Association of Cold Ischemia Time With Acute Renal Transplant Rejection

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Background. Kidney transplantation holds much promise as a treatment of choice for patients with end-stage kidney disease. The impact of cold ischemia time (CIT) on acute renal transplant rejection (ARTR) remains to be fully studied in a large cohort of renal transplant patients. **Methods.** From the Organ Procurement and Transplantation Network database, we analyzed 63 798 deceased donor renal transplants performed between 2000 and 2010. We assessed the association between CIT and ARTR. We also evaluated the association between recipient age and ARTR. **Results.** Six thousand eight hundred two (11%) patients were clinically diagnosed with ARTR. Longer CIT was associated with an increased risk of ARTR. After multivariable adjustment, compared with recipients with CIT < 12 hours, the relative risk of ARTR was 1.13 (95% confidence interval, 1.04-1.23) in recipients with CIT ≥ 24 hours. The association of CIT and ARTR was more pronounced in patients undergoing retransplantation: compared with recipients with CIT less than 12 hours, the relative risk of ARTR was 1.66 (95% confidence interval, 1.01-2.73) in recipients with CIT of 24 hours or longer. Additionally, older age was associated with a decreased risk of ARTR. Compared with recipients aged 18 to 29 years, the relative risk of ARTR was 0.50 (95% confidence interval, 0.45-0.57) in recipients 60 years or older. Longer CIT was also associated with increased risk of death-censored graft loss. Compared with recipients with CIT less than 12 hours, the hazard ratio of death-censored graft loss was 1.22 (95% confidence interval, 1.14-1.30) in recipients with CIT of 24 hours or longer. **Conclusions.** Prolonged CIT is associated with an increased risk of ARTR and death-censored graft loss. Older age was associated with a lower risk of ARTR.

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The number of patients in need of kidney transplantation continues to increase.[1] In 2014, the number of prevalent cases of end-stage kidney disease (ESKD) in the United States was 678 383, and 70% of those patients were treated with dialysis. In that same year, 17 914 kidney transplants were performed in the United States, whereas 88 231 candidates were on the waiting list. The number of incident ESKD cases in the United States was 120 688 in 2014, and patients aged 65 years and older had the highest ESKD incidence rate among all age groups.[2] The scarcity of viable kidneys for transplantation has led clinicians to reconsider previously unacceptable durations of cold ischemia time (CIT). However, ischemia depletes energy production, inactivates ion channels, and eventually leads to cell death.[3] After reperfusion of the donor organ, ischemia-reperfusion injury (IRI) induces an inflammatory response in the allograft.[4,5] As a result, allografts with long CIT have been linked with increased immunogenicity and acute allograft rejection.[6-8]

However, the results of prior studies on CIT and renal transplant outcomes have been inconsistent. One study of 14 000 renal transplants from extended criteria donors reported no association between CIT and acute renal transplant rejection (ARTR),[9] whereas another study of 611 transplant recipients reported a higher incidence of ARTR with increasing CIT.[10] Small studies demonstrating a link between CIT and ARTR also were not adequately powered to identify long-term outcomes in patients of diverse age ranges.[11,12]

Moreover, aging is associated with declining immunity in renal transplant recipients.[13,14] This is explained by a smaller population of lymphocyte progenitors and decreased

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number of T and B cells in older compared with younger recipients.[15] Animal studies have shown a decreased memory T cell response to CD28 costimulation in older mice[16] and in humans, vaccinated elderly individuals had reduced responses to influenza virus.[17]

The association between CIT and graft loss has been investigated in prior studies. Salahudeen et al[18] showed a significant association between prolonged CIT and decreased long-term survival of cadaveric renal allografts in 6465 recipients. However, 2 other studies with smaller cohorts found that CIT does not have a significant association with graft loss in deceased donor renal transplant recipients.[19,20]

We therefore examined the association between CIT and ARTR in a large cohort of renal transplant recipients. In this study, we hypothesize that recipients of kidneys with prolonged CIT are more prone to ARTR. Furthermore, due to declining immunity associated with aging, older renal transplant recipients have a lower risk of acute rejection compared with younger recipients. Also, we hypothesize that due to the deleterious effects of IRI on the graft tissue, recipients of kidneys with prolonged CIT have a higher risk of graft loss.

MATERIALS AND METHODS

Data Sources and Study Population

We used registry data collected by the United Network for Organ Sharing (UNOS), a nonprofit organization that manages the nation's organ transplant system. UNOS uses Organ Procurement and Transplantation Network (OPTN) data which is collected with the help of professionals from hospitals, histocompatibility laboratories, and organ procurement organizations.[21,22]

Our analysis includes patients who underwent solitary deceased donor renal transplantation between 2000 and 2010. From 95 950 reported transplants, we excluded 32 152 transplants because of missing data for CIT and/or ARTR. We excluded 64 64 transplants (20%) due to missing data for CIT, 22 952 transplants (71%) with missing data for ARTR, and 27 36 (9%) transplants with missing data for both CIT and ARTR within 6 months of surgery. We did not observe a pattern of missingness by year. The remaining 63 798 renal transplants were included in our analyses. The study group was limited to adult recipients.

The reported clinical and research activities are consistent with the Principles of the Declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism." Informed consent was not required for the registry data.[23]

CIT, ARTR, and Other Variables

After surgical removal of the organs for transplantation, kidneys are stored in cold solution to preserve their viability.[24] CIT is the time between cold storage of the organ and the time it is warmed by having restored blood supply. In the OPTN database, CIT was recorded in hours. For our analysis, we divided CIT into 4 quantiles (<12, 12-17.9, 18-23.9, ≥24 hours). In the OPTN database, ARTR was defined as clinically overt and drug-treated acute graft rejection (Yes/No) in the 6-month posttransplant period.

Age of the transplant recipient and donor was recorded in years in the OPTN database. For our analysis, recipient and donor age were categorized by decade of life. Recipient body mass index (BMI) was categorized into 4 groups (<20, 20-24.9, 25-29.9, ≥30 kg/m^2) for the multivariate analysis. Dialysis vintage was also categorized into 4 groups (<6 months, 6 months to <2 years, 2 to <5 years and ≥5 years).[25] Percent calculated panel reactive antibody (CPRA) levels were grouped as 0%, 1% to 20%, 21% to 80%, and 81% to 100%.

Statistical Analysis

We studied the association between CIT and ARTR using univariable and multivariable logistic regressions. Odds ratios (with 95% confidence intervals) are used to express differences in the likelihood of acute rejection across different levels of CIT. The group with the shortest CIT (<12 hours CIT) was designated as the reference group. Our multivariable analysis of the association between CIT and ARTR adjusted for age of the recipients and donors, sex of the recipients and donors, ethnicity of the recipients and donors, recipient BMI, HLA mismatching, extended criteria donor, donation after circulatory death, CPRA, cause of death for the donor, dialysis vintage, retransplantation, and year of transplantation. Our regression model evaluating the association between recipient age and ARTR adjusted for the same covariates.

The association between CIT and death-censored graft loss was evaluated with Cox proportional hazards regression models. Graft losses within the first week of transplantation due to vascular surgical complications were excluded from the analyses.[26] The CIT less than 12 hours group was designated as the reference group, and our multivariable analysis adjusted for age of the recipients and donors, sex of the recipients and donors, ethnicity of the recipients and donors, diabetes history of the recipients and donors, hypertension history of the recipients and donors, recipient BMI, HLA mismatching, extended criteria donor, donation after circulatory death, CPRA, cause of death for the donor, dialysis vintage, retransplantation, and year of transplantation. The *P* value for trend was obtained by introducing CIT categories into the regression model and assessing for a linear trend.

Statistical analysis was performed using SAS software, version 9.4 and JMP Pro software, version 13.0.0. (SAS Institute, Inc., Cary, NC).

RESULTS

Demographics

Recipient and donor demographic characteristics are shown in Table 1. All characteristics are stratified by CIT group. The mean recipient age was 51 ± 13 years and mean donor age was 38 ± 17 years for the entire study period. The sex distribution was the same for recipients and donors (61% male and 39% female).

Association Between CIT and ARTR

The mean CIT was 18.3 ± 8.4 hours and the highest recorded CIT was 60 hours. Six thousand eight hundred two patients were clinically diagnosed with ARTR, and the overall incidence of ARTR within 6 months of surgery was 11%. During the study period, 15 245 renal transplantations were performed with CIT of 24 hours or longer. The relative risk of ARTR was higher for each recipient group with CIT of 12 hours or longer compared with recipients with CIT less than 12 hours. Compared with recipients with CIT less than 12 hours, the relative risk of ARTR was 1.17 (95% confidence

TABLE 1.

Baseline characteristics of recipients and donors in the OPTN database between 2000 and 2010

Covariates	All participants	CIT			
		<12 h	12-17.9 h	18-23.9 h	≥24 h
No. recipients	63 798	14 128 (22%)	18 016 (28%)	16 409 (26%)	15 245 (24%)
Age (mean ± SD)					
Recipient, y	63 798	51 ± 13	51 ± 13	51 ± 13	51 ± 13
Donor, y	63 798	38 ± 16	38 ± 17	38 ± 17	38 ± 17
Sex (M, %)					
Recipient	38 534	61	61	60	60
Donor	37 934	59	60	60	59
Recipient ethnicity (%)					
White	30 668	48	48	50	46
Black	19 772	30	32	30	32
Asian	3546	7	6	5	5
Hispanic	8444	12	13	13	15
Other	1368	3	3	2	2
Donor ethnicity (%)					
White	45 540	71	73	72	70
Black	7849	12	12	12	13
Asian	1403	3	2	2	2
Hispanic	8295	13	12	13	14
Other	711	1	1	1	1
Recipient BMI (%)					
< 20 kg/m^2	3578	6	6	6	6
20-24.9 kg/m^2	16 739	29	29	29	29
25-29.9 kg/m^2	19 944	34	34	35	35
≥ 30 kg/m^2	17 695	31	31	30	30
Recipient CMV seropositive (%)	4015	6	6	7	7
Pretransplant dialysis (%)					
Yes	51 298	81	80	80	80
No	12 497	19	20	20	20
Dialysis vintage: mean (SD), y	54 763	3.2 ± 3.1	3.2 ± 3.2	3.1 ± 3.2	3.1 ± 3.4
Extended criteria donor (Yes %)	10 773	16	17	17	16
Donation after circulatory death (Yes %)	5338	8	9	9	8
Cause of death for donor (%)					
Anoxia	10 704	17	17	16	16
Cerebrovascular accident	24 531	38	39	38	39
Head trauma	26 562	42	41	43	41
Other	2000	3	3	3	4
HLA mismatch (%)					
0	8937	6	11	20	17
1	927	1	1	2	2
2	3256	5	5	5	5
3	8878	15	15	13	14
4	15 908	27	26	23	24
5	17 427	31	28	25	26
6	8446	15	14	12	12
CPRA groups (%)					
0	37 513	70	69	67	67
1-20	8186	14	15	15	16
21-80	5842	10	10	11	11
81-100	3271	6	6	7	6

CMV, cytomegalovirus; M, male.

interval, 1.09-1.26) in recipients with CIT of 24 hours or longer (Table 2).

After adjusting for covariates, the relative risk of ARTR was higher for each group with CIT of 12 hours or longer compared with recipients with CIT less than 12 hours. Compared with recipients with CIT < 12 hours, the relative risk of ARTR was 1.13 (95% confidence interval 1.04, 1.23) in recipients with CIT ≥ 24 hours (Table 2). The relative risk of

TABLE 2.

Association of CIT with ARTR in the OPTN database between 2000 and 2010 (N = 6802)

		Univariable analysis			Multivariable analysis[a]		
CIT	N	Odds ratio (95% CI)	*P*-value	P_{trend}	Odds ratio (95% CI)	*P*-value	P_{trend}
<12 h	1394	1.00			1.00		
12-17.9 h	1874	1.06 (0.99-1.14)	0.24		1.02 (0.95-1.11)	0.08	
18-23.9 h	1804	1.12 (1.05-1.22)	0.09		1.12 (1.03-1.21)	0.05	
≥24 h	1730	1.17 (1.09-1.26)	0.001		1.13 (1.04-1.23)	0.01	
				<0.001			<0.001

[a] The multivariable analysis adjusted for age of the recipients and donors, sex of the recipients and donors, ethnicity of the recipients and donors, recipient BMI, HLA mismatching, extended criteria donor, donation after circulatory death, calculated panel-reactive antibody, cause of death for the donor, dialysis vintage, retransplantation and year of transplantation.

CIT groups for ARTR remained similar for the CIT groups after adjusting for kidney biopsies. Compared with recipients with CIT less than 12 hours, the relative risk of ARTR was 1.14 (95% confidence interval, 1.05-1.24) in recipients with CIT of 24 hours or longer.

The association between CIT and ARTR was also evaluated among recipients with retransplantation since those recipients carry a higher risk for ARTR. Among recipients with retransplantation, the association between CIT and ARTR was more pronounced in recipients with CIT of 24 hours or longer. Compared with recipients with CIT less than 12 hours, the relative risk of ARTR was 1.66 (95% confidence interval 1.01, 2.73) in recipients with CIT of 24 hours or longer (Table 3).

Age of the Renal Transplant Recipient and Risk of ARTR

We assessed the association between recipient age and ARTR. After multivariable adjustment, the relative risk of ARTR was lower for recipients 30 years or older compared with recipients 18 to 29 years old. Compared with recipients aged 18 to 29 years, the relative risk of ARTR was 0.87 (95% confidence interval, 0.77-0.98) in recipients aged 30 to 39 years, 0.73 (95% confidence interval, 0.65-0.82) in recipients aged 40 to 49 years, 0.61 (95% confidence interval, 0.54-0.68) in recipients aged 50 to 59 years, and 0.50 (95% confidence interval, 0.45-0.57) in recipients 60 years or older (Figure 1).

TABLE 3.

Association of CIT with ARTR in the OPTN database for recipients with retransplantation between 2000 and 2010 (N = 1082)

		Univariable analysis		Multivariable analysis[a]	
CIT	N	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
<12 h	198	1.00		1.00	
12-17.9 h	317	0.86 (0.55-1.37)	0.53	0.77 (0.47-1.29)	0.32
18-23.9 h	276	1.30 (0.82-2.03)	0.26	1.29 (0.78-2.14)	0.31
≥24 h	291	1.49 (0.96-2.31)	0.07	1.66 (1.01-2.73)	0.04

[a] The multivariable analysis adjusted for age of the recipients and donors, sex of the recipients and donors, ethnicity of the recipients and donors, recipient BMI, HLA mismatching, extended criteria donor, donation after circulatory death, calculated panel-reactive antibody, cause of death for the donor, dialysis vintage, and year of transplantation.

Age of the Renal Transplant Recipient and Delayed Graft Function

In our study group, the incidence of overall delayed graft function (DGF) was 24%. The incidence of DGF was 19% in recipients aged 18 to 29 years, 23% in recipients aged 30 to 39 years, 23% in recipients 40 to 49 years, 24% in recipients 50 to 59 years, and 24% in recipients 60 years or older. We evaluated the association between recipient age and DGF. In univariable analysis, older age was associated with an increased risk of DGF (Table 4). However, after multivariable adjustment, only recipients 60 years or older had an increased risk of DGF compared with younger recipients (18-29 years old). The relative risk of DGF in recipients 60 years or older was 1.11 (95% confidence interval, 1.01-1.23) compared with recipients aged 18 to 29 years (Table 4). Furthermore, after adjustment for DGF and other variables, the relative risk for the association between recipient age and ARTR remained essentially unchanged compared with the analysis without adjustment for DGF. Compared with recipients aged 18 to 29 years, the relative risk for ARTR was 0.84 (95% confidence interval 0.75, 0.96) in recipients aged 30 to 39 years, 0.72 (95% confidence interval, 0.64-0.80) in recipients aged 40 to 49 years, 0.58 (95% confidence interval 0.52, 0.65) in recipients aged 50 to 59 years, and 0.48 (95% confidence interval 0.43, 0.54) in recipients ≥60 years old.

CIT and Death-Censored Graft Loss

We evaluated the association between CIT and death-censored graft loss. 8035 recipients experienced graft loss during the study period. The relative risk of death-censored graft loss was higher for each recipient group with CIT of 12 hours or longer compared with recipients with CIT less than 12 hours. Compared with recipients with CIT less than 12 hours, the hazard ratio of death-censored graft loss was 1.19 (95% confidence interval, 1.12-1.27) in recipients with CIT of 24 hours or longer (Table 5). After multivariable adjustment, compared with recipients with CIT < 12 hours, the hazard ratio of death-censored graft loss was 1.22 (95% confidence interval, 1.14-1.30) in recipients with CIT of 24 hours or longer (Table 5).

DISCUSSION

In our study, we found that the occurrence of ARTR increases with CIT among 63 798 recipients undergoing deceased

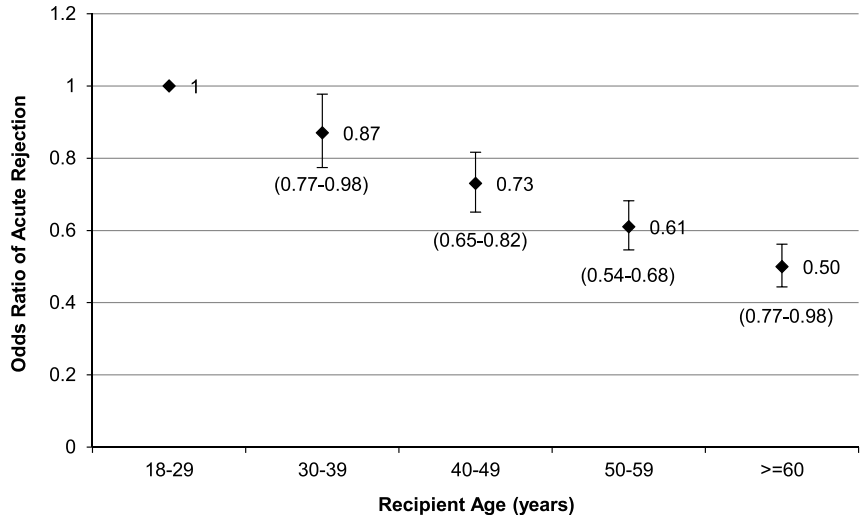

FIGURE 1. Risk of ARTR declines with older recipient age. Recipients were grouped by decade of life and the association of age with ARTR was evaluated with logistic regression analysis. The odds ratio of ARTR was lower among older recipients compared with younger recipients (*P* value <0.001). The multivariable analysis adjusted for CIT, age of the donors, sex of the recipients and donors, ethnicity of the recipients and donors, recipient BMI, HLA mismatching, extended criteria donor, donation after circulatory death, CPRA, cause of death for the donor, dialysis vintage, retransplantation, and year of transplantation. Confidence intervals for the odds ratios are shown below the data points.

donor renal transplantation. Additionally, the risk of ARTR is decreased in older recipients.

IRI has received increasing attention as an instigator of alloimmune responses and the main cause of intragraft inflammatory responses.[27] An increase in proinflammatory cytokines results in a proinflammatory milieu that tips the balance in favor of effector immune responses as opposed to regulatory immune responses.[28,29]

The association of CIT with renal transplant outcomes has been inconsistent in the literature. One study reported no significant difference in the incidence of ARTR despite varied CIT exposure time among 45 patients.[30] Another study of 40 paired renal transplantations did not report any difference in graft rejection rates despite significant differences in CIT exposure time between paired transplantations.[31] On the other hand, a European study of 859 deceased donor renal transplants reported an independent positive association between CIT and ARTR.[32] Moreover, this inconsistency applies to studies on graft survival as well.[9,33]

Interestingly, when we examined the association between CIT and ARTR among the subset of recipients with retransplantation, the association between CIT and ARTR was more pronounced in recipients of highly ischemic kidneys (CIT ≥ 24 hours). This finding might suggest that IRI can further potentiate the antigraft alloimmune responses in sensitized hosts. These data may imply using kidneys with shorter ischemia time for patients undergoing retransplantation.

For graft survival, CIT was reported to be an independent predictor of graft survival among 518 deceased donor renal transplant recipients.[34,35] Another study reported an association between prolonged CIT and graft failure among 6322 renal transplant recipients.[36] On the other hand, no association was found between CIT and graft survival among 38 000 living donor renal transplant recipients.[37] However, the CIT range in this study was limited to 0 to 8 hours. We expand on these reports by analyzing a much larger study population with a broader range of CIT exposure times (0-60 hours) among deceased donor renal transplant recipients. We found that prolonged CIT is associated with an increased risk of graft loss.

In the literature, DGF is defined with different criteria and studies reported inconsistent associations with long-term

TABLE 4.

Association of recipient age with DGF in the OPTN database between 2000 and 2010 (N = 14 992)

		Univariable analysis		Multivariable analysis[a]	
Recipient age, y	N	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
18-29	735	1.00		1.00	
30-39	2056	1.27 (1.16-1.40)	<0.0001	1.11 (0.99-1.23)	0.06
40-49	3206	1.25 (1.14-1.37)	<0.0001	1.06 (0.96-1.17)	0.26
50-59	4498	1.36 (1.25-1.49)	<0.0001	1.09 (0.99-1.21)	0.08
≥60	4497	1.36 (1.24-1.48)	<0.0001	1.11 (1.01-1.23)	0.03

[a] The multivariable analysis adjusted for CIT, age of the donor, sex of the recipients and donors, ethnicity of the recipients and donors, recipient BMI, HLA mismatching, extended criteria donor, donation after circulatory death, calculated panel-reactive antibody, cause of death for the donor, dialysis vintage, retransplantation, and year of transplantation.

TABLE 5.

Association of CIT with death-censored graft loss in the OPTN database between 2000 and 2010 (N = 8035)

		Univariable analysis			Multivariable analysis[a]		
CIT	N	Hazard ratio (95% CI)	*P*-value	P_{trend}	Hazard ratio (95% CI)	*P*-value	P_{trend}
<12 h	1478	1.00			1.00		
12-17.9 h	2259	1.09 (1.02-1.17)	0.08		1.09 (1.02-1.17)	0.01	
18-23.9 h	2136	1.11 (1.04-1.18)	0.02		1.17 (1.10-1.25)	<0.001	
≥24 h	2162	1.19 (1.12-1.27)	<0.001		1.22 (1.14-1.30)	<0.001	
				<0.001			<0.001

[a] The multivariable analysis adjusted for age of the recipients and donors, sex of the recipients and donors, ethnicity of the recipients and donors, diabetes history of the recipients and donors, hypertension history of the recipients and donors, recipient BMI, HLA mismatching, extended criteria donor, donation after circulatory death, CPRA, cause of death for the donor, dialysis vintage, retransplantation and year of transplantation.

renal transplant outcomes. A study with 710 deceased donor renal transplants did not demonstrate a relationship between DGF and ARTR.[38] Another study with 734 cadaveric transplants found DGF was associated with acute rejection.[39] Additionally, a study from Europe with 1784 deceased donor renal transplants showed that increasing recipient age is a risk factor for ARTR during the DGF period.[40] In our data, adjustment for DGF in our multivariable model did not substantially affect the association between recipient age and ARTR.

With an aging chronic kidney disease population, more kidney transplants are being offered to older hosts.[14] For this reason, aging immunity has been the subject of intense research.[13,41] Aging causes a decline in the immune response.[41] In elderly patients, compromised proliferation of lymphocytes[42,43] and defective responsiveness of memory T cells to CD28 costimulation[16,17] may explain this decline.[42,43]

Our study is limited by the UNOS registry format in which ARTR is defined clinically. We were unable to examine the association of CIT with ARTR subtypes. We had missing data for CIT and ARTR. A previous study found underreporting of ARTR in the OPTN database, but among the reported cases, the diagnosis was valid.[44] The missingness of rejection data varies by the transplant centers[44,45] and is not likely to be differential with respect to our exposure variable, so the findings presented are internally valid. We evaluated the association of CIT with death-censored graft loss which does not include death as an outcome. The results for the association between CIT and death-censored graft loss should be interpreted cautiously due to the possibility of differential censoring of patients with a functioning graft at the time of death.

In summary, we report the largest study on the association between CIT and ARTR among renal transplant recipients in the United States and found that longer CIT is associated with increased ARTR and death-censored graft loss. Older recipient age was associated with a decreased risk of ARTR.

Future studies are needed to examine the association between ischemia time and other outcomes, including hospitalizations, financial cost and/or death-censored allograft survival in older transplant recipients.

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