusted risk of both DPT and SGF (OR 6.64 (95% CI 5.49–8.03) and OR 1.76 (95% CI 1.56–2.00) for patients on dialysis for 6 or more years, for DPT and SGF, respectively. A strong association between duration of dialysis and DGF exists, and investigations into the mechanisms by which dialysis influences DGF may lead to useful interventions to limit this complication.

Introduction

Delayed graft function (DGF) is associated with increased risk of early acute rejection, peri-operative death, longer post-transplant hospitalization and cost and shortened allograft survival.[1–5] Cold ischemia time, donor age, cause of donor death, human leukocyte antigen (HLA) mismatch, elevated panel reactive antibodies (PRA), black recipient race, and recipient age have been previously identified as risk factors for DGF.[1] In a registry study of pediatric kidney transplantation, dialysis prior to transplantation was associated with a six times higher rate of DGF defined as the need for dialysis in the first week post-transplantation (DPT) when compared to pre-emptive transplants.[6] Whether this just reflects the increased likelihood of dialysis after transplantation among patients who had been already on dialysis prior to transplant

because of reasons other than ischemia reperfusion injury (IRI) like transient hyperkalemia or fluid overload, or whether dialysis treatment actually directly increases the risk and severity of IRI is unclear. Although different pathologic process can lead to DGF, the large majority of cases are due to IRI with associated acute tubular necrosis; therefore, DGF, in the majority of cases, is a surrogate marker for IRI.

Most registry studies have operationally defined DGF as the need for DPT. This variable may be significantly biased in patients already on dialysis at the time of transplant and, therefore, may not reflect the degree of IRI in the donor kidney. Clearly, better residual native kidney function may decrease the likelihood of the need for dialysis post-transplant in patients with IRI. Residual kidney function tends to deteriorate over time while on dialysis.[7–9] Recently, a new variable that deals with whether

a 25% drop in the pretransplant creatinine was seen in the first 24-h post-transplant has been added to the United Network of Organ Sharing database as a marker for DGF and IRI. This variable should be less subject to bias, based on the dialysis status and duration at the time of transplant. The purpose of the present study was to determine if dialysis and duration of dialysis impacted DGF based on the two definitions.

Materials and methods

Between January 1, 2000 and December 31, 2003, all primary adult deceased donor renal transplants were identified in the Organ Procurement and Transplant Network database obtained from the Standard Transplant Analysis and Research File. During this period, 95% of cases had data regarding the two endpoints of interest, DPT and a 25% decline in creatinine in the first 24-h post-transplant or slow graft function (SGF). Also, 92.4% of cases in this time period had complete data for dialysis status at transplant and duration of dialysis prior to transplant. Only patients with complete data for the two definitions of DGF and for status and duration of dialysis at time of transplant were included in the study.

The duration of dialysis prior to transplantation was determined from the date of first dialysis to the date of transplantation. To analyze the impact of dialysis duration and status on the probability of DGF based on the two definitions in the deceased donor cohort, multivariable binary logistic regression was used to calculate the adjusted odds ratios. Fourteen variables including recipient and donor age (grouped by decade), gender and race (Caucasian, African-American, or other), donor hypertension, or diabetes mellitus, whether the donor kidney was pumped, HLA mismatch, duration of dialysis, cold ischemia time (<12-h, 12–24 h, 24–36 h, more than 36 h, or unknown), most recent PRA (0%, 1–49%, >49% or unknown), cause of donor death (stroke or no stroke), nonheart beating donor, final creatinine of the donor (<1.0 mg/dl, 1–1.4 mg/dl, >1.4 mg/dl or unknown), and cause of kidney failure in the recipient (diabetes mellitus, hypertension, glomerulonephritis, or other) were used in the regression models. With the exception of two variables in the model, the data were over 99% complete. Only cold ischemia time, in which the data were incomplete in 15% of cases, and most recent PRA, in which the data were incomplete in 3.2% of cases, were unknown categories added to these variables. All variables were categorically defined. Binary logistic regression analysis was carried out with multiple interaction variables to determine if significant interactions between the donor and recipient characteristics and the duration of dialysis prior to transplantation existed. The interaction variables

included duration of dialysis in months multiplied by the following variables: donor gender, donor race, creatinine of donor, recipient's most recent PRA, donor hypertension, donor diabetes mellitus, donor heartbeat and donor death because of stroke. Binary logistic regression analysis was carried out with and without the interaction variables to determine if it changed the significance of the primary association of duration of dialysis with DGF. All tests of significance were two-sided with an alpha level of 0.05. Statistical analysis was performed with SPSS version 11.0 (SPSS Inc., Chicago, IL, USA).

Finally, because of the possibility that duration of dialysis selected for unmeasured donor factors that may influence outcome, a subset analysis of recipient pairs from the same donor was carried out on the population in which one recipient of a donor kidney had less than a year of dialysis prior to transplant, and the recipient of the second donor kidney had four or more years of dialysis. This controlled for unmeasured donor factors since each pair came from the same donor.

Results

A total of 30 294 primary deceased donor kidney transplants (92.5% of all primary deceased donor kidney transplants) were identified that met the inclusion criteria for the study. Table 1 shows the characteristics of the study populations based on the duration of dialysis prior to transplant. As exposure to dialysis increased, an increase in donor characteristics such as the donor age, the percentage of African-American donors, the percentage of donors with hypertension, and diabetes mellitus was noted. The most striking trend noted was the fourfold increase in the percentage of African-American recipients, as exposure to dialysis increased. HLA mismatch, the percentage of the most recent PRA > 49%, and mean cold ischemia time all increased as exposure to dialysis increased.

Figure 1 shows the incidence of DGF defined by the two endpoints based on the duration of dialysis. For both definitions, the rate of DGF increased as the duration of dialysis prior to transplantation increased. Only 5.7% of pre-emptively transplanted patients required DPT and 33.4% of pre-emptively transplanted patients had a < 25% drop in their pretransplant creatinine in the first 24 h. The rate of DPT increased to 32% in recipients on dialysis over 72 months prior to transplantation, and incidence of a < 25% drop in their pretransplant creatinine increased to 49.9%. The percentage of patients attaining either endpoint was always higher for SGF definition of SGF in each time strata.

Tables 2 and 3 show the adjusted odds ratio of DGF based on the two definitions one related to requirement

Table 1. Characteristics of deceased donor recipient population based on duration of dialysis prior to transplant.

	Duration of dialysis prior to transplantation							
	Pre-emptive (n = 3021)	1–11 months (n = 3668)	12–23 months (n = 5658)	24–35 months (n = 5331)	36–47 months (n = 4262)	48–59 months (n = 3026)	60–71 months (n = 3317)	72 or more months (n = 2011)
Mean donor age (SD) (years)	33.6 ± 16.2	34.1 ± 16.7	35.0 ± 17.1	35.7 ± 17.2	36.9 ± 17.1	36.8 ± 17.0	37.2 ± 17.0	36.8 ± 17.0
Per cent of donors male (%)	61.1	58.9	60.3	60.3	59.6	58.3	60.3	61.0
Per cent donors African-American (%)	9.4	9.2	10.1	12.1	12.9	12.7	14.4	15.2
Per cent of donors with Diabetes mellitus (%)	3.8	3.3	3.5	4.3	4.1	4.2	4.6	5.3
Per cent of donors with hypertension (%)	14.8	16.3	17.3	18.4	20.4	21.1	20.7	21.5
Percentage of nonheart beating donors (%)	2.7	3.2	2.9	3.0	3.1	3.3	3.4	3.1
Per cent of donor deaths because of stroke (%)	34.5	35.2	36.6	37.5	39.8	40.0	40.9	41.0
Per cent of donor kidneys pumped (%)	14.8	13.3	13.0	13.1	12.1	11.2	13.3	14.1
Median donor creatinine (p25%, p75%) (mg/dl)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	1.0 (0.7–1.2)	0.9 (0.7–1.2)	1.0 (0.7–1.2)	1.0 (0.7–1.3)
Mean recipient age (SD) (years)	46.8 ± 14.7	45.7 ± 15.5	46.9 ± 15.3	48.5 ± 14.6	49.1 ± 13.7	49.7 ± 13.0	48.9 ± 12.6	47.8 ± 12.0
Per cent recipients male (%)	57.8	61.9	60.7	61.1	61.7	61.5	60.2	56.3
Per cent recipients African-American (%)	13.8	14.5	20.5	25.5	31.2	38.0	43.4	49.5
Per cent of recipients with diabetic nephropathy (%)	31.5	35.8	37.6	34.5	30.4	27.1	23.3	14.8
Median cold ischemia time (p25%, p75%) (h)	16.0 (11.0–21.7)	17.0 (12.0–23.0)	17.0 (12.0–23.0)	17.5 (12.0–24.0)	18.0 (12.0–24.0)	18.0 (12.4–24.0)	18.0 (13.0–24.0)	19.0 (13.0–24.0)
Mean human leukocyte antigen mismatch	3.4 ± 1.9	3.2 ± 2.0	3.4 ± 1.9	3.5 ± 1.8	3.8 ± 1.7	3.9 ± 1.6	4.1 ± 1.5	4.0 ± 1.7
Per cent peak panel reactive antibodies >49% (%)	3.0	3.1	3.2	3.8	3.8	3.9	5.2	9.2

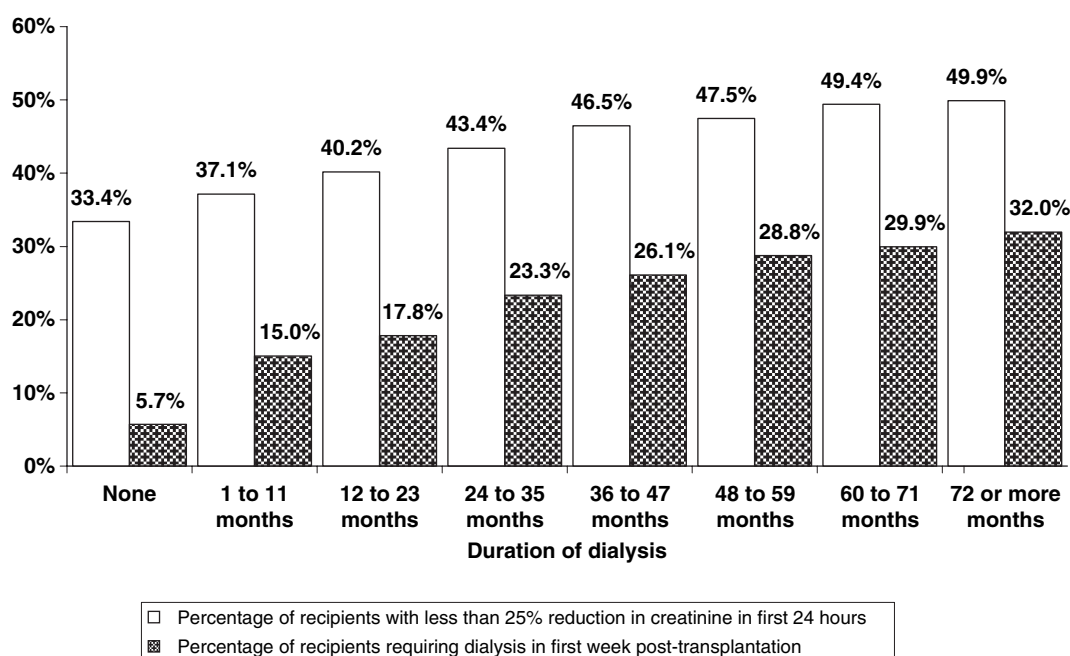


Figure 1 The incidence of delayed graft function based on duration of dialysis prior to transplant in deceased donor recipients.

of post-transplant dialysis and another based on SGF. The relationship between the two endpoints for DGF both strongly correlate with duration of dialysis, although the risk ratios increase more dramatically in the endpoint of dialysis in the first week because of the very low initial incidence of dialysis in the pre-emptive population. Interaction testing did not alter significantly the relationship between duration of dialysis and DGF for the two binary logistic regression analyses.

Finally, 1774 pairs of recipients were identified in the population in whom one kidney of specific donor was transplanted into a recipient with <1 year of dialysis and the second kidney of the donor was transplanted into a recipient with four or more years of dialysis. Figure 2 shows the difference in the rates of DGF based on the two definitions among the recipient pairs. For both definitions of DGF, the recipients with the longest duration of dialysis had a statistically significant higher rate of DGF. Since the recipient characteristics of the two groups were different with regard to recipient race and age, most recent PRA, HLA mismatch and cold ischemia time, binary logistic regression was carried out to adjust for these differences; the adjusted odds ratio for DPT in case of the long duration of dialysis was 2.77 (95% CI 2.26–3.40) and the adjusted odds ratio of SGF was 1.29 (95% CI 1.11–1.50).

Discussion

Previous analyses of risk factors for DGF have focused on mainly donor and organ procurement factors. This analy-

sis is the first to examine the dialysis status of recipient and duration of dialysis as a risk factor for DGF and shows that the duration of renal replacement therapy is an important risk factor associated with DGF. For both definitions used, there was a strong correlation between duration of dialysis and the incidence of DGF. Although it is likely that residual function significantly biases the use of DPT as a marker for IRI and that patients on dialysis at the time of transplantation are more likely to require dialysis in the post-transplant period for hyperkalemia and volume overload, the fact that SGF, an endpoint less inherently biased, also strongly correlates with the duration of dialysis suggests that duration of dialysis pretransplant may be causally related to IRI, the most common cause of DGF.

Whether on account of a causal effect or because of the association with the residual function, the major effect of duration of dialysis on the traditional definition of DGF (i.e. DPT) will bias results from previous studies, when not taken into account. For instance, patients with long dialysis exposures were more likely to receive a poorer HLA match, have a high PRA, and also likely to be African-American. Previous analysis of DGF defined as DPT showed a strong association between these factors and DGF [1]. Our analysis showed a much weaker association between DGF and these factors when one accounts for duration of dialysis. The operational definition of DGF as dialysis in the first week as a marker for IRI is seriously flawed by the inherent bias that transplant recipients on dialysis at the time of transplantation are more likely to

Table 2. Logistic regression analysis of the risk of dialysis in the first week post-transplant.

Variable (reference group)	OR	95.0% CI		Significant
		Lower	Upper	
Duration of dialysis prior to transplant (none)				
1–11 months	2.85	2.37	3.42	<0.001
12–23 months	3.33	2.79	3.96	<0.001
24–35 months	4.57	3.84	5.43	<0.001
36–47 months	5.02	4.22	5.98	<0.001
48–59 months	5.70	4.75	6.82	<0.001
60–71 months	5.96	4.98	7.13	<0.001
72 or more months	6.64	5.49	8.03	<0.001
Cold ischemia time (<12 h)				
12–23 h	1.67	1.52	1.83	<0.001
24–35 h	2.65	2.39	2.93	<0.001
36 or more hours	3.92	3.31	4.63	<0.001
Unknown	1.45	1.29	1.62	<0.001
Donor age (20–29 years)				
0–9 years	1.09	0.92	1.29	NS
10–19 years	0.95	0.85	1.06	NS
30–39 years	1.43	1.28	1.59	<0.001
40–49 years	1.55	1.40	1.72	<0.001
50–59 years	1.81	1.62	2.02	<0.001
60 or more years	2.16	1.90	2.47	<0.001
Donor male	1.06	1.00	1.13	NS
Donor race (Caucasian)				
African-American	1.02	0.93	1.12	NS
Other	0.93	0.86	1.02	NS
Donor hypertension	1.33	1.23	1.44	<0.001
Donor diabetes mellitus	0.98	0.85	1.13	NS
Nonheart beating donor	3.70	3.18	4.30	<0.001
Donor cause of death stroke	1.26	1.18	1.36	<0.001
Donor kidney pumped (No)				
Yes	0.51	0.46	0.56	<0.001
Unknown	0.95	0.55	1.64	NS
Donor creatinine (<1.0 mg/dl)				
1.0–1.4 mg/dl	1.25	1.17	1.33	<0.001
>1.4 mg/dl	2.02	1.84	2.22	<0.001
Kidney diagnosis (hypertensive renal disease)				
Diabetic nephropathy	1.26	1.16	1.37	<0.001
Glomerulonephritis	1.03	0.93	1.13	NS
Other renal disease	1.04	0.96	1.13	NS
Recipient age (20–29 years)				
0–9 years	0.85	0.56	1.27	NS
10–19 years	0.77	0.58	1.02	NS
30–39 years	1.01	0.88	1.16	NS
40–49 years	0.96	0.84	1.10	NS
50–59 years	1.11	0.98	1.27	NS
60 or more years	1.12	0.98	1.28	NS
Recipient male	1.32	1.24	1.40	<0.001
Recipient race/ethnicity (Caucasian)				
African-American	1.28	1.19	1.38	<0.001
Hispanic	1.00	0.91	1.10	NS
Other	0.91	0.80	1.03	NS
Human leukocyte antigen mismatch (0)				
1	1.03	0.84	1.27	NS
2	1.11	0.97	1.28	NS

Table 2. continued

Variable (reference group)	OR	95.0% CI		Significant
		Lower	Upper	
3	1.15	1.02	1.28	NS
4	1.09	0.98	1.22	NS
5	1.22	1.10	1.36	<0.001
6	1.19	1.05	1.34	0.006
Most recent panel reactive antibodies (0%)				
1–49%	1.05	0.96	1.13	NS
>49%	1.18	1.02	1.37	0.03
Unknown	1.23	1.05	1.45	0.013

require dialysis after transplantation because of less residual native kidney function, and this effect increases with time on dialysis. Furthermore, a proportion of patients requiring DPT are due to graft losses from surgical mishaps, humoral rejections, and vascular thromboses and early post-operative hyperkalemia or volume overload that may not be related to IRI.

Even though creatinine reduction in the first 24 h appears to be the least biased of the clinical markers, it too is influenced by both residual function and other variables important in the kinetics of creatinine excretion such as the pretransplant creatinine level, the GFR achieved in the first 24 h, the rate of production and volume of distribution of creatinine. Duration of dialysis does affect the pretransplant creatinine level and the GFR achieved in the first 24 h by its effect on residual native function (i.e. patients on dialysis longer have less residual native kidney function). Also African-American recipients make up a greater proportion of the patients with longer dialysis exposures, and are known to have higher rates of creatinine production than other racial groups. The shortcoming of the present clinical endpoints used to measure IRI makes it difficult to determine if the effect of duration of dialysis on DGF is purely the result of residual native kidney function or if over a period of time dialysis changes the recipient milieu in such a way as to increase the incidence of IRI. Efforts to identify specific biomarkers for IRI would help unravel this conundrum.

Although the association between DGF and duration of dialysis by no means proves a causal link to IRI, some experimental and clinical evidence support this contention. In the only animal study of the recipient milieu and IRI, pre-existing chronic renal failure in recipient rats because of previous 5/6 nephrectomy blunted IRI and was associated with earlier epithelial regeneration and repair of the transplanted kidney when compared with recipient rats with normal renal function

Table 3. Logistic regression analysis of the risk of slow graft function.

Variable (reference group)	OR	95.0% CI		Significant
		Lower	Upper	
Duration of dialysis prior to transplant (none)				
1–11 months	1.15	1.03	1.28	0.010
12–23 months	1.28	1.16	1.41	<0.001
24–35 months	1.42	1.28	1.56	<0.001
36–47 months	1.53	1.38	1.69	<0.001
48–59 months	1.57	1.40	1.75	<0.001
60–71 months	1.71	1.53	1.91	<0.001
72 or more months	1.76	1.56	2.00	<0.001
Cold ischemia time (<12 h)				
12–23 h	1.53	1.43	1.63	<0.001
24–35 h	2.10	1.94	2.28	<0.001
36 or more hours	2.90	2.48	3.39	<0.001
Unknown	1.75	1.61	1.91	<0.001
Donor age (20–29 years)				
0–9 years	1.40	1.23	1.58	<0.001
10–19 years	1.03	0.95	1.12	NS
30–39 years	1.38	1.27	1.51	<0.001
40–49 years	1.46	1.34	1.58	<0.001
50–59 years	1.70	1.56	1.87	<0.001
60 or more years	2.01	1.80	2.26	<0.001
Donor male	0.89	0.84	0.94	<0.001
Donor race (Caucasian)				
African-American	1.06	0.98	1.14	NS
Other	0.96	0.89	1.03	NS
Donor hypertension	1.26	1.18	1.36	<0.001
Donor diabetes mellitus	1.04	0.92	1.18	NS
Nonheart beating donor	3.33	2.87	3.85	<0.001
Donor cause of death stroke	1.13	1.07	1.20	<0.001
Donor kidney pumped (No)				
Yes	0.47	0.44	0.51	<0.001
Unknown	1.06	0.68	1.65	NS
Donor creatinine (<1.0 mg/dl)				
1.0–1.4 mg/dl	1.22	1.15	1.28	<0.001
>1.4 mg/dl	1.80	1.66	1.96	<0.001
Kidney diagnosis (hypertensive renal disease)				
Diabetic nephropathy	1.12	1.05	1.20	<0.001
Glomerulonephritis	1.01	0.94	1.10	NS
Other renal disease	1.00	0.93	1.07	NS
Recipient age (20–29 years)				
0–9 years	0.68	0.52	0.91	0.008
10–19 years	0.71	0.58	0.87	0.001
30–39 years	1.01	0.90	1.12	NS
40–49 years	1.00	0.90	1.11	NS
50–59 years	1.14	1.03	1.26	0.015
60 or more years	1.13	1.02	1.26	0.024
Recipient male	1.31	1.25	1.38	<0.001
Recipient race/ethnicity (Caucasian)				
African-American	1.05	0.99	1.12	NS
Hispanic	0.90	0.83	0.97	0.009
Other	0.83	0.75	0.92	<0.001
Human leukocyte antigen mismatch (0)				
1	1.04	0.88	1.22	NS
2	1.13	1.01	1.27	0.027

Table 3. continued

Variable (reference group)	OR	95.0% CI		Significant
		Lower	Upper	
3	1.12	1.02	1.23	0.013
4	1.12	1.03	1.23	0.008
5	1.22	1.12	1.33	<0.001
6	1.21	1.09	1.33	<0.001
Most recent panel reactive antibodies (0%)				
1–49%	1.09	1.02	1.16	0.013
>49%	1.17	1.03	1.32	0.014
Unknown	1.51	1.31	1.74	<0.001

[10]. This study is consistent with the hypothesis that the compensatory changes associated with advanced chronic renal failure may actually promote early graft function in the transplant setting. Initiation of dialysis is usually associated with an accelerated decline in residual renal function and urine output, in part, because of the alteration of the compensatory mechanisms used maintains renal function in advanced renal failure. Registry studies have shown that pre-emptive transplantation is associated with a lower risk of early acute rejection [11,12]. This clinical observation appeared to be counter-intuitive to our understanding of immune function in uremia that patients on dialysis have more functional immune impairment. The data from this study provide a potential physiologic nexus to explain this paradoxical finding. If the hypothesis that IRI leads to events in the graft that make it more immunogenic, then the higher incidence of DGF and thus IRI in patients on dialysis prior to transplantation may explain the rate of acute rejection seen in recipients on dialysis at the time of transplant.

Delayed graft function is both detrimental to recipient outcomes post-transplant and costly to the healthcare system as a whole. Efforts to limit this complication have, for the most part, concentrated on decreasing cold ischemia time and improving donor management prior to organ procurement. This study suggests that potentially modifiable recipient factors exist that may be as important as cold ischemia time in the incidence of DGF. Further investigations of the mechanisms by which type and duration of dialysis influence IRI may lead to useful interventions to limit this complication.

Authorship

DSK designed and performed the research/study. DSK, MC, SP and JT analyzed the data. DSK, MC and SP wrote the paper.

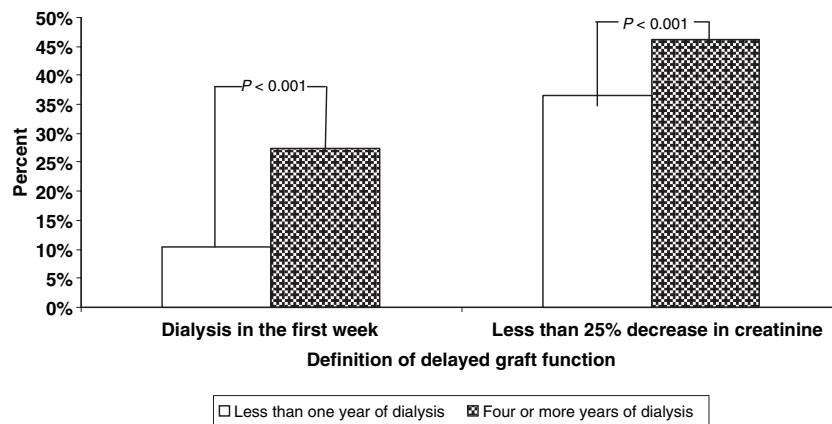


Figure 2 Rates of delayed graft function in pairs of recipients with the same donor but either a dialysis exposure of less than one year or four or more years. Significance was determined using Pearson's chi-squared test.

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