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CHAPTER 14

Renal Transplant Outcomes in Waitlist Candidates with a Previous Inactive Status Due to Being Temporarily Too Sick

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INTRODUCTION

Inactive status on the United Network for Organ Sharing (UNOS) waiting list refers to candidates who are considered temporarily unsuitable for transplantation. While inactive, candidates will not receive a deceased donor organ offer. In the past, candidates who had been inactive longer than thirty consecutive days would not be allowed to accrue further waiting time until they converted back to active status. Since November 2003 when this rule was changed, candidates may accrue waiting time during the entire period of inactivity (1). This change has led to a more liberal use of inactivation status. As a result, currently 40% of the candidates on the kidney transplant waiting list are designated as inactive (2-4).

Transplant centers are obligated to define the reason why a candidate is considered inactive. There are many potential reasons for inactivation – for example, temporarily too sick, incomplete candidate work-up, insurance issues, or weight inappropriate for transplant (5). Reason 7 refers to candidates who are "temporarily too sick" for transplantation and is the most common reason for inactivation if the inactivation occurs after thirty days from the initial listing. Candidates who are assigned as inactive may later return to active status and ultimately receive kidney transplants (6).

There were a few previous studies that examined the impact of inactivation on pre-and post-transplant outcomes (7, 8). Inactive candidates were generally older, had more comorbidities, longer waiting times, lower rates of eventual transplantation, and higher waitlist mortality. Of those who achieved active status once again and were eventually transplanted, the mortality rate was reported to be comparable to recipients who remained active at all times. However, those studies examined post-transplant outcomes without stratifying inactive candidates by their reasons for inactivation. Inactive candidates from all reasons may not represent "sicker" patients. There are many reasons for inactivation other than medical issues, such as incomplete work-up or insurance issues. Given that the transition from active to inactive status due to reason 7 on the waitlist may be a surrogate marker for overall medical co-morbidities, we hypothesized that inactive candidates with reason 7, once transplanted, would have worse post-transplant outcomes than recipients who were active at all times while on the waitlist. Here, we examined the association of being inactive specifically due to being too sick

for transplant (reason 7) with both short (30 days) and long-term (3 years) post-transplant outcomes of deceased donor kidney transplant (DDKT) recipients.

MATERIALS AND METHODS

We used data from the Organ Procurement Transplant Network (OPTN)/UNOS as of October 19, 2012. Candidates older than 18 years old with an initial kidney listing date between May 1, 2006, and July 31, 2012, were identified. The reason that our cohort started on May 1, 2006, was because the OPTN began collecting data on reason for inactivation after this date. Candidates who had any history of a previous transplant or were listed on any other waiting lists in addition to the kidney transplantation waiting list were excluded. To assess post-transplant outcomes, candidates on the waitlist who eventually received living donor kidney transplant (LDKT) or who had not received kidney transplant were excluded from our study. The percentage of recipients who were inactivated at least once and the reasons for inactivation were analyzed and stratified from this pool of patients. Then, the recipients who were inactivated because of any reason other than reason 7 were excluded. For the final analyses to assess patient survival and graft survival, recipients were divided into: 1) those without any history of being inactive [active group (n=15,473)]; and 2) those placed on inactive status for reason 7 at least once while on the waitlist [reason 7 group (n=5,014)].

Baseline recipient, donor, and transplant characteristics were described using medians (with 25th and 75th percentiles) or frequencies, whichever were appropriate. The Kruskal-Wallis and chi-square tests were used to compare for significant differences in continuous and categorical variables, respectively.

Graft and patient survival were described using the Kaplan–Meier product limit method and the differences were evaluated using the log-rank test. The primary endpoints were 3-year post-transplant patient and kidney allograft survival. For patient survival, patients were followed until death or last follow-up date. Kidney graft survival was determined from the date of transplantation to the date of death, kidney failure (defined as re-transplantation or return to dialysis), or last follow-up. Death-censored kidney graft survival was also analyzed. In addition, subgroup analyses were performed to compare the patient survival in the reason 7 group with the recipients who were active at all times while on the waitlist and carried the diagnosis of diabetes mellitus (DM) or were 60 or older at the time of transplantation. Perioperative period in this study is defined as the period beginning with the start of the operation to 30 days after kidney transplantation.

Cox proportional hazards regression was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) of death and overall and death-censored kidney graft survival. In the multivariate model, we adjusted the covariates for recipients' age, gender, race, percentage of peak panel reactive antibodies, number of human leukocyte antigen mismatches at the DR locus, BMI (kg/m^2), functional status, cause of end-stage renal disease (ESRD), primary insurance, dialysis duration prior to transplantation, donors' age, gender, race, history of hypertension, and donor/recipient cytomegalovirus sero-pairing.

All reported p values were two-tailed and $p<0.05$ and was considered significant. Analyses were conducted using STATA Statistical Software, version 12.1 (Stata Corp LP, College Station, TX).

RESULTS

Patients and Baseline Characteristics

Approximately 48% of DDKT recipients were inactive at least once while on the waitlist. Incomplete pre-transplant work-up (reason 3) was the most common reason for inactive status (50.35%), followed by being temporarily too sick (reason 7, 28.01%), insurance issues (reason 4, 19.38%), and candidate choice (reason 2, 10.60%) (Table 1). Recipients who were assigned as inactive for any other reasons not including reason 7 or who eventually received an LDKT were excluded from our cohort. The final study population consisted

of 20,487 DDKT recipients: 5,014 had a history of inactivation for reason 7 while on the waitlist (reason 7 group) and 15,473 were active at all times while on the waitlist (active group). Baseline characteristics of these two groups are described in Table 2. Recipients in the reason 7 group were older, were proportionally more male, had diabetes as a cause of ESRD, had poorer functional status, and had longer dialysis times before transplantation when compared with the active group. Recipients in the reason 7 group were also more likely to be mismatched at both DR loci and more likely to have malignancies and peripheral vascular diseases.

Table 1. Reasons for inactive status in kidney transplant waitlisted recipients between years 2006 and 2012.

Reasons[1,2]	Recipients (n)	Recipients (%)
Reason 3: Candidate work-up incomplete	12007	50.35
Reason 7: Temporarily too sick	6680	28.01
Reason 4: Insurance issues	4622	19.38
Reason 2: Candidate choice	2528	10.60
Reason 12: Transplant pending	1125	4.72
Reason 9: Weight currently inappropriate for transplant	624	2.62
Reason 8: Temporarily too well	587	2.46
Reason 5: Medical non-compliance	438	1.84
Reason 1: Candidate cannot be contacted	345	1.45
Reason 6: Inappropriate substance use	115	0.48
Reason 10: Transplanted-removal pending UNET data correction	80	0.34
Reason 13: Physician/surgeon unavailable	5	0.02

[1]The percentage of all of the reasons combined exceeds 100 percent because each recipient might have more than one reason for inactive status. [2]There is no Reason 11 in the United Network for Organ Sharing Database.

Patient Survival

Figure 1 shows unadjusted Kaplan-Meier curves for patient survival. The patient survival in the reason 7 group was similar to that of the active group in the first 2 months post transplantation and then started to decline. At 3 years, reason 7 was associated with a 3.79% decrease in patient survival (reason 7 versus active group: 88.14% versus 91.93%; p<0.01). On univariate analysis, reason 7 recipients had a 44% increased risk of death (HR 1.44, CI 1.25 - 1.65) when compared with the active group. After adjusting for various confounding factors, reason 7 was still associated with a significant increased risk of death (HR 1.20, CI 1.04 - 1.38) (Table 3).

Overall Graft Survival

Figure 2 shows unadjusted Kaplan-Meier curves for kidney graft survival. In the first 30 days after transplant, there was no difference in overall graft survival between the two groups. After a 3-year follow up, kidney survival was significantly lower in the reason 7 group compared to the active group (78.56% versus 83.23%, respectively; p<0.01). As shown in Table 3, reason 7 recipients had a 27% increased risk of graft loss in the unadjusted model

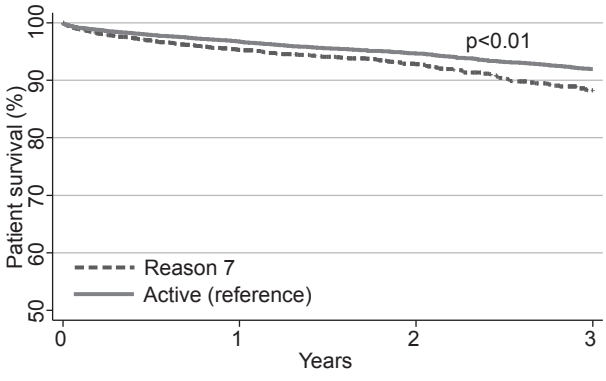

Figure 1. Kaplan-Meier curves for patient survival in deceased donor kidney transplant recipients by waitlist activity.

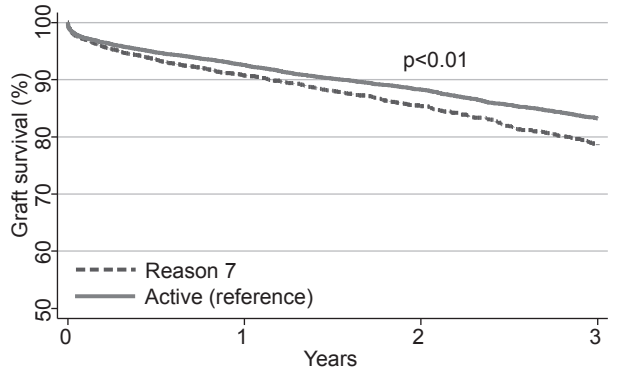

Figure 2. Kaplan-Meier curves for overall graft survival in deceased donor kidney transplant recipients by waitlist activity.

Table 2. Baseline characteristics of adult deceased donor kidney transplant recipients.

	DDKT recipients				DDKT recipients		
	Reason 7 (N=5,014)	Active (N=15,473)	*p* value		Reason 7 (N=5,014)	Active (N=15,473)	*p* value
Age, median (25th, 75th)	58 (49, 66)	56 (46, 64)	<0.001	Hypertension	42.28	44.80	0.002
Male (%)	64.5	59.48	<0.001	Diabetes	44.12	39.48	<0.001
Race (%)				Malignancy	8.0	5.32	<0.001
Caucasian	55.15	47.02	<0.001	Peripheral vascular disease	6.64	4.27	<0.001
Black	28.28	31.57	<0.001	Functional status (%)			
Hispanic	10.35	14.31	<0.001	Able to carry on normal activity	71.98	74.59	<0.001
Other	6.22	7.10	0.034	Unable to carry on normal activity	23.25	20.72	<0.001
Preemptive transplantation (%)	5.19	12.38	<0.001	Unknown	4.77	4.69	0.828
BMI				Primary insurance (%)			
<25	25.99	28.66	<0.001	Private	41.58	42.18	0.455
25-29.9	34.46	35.09	0.421	Medicare	50.02	49.44	0.476
≥30	39.43	36.17	<0.001	Medicaid	4.69	5.91	0.001
Peak PRA (%)				Others	3.71	2.46	<0.001
Missing	5.88	4.41	<0.001	Donor factors			
0-10%	65.52	66.16	0.403	Age, median (25th, 75th)	42 (26, 52)	42 (26, 53)	0.948
10-30%	11.13	10.48	0.193	Male (%)	58.42	59.57	0.147
>30%	17.47	18.96	0.019	Hypertension (%)	29.62	30.36	0.318
HLA-DR mismatch (%)				ECD (%)	27.24	29.05	0.014
0	15.94	25.41	<0.001	Trauma cause of death (%)	35.92	35.71	0.792
1	47.15	41.59	<0.001	CMV serostatus (%)			
2	36.92	33.00	<0.001	D-/R-	13.34	11.96	0.01
Dialysis time in days, median (25th, 75th)	1258 (793, 1765)	846 (396, 1412)	<0.001	D-/R+	24.61	23.56	0.130
Median kidney waiting time in days (25th, 75th)	911 (616, 1220)	429 (164, 808)		D+/R+	40.45	44.48	<0.001
Cause of ESRD (%)				D+/R-	20.16	18.18	0.002
Glomerulonephritis	14.02	14.34	0.573	Cold ischemic time, mean (hours ± SD)	17.2 ± 10.0	18.7 ± 10.6	<0.001
Diabetes	33.51	29.52	<0.001				
Hypertension	23.97	28.17	<0.001				
Polycystic kidney disease	10.17	8.59	0.001				
Other	18.33	19.38	0.099				

Abbreviations: BMI – body mass index; CMV – cytomegalovirus; DDKT – deceased donor kidney transplantation; ECD – extended criteria donor; ESRD – end-stage renal disease; HLA – human leukocyte antigen; PRA – panel reactive antibodies; SD – standard deviation.

(HR 1.27, CI 1.16-1.40) and a 16% increased risk after multivariate adjustment (HR 1.16, CI 1.06-1.28) when compared with the active group.

Death-censored Graft Survival

Figure 3 shows unadjusted death-censored kidney graft survival for both study groups. At 3-years post transplantation, death-censored graft survival was significantly worse in the reason 7 group when compared to the active group (88.66% versus 90.23%, respectively; p=0.02). Univariate and multivariate Cox analysis demonstrated a 16% increased (HR 1.16, CI 1.02-1.32) and a 15% increased (HR 1.15, CI 1.01-1.31) risk of death-

Table 3. Unadjusted and adjusted risk for death, overall graft survival, and death-censored graft survival in adult deceased donor kidney transplant.

	Unadjusted HR (95% CI)	*p* value	Adjusted* HR (95% CI)	*p* value
Patient survival				
Active DDKT	reference	----	reference	----
Reason 7 DDKT	1.44 (1.25-1.65)	<0.01	1.20 (1.04-1.38)	0.01
Overall graft survival				
Active DDKT	reference	----	reference	----
Reason 7 DDKT	1.27 (1.16-1.40)	<0.01	1.16 (1.06-1.28)	<0.01
Death-censored graft survival				
Active DDKT	reference	----	reference	----
Reason 7 DDKT	1.16 (1.02-1.32)	0.02	1.15 (1.01-1.31)	0.035

Abbreviations: CI – confidence interval; DDKT – deceased donor kidney transplant; HR – hazard ratio. *Adjusted for recipients' factors, including: age, gender, race, percentage of peak panel reactive antibodies, number of human leukocyte antigen mismatches at the DR locus, body mass index (kg/m^2), functional status, diabetes as a cause of end-stage renal disease, and primary insurance; and for donors' factors, including: age, gender, race, history of hypertension, cause of death, and expanded criteria donor. Cytomegalovirus sero-status of both recipient and donor is an additional factor in graft survival analyses but not in patient survival analyses.

censored graft loss, respectively, in the reason 7 group when compared to the active group (Table 3).

Subgroup Analyses

Subgroup analyses were performed to compare patient survival between the reason 7 group and active recipients who had DM as an underlying disease and with active recipients who were 60 years old or older at the time of transplantation. We found no difference in 3-year post-transplant patient survival between the reason 7 group and active recipients with DM (88.14% versus 88.63%, respectively; p=0.875). Similarly, there was no difference in patient survival observed when the reason 7 group was compared with active recipients aged 60 or older at the time of transplantation (88.14% versus 86.71%, respectively; p=0.831).

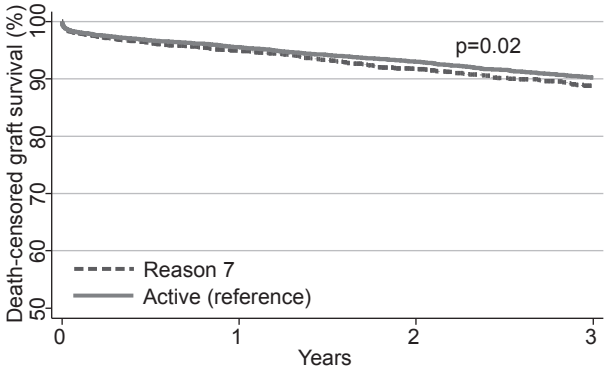

Figure 3. Kaplan-Meier curves for death-censored graft survival in deceased donor kidney transplant recipients by waitlist activity.

DISCUSSION

We found that perioperative patient and kidney survival rates (within 30 days after transplant) were comparable between recipients deemed temporarily medically unsuitable for transplant (reason 7) while on the waitlist and recipients who were active at all times on the waitlist. However, the long-term outcomes (at 3 years), including both patient and graft survival, were poorer in the reason 7 group. Despite the statistically significant risk analyses, survival differences between the two groups ranged only between 1.6 to 4.7 percent at three years, which might not be of clinical importance.

In our study, more than 40% of recipients were inactive at least once before transplantation. This finding was in agreement with previous literature that concluded that increasing candidates in the transplant pool each year was majorly due to inactive candidates, whereas numbers of active candidates remained approximately the same (5, 8). It also implies that the organ shortage is overestimated because the increasing number of candidates does not represent the true number of candidates who are eligible for organ allocation.

The common reasons for inactivation were: 1) work-up incomplete (reason 3); 2) being "temporarily too sick (reason 7); 3) insurance issues (reason 4); and, 4) candidate choice (reason 2). There was only one previous study that reported the reason for inactive status. Delmonico et al. demonstrated that if the inactivation occurred within 30 days of listing, the most common reason was "candidate incomplete work-up". However, if candidates had been listed longer than 30 days, the most common reason for inactive status was "reason 7" or "being temporarily too sick" (5). It is likely that the majority of candidates who initially had incomplete work-ups returned to active status within 30 days of listing given that some transplant centers routinely place all candidates on the waitlist initially in inactive status during the process of pre-transplant evaluation in order for candidates to accrue waiting time (5, 9). In our study, we did not categorize reason for inactivity according to the timing of listing (within and more than 30 days), but the result of reasons for inactivity overall was consistent with the earlier study (5).

There are a few studies to date that examine the association between waitlist activity and pre-/post-transplant outcomes. It is evident in all studies that candidates who were placed on inactive status were less likely to get transplanted and more likely to die or get delisted while they were on the waitlist (5, 7-9). The impact on post-transplant outcomes of being inactive, however, has yet to be elucidated. The first study that explored such association was a single-center study conducted by Shafi et al., in which they found no difference in patient survival between active and inactive patients. A small sample size was a major limitation of the study and might mask the true effect of waitlist activity (7). Grams et al. used a national database and also found no difference in patient and graft survival between active and inactive patients who eventually received DDKT (8). Interestingly, Norman et al. demonstrated that recipients who were placed on inactive status twice or more had a 14% increased risk of death post transplant, but no increase in mortality if recipients were placed on inactive status only once while on the waitlist (9).

It is worth noting that all three studies mentioned above included all causes of inactivation regardless of whether the reasons were medical or logistical. Decisions to place candidates on inactive status are arbitrary because different centers may use inactive status for different reasons. As the most common cause of being inactive is "incomplete work up", it is possible that some of those inactive patients in previous studies were as healthy as active patients and were placed on the waitlist as inactive before the medical evaluation was completed. Therefore, the study population in prior studies did not necessarily reflect inactive candidates who were "sicker" and deemed unsuitable for transplant because of medical issues. Therefore, our study is, to our knowledge, the first study that examined post-transplant patient and graft survival in candidates who were once inactive on the waitlist due to reason 7 only. By doing so, we hope that it would serve as a better surrogate marker for sicker patients with complex medical co-morbidities.

Previous literature suggests that kidney transplantation provides long-term survival benefits in diabetic and elderly patients despite minor inferiority in post-transplant outcomes compared to younger and non-diabetic patients (10-17). In our subgroup analysis, we have proven that the reason 7 group had comparable patient survival to DM and elderly groups. This finding suggests that reason 7 candidates tend to fare as well as other high-risk groups and should not be discouraged from transplantation once they return to active status. Nevertheless, close attention should be paid to recipients with a history of reason 7 in order to identify potential medical problems during the follow-up period.

There are some limitations in our study. First, we did not account for duration and timing of inactive status, which would help us better understand the extent of the associations between inactive status and post-transplant outcomes. Second, there is currently no standardized criteria for placing candidates on inactive status. As a result, there may be disparities among transplant centers in how they define the inactive status on the waitlist. Third, we did not have enough data to analyze causes

of death in kidney transplant recipients, which would have given us a better picture of why reason 7 patients did poorer than active patients. For example, given a higher proportion of malignancy in the reason 7 group, it is possible that they had worse patient survival merely because they died from advanced cancer. Last, we only focused on post-transplant outcomes and did not analyze the overall beneficial effect of the OPTN policy change regarding waiting time accrual.

In summary, reason 7 is the second most common reason for candidates being placed on inactive status. Once reason 7 patients are re-activated and receive kidney transplants, their perioperative mortality and graft loss rates are comparable to the active group. However, after 3 years of follow up, recipients with a history of reason 7 have slightly, but significantly, worse outcomes. Candidates with a history of reason 7 should not be discouraged from transplantation once they return to active status. OPTN should develop standardized criteria for placing candidates on inactive status to reduce disparities among transplant centers.

ACKNOWLEDGEMENT

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SUMMARY

Background: In 2003, the United Network for Organ Sharing (UNOS) changed its policy to allow candidates with 'inactive' status to accrue time on the waitlist. In this study, we assessed the transplant outcomes among deceased donor kidney transplant (DDKT) recipients who were temporarily inactive specifically due to medical reason, i.e., being temporarily too sick (reason 7).

Methods: Using the UNOS database, adult DDKT recipients were divided into two groups: those who had never been inactivated (active group) and those with a history of being inactive due to reason 7 (reason 7 group). Patient and graft survival, 3-year risk of death, and graft failure were examined and compared.

Results: After 3 years of follow-up, patient survival in the reason 7 group was significantly lower than that of the active group (88.14% versus 91.93%, p<0.01). The reason 7 group had a 20% increased risk of death (hazard ratio, HR 1.20, confidence interval, CI 1.04 - 1.38), a 16% increase in graft failure (HR 1.16, CI 1.06-1.28), and a 15% decrease in death-censored graft failure (HR 1.15, CI 1.01-1.31).

Conclusion: Recipients with a history of reason 7 have lower patient and graft survival when compared to the active group. Nonetheless, the margins of difference are minimal. Candidates with a history of reason 7 should not be discouraged from transplantation once they return to active status. Standardized criteria for placing candidates on inactive status should be developed to reduce disparities among transplant centers.

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