

Survival and Hospitalization for Intensive Home Hemodialysis Compared with Kidney Transplantation

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ABSTRACT

Canadian patients receiving intensive home hemodialysis (IHD; ≥ 16 hours per week) have survival comparable to that of deceased donor kidney transplant recipients in the United States, but a comparison with Canadian kidney transplant recipients has not been conducted. We conducted a retrospective cohort study of consecutive, adult IHD patients and kidney transplant recipients between 2000 and 2011 at a large Canadian tertiary care center. The primary outcome was time-to-treatment failure or death for IHD patients compared with expanded criteria, standard criteria, and living donor recipients, and secondary outcomes included hospitalization rate. Treatment failure was defined as a permanent switch to an alternative dialysis modality for IHD patients, and graft failure for transplant recipients. The cohort comprised 173 IHD patients and 202 expanded criteria, 642 standard criteria, and 673 living donor recipients. There were 285 events in the primary analysis. Transplant recipients had a reduced risk of treatment failure/death compared with IHD patients, with relative hazards of 0.45 (95% confidence interval [95% CI], 0.31 to 0.67) for living donor recipients, 0.39 (95% CI, 0.26 to 0.59) for standard criteria donor recipients, and 0.42 (95% CI, 0.26 to 0.67) for expanded criteria donor recipients. IHD patients had a lower hospitalization rate in the first year of treatment compared with standard criteria donor recipients and in the first 3 months of treatment compared with living donor and expanded criteria donor recipients. In this cohort, kidney transplantation was associated with superior treatment and patient survival, but higher early rates of hospitalization, compared with IHD.

J Am Soc Nephrol 25: 2113–2120, 2014. doi: 10.1681/ASN.2013111180

Kidney transplant recipients have been shown to have higher cumulative survival and lower rates of hospitalization compared with patients on conventional in-center hemodialysis (4 hours per treatment, three treatments per week).^{1–5} Although kidney transplantation remains the gold standard form of RRT, intensive home hemodialysis (IHD; ≥ 16 hours per week) is emerging as a treatment option with multiple clinical advantages. IHD patients have good adverse event-free survival⁶ and have very low rates of hospital admission and duration of hospital stay.⁷ Similar to kidney transplant recipients, patients receiving IHD have been shown to have superior outcomes to those patients on conventional in-center hemodialysis.^{8–11}

Thus far, only one study has directly compared IHD to kidney transplantation.¹² In a matched

evaluation of Canadian IHD patients and United States kidney transplant recipients, survival on IHD was comparable to survival after a deceased donor kidney transplant.¹² However, the findings of that study need to be interpreted with caution because patient survival among Canadian kidney transplant recipients has been shown to be superior

Received November 12, 2013. Accepted January 10, 2014.

Published online ahead of print. Publication date available at www.jasn.org.

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to United States kidney transplant recipients¹³ and outcomes outside of death (e.g., hospitalization) were not examined. Acknowledging that a randomized trial of these therapies is unlikely, high-quality observational studies comparing the outcomes of IHHD versus kidney transplantation may educate physicians and patients about the relative benefits of both therapies. Furthermore, prolonged waiting times for deceased donor kidney transplants emphasize the importance of identifying bridging therapies that minimize the risk of morbidity or mortality.

Therefore, the purpose of this study was to compare patient survival, treatment survival, hospitalization rates, and duration of hospitalization in a contemporary cohort of Canadian IHHD patients and kidney transplant recipients. We hypothesized that kidney transplant recipients would have superior patient and treatment survival compared with IHHD patients, but the rate of hospitalization would be more favorable for IHHD patients.

RESULTS

Primary Outcome

The cohort consisted of 173 IHHD patients, and 673 living donor (LD) recipients, 642 standard criteria donor (SCD) recipients, and 202 expanded criteria donor (ECD) recipients (Figure 1). Seventeen patients with unknown SCD/ECD status were reclassified as SCD recipients (15 of whom were transplanted between 2000 and 2003). Baseline characteristics of each patient group are shown in Table 1. There were observed differences in most demographic factors, dialysis vintage, and medical comorbidities. Overall, the burden of comorbidity was highest among ECD recipients, although IHHD patients had a higher prevalence of congestive heart failure and non-skin malignancy.

In the primary analysis, there were 285 events (time at risk of 8370.1 person-years). Kaplan–Meier survival curves for time-to-treatment failure or death (stratified by IHHD and kidney transplant recipient type) are shown in Figure 2. Compared with IHHD patients, the hazard ratio (HR) for

treatment failure or death associated with receipt of a LD kidney transplant was 0.45 (95% confidence interval [95% CI], 0.31 to 0.67; $P < 0.001$; Table 2). SCD and ECD patients also had a reduced risk of treatment failure/death compared with IHHD patients (SCD recipients: HR, 0.39 [95% CI, 0.26 to 0.59]; ECD recipients: HR, 0.42 [95% CI, 0.26 to 0.67]; Table 2).

Sensitivity Analyses

Baseline characteristics of the propensity score matched (PSM) cohorts are noted in Supplemental Tables 1 and 2. Results in the PSM cohort ($n = 226$) of deceased donor transplant recipients and IHHD patients were similar to the primary analysis (Table 2). However, in the PSM cohort comparing LD kidney transplant recipients to IHHD patients ($n = 306$), there was attenuation of the relative hazard (HR, 0.61 [95% CI, 0.38 to 0.99]; $P = 0.04$). Forty-two IHHD patients had contraindications to transplantation. Reasons for ineligibility for transplantation were malignancy ($n = 17$), cardiac (acute coronary syndrome within 6 months, $n = 4$; nonuremic severe irreversible congestive heart failure, $n = 2$), active autoimmune disease ($n = 6$), active infection ($n = 4$), recent stroke ($n = 1$), cardiac amyloid ($n = 1$), assessed by transplant and deemed ineligible due to burden of comorbidity ($n = 3$), and other reasons (e.g., aplastic anemia with recent stem cell transplant, new pulmonary embolism, recent lung transplant, or pregnancy; $n = 4$). After excluding these IHHD patients, the results of the reanalysis were comparable to the primary analysis. In the two PSM cohort analyses that excluded patients with a contraindication, a further attenuation in the HRs was observed along with greater imprecision in the point estimates (comparing deceased donor recipients with IHHD patients: HR, 0.55 [95% CI, 0.27 to 1.11], $P = 0.09$; comparing LD kidney transplant recipients with IHHD patients: HR, 0.64; 95% CI, 0.36 to 1.14; $P = 0.13$).

Secondary Outcomes

There were 1030 first hospitalizations among patients in the study cohort, (time at risk of 4027.6 person-years). Time to first hospitalization is shown in Figure 3. Adjusted hospitalization rates were higher for all kidney transplant recipients during the first month after discharge from initial admission compared with IHHD patients in the first month of treatment at home, with incidence rate ratios of 15.16 (95% CI, 4.83 to 47.62) for LD recipients, 18.77 (95% CI, 5.86 to 60.12) for SCD recipients, and 16.39 (95% CI, 4.91 to 54.74) for ECD recipients (Table 3). IHHD patients had reduced hospitalization rates for the first year of therapy compared with SCD recipients, and for first 3 months of therapy compared with LD and ECD recipients. After 1 year of follow-up, hospitalization rates were similar for IHHD versus SCD or ECD recipients, and lower for LD recipients compared with IHHD patients (IRR, 0.64 [95% CI, 0.47 to 0.87]). Similarly, early after treatment initiation, adjusted hospital length of stay was shorter for IHHD patients compared with all kidney transplant recipient

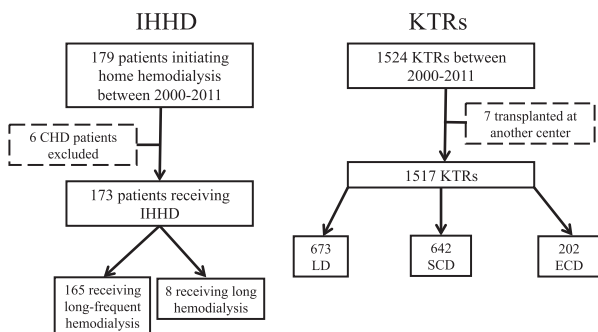


Figure 1. Derivation of study cohort. CHD, conventional in-center hemodialysis; KTR, kidney transplant recipient.

Table 1. Baseline characteristics of study cohort

Characteristic	IHHD (n=173)	LD (n=673)	SCD (n=642)	ECD (n=202)
Age (yr)	45±13	46±13	48±12	59±10
Caucasian	119 (69)	524 (78)	428 (67)	117 (58)
Men	107 (62)	394 (59)	410 (64)	138 (68)
Active smoker ^a	29 (17)	67 (10)	60 (9)	25 (12)
Dialysis vintage ^b	0.3 (0.2–1.7)	1.2 (0.2–2.6)	4.7 (3.0–6.7)	4.1 (3.1–5.9)
Dialysis vintage>3 mo	107 (62)	492 (73)	630 (98)	202 (100)
Cause of ESRD				
Diabetes	27 (16)	123 (18)	228 (36)	64 (32)
Polycystic kidney disease	17 (10)	95 (14)	62 (10)	21 (10)
Hypertension/ischemic	12 (7)	41 (6)	57 (9)	22 (11)
GN	66 (38)	253 (38)	181 (28)	69 (34)
Comorbidities ^c				
Coronary artery disease	20 (12)	93 (14)	141 (22)	61 (30)
Congestive heart failure	21 (12)	22 (3)	25 (4)	15 (7)
Diabetes	44 (25)	159 (24)	274 (43)	82 (41)
Cerebrovascular disease	10 (6)	18 (3)	35 (5)	14 (7)
Peripheral vascular disease	12 (7)	43 (6)	38 (6)	30 (15)
Non-skin cancer	26 (15)	29 (4)	22 (3)	7 (3)
Chronic lung disease	6 (3)	34 (5)	40 (6)	15 (7)

Data are presented as the mean±SD, n (%), or median (interquartile range).

^aData on smoking status were missing for 43 patients (coded as nonsmoker).

^bThere were 24 patients (1.4%) who had missing values imputed.

^cThere were 27 patients who were missing one or more comorbidities.

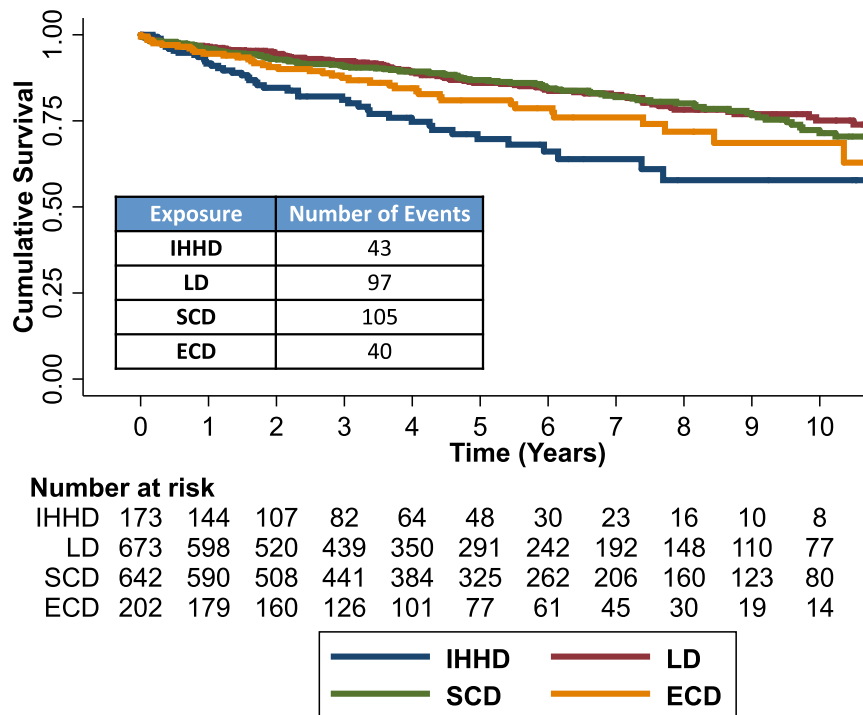


Figure 2. Time-to-treatment failure or death comparing IHHD patients and kidney transplant recipient subtypes (LD, SCD, and ECD recipients). Log-rank $P<0.001$.

subtypes. After the first year, the duration of hospitalization was shorter for LD, SCD, and ECD kidney transplant recipients (Table 3).

DISCUSSION

In this large single-center comparison of IHHD and kidney transplantation, we identified that LD, SCD, and ECD kidney transplant recipients had superior patient and treatment survival compared with IHHD patients. This advantage persisted after multivariable adjustment, propensity score matching, and exclusion of IHHD patients with a contraindication to transplantation. By contrast, treatment with IHHD was associated with a reduced early admission rate and duration of hospital stay compared with transplantation.

We hypothesize that the survival advantage for kidney transplant recipients over IHHD patients observed in our study is primarily due to the beneficial effects of transplantation. There are many factors that are associated with mortality in dialysis, including hyperphosphatemia,¹⁴ the long interdialytic break,¹⁵ left ventricular hypertrophy,¹⁶ and inadequate clearance of uremic toxins. Although these putative associations are potentially mitigated with IHHD,^{17,18} the same can be said about transplantation,¹⁹ which most closely approximates normal kidney function. Furthermore, transplantation has the added benefit of avoiding the mortality risk associated with vascular access²⁰ and dialysis treatment-related complications.²¹ Kidney transplant recipients face an increased risk of surgical complications, infections, and acute rejection, which may be reflected in an increased risk of early hospital readmission²² and length of stay. Accordingly, a lower early rate of hospital admission was observed for IHHD patients. By contrast, the higher admission rate (compared with LD recipients) and longer duration of hospitalization for IHHD patients (compared with all kidney transplant recipient subtypes) after 1 year may reflect late dialysis-related complications, such as the need for vascular access interventions,²³ or impending patient burnout on home therapy.

Our findings differ from previous comparisons of dialysis and kidney transplantation. Kjellstrand *et al.* found similar survival comparing a multicenter short daily hemodialysis cohort with US Renal Data System deceased donor transplant recipients.²⁴ However, this study did not explicitly attempt to adjust for multiple potential confounders. As

Table 2. Relative hazard for time-to-treatment failure or death comparing IHHD patients and kidney transplant recipients

Group	Patients (n)	Events (n)	Relative Hazard (95% CI)	P Value
Primary analysis	1690	285		
IHHD	173	43	1.00 (ref)	
LD	673	97	0.45 (0.31 to 0.67)	<0.001
SCD	642	105	0.39 (0.26 to 0.59)	<0.001
ECD	202	40	0.42 (0.26 to 0.67)	<0.001
Sensitivity analyses				
Adjusted analysis excluding patients with exposure to IHHD or transplant before follow-up start ^a	1400	236		
IHHD	116	31	1.00 (ref)	
LD	574	82	0.44 (0.28 to 0.68)	<0.001
SCD	523	87	0.39 (0.24 to 0.61)	<0.001
ECD	187	36	0.40 (0.23 to 0.67)	0.001
PSM cohort of IHHD patients and deceased donor KTRs	226	44		
IHHD	113	29	1.00 (ref)	
Deceased donor KTR	113	15	0.40 (0.21 to 0.74)	0.004
Adjusted for variables with standardized differences >10 ^b				
IHHD			1.00 (ref)	
Deceased donor KTR			0.40 (0.21 to 0.74)	0.004
PSM cohort of IHHD patients and LD KTRs	306	69		
IHHD	153	38	1.00 (ref)	
LD	153	31	0.61 (0.38 to 0.99)	0.04
Adjusted for variables with standardized differences >10 ^c				
IHHD			1.00 (ref)	
LD			0.65 (0.40 to 1.05)	0.08
Adjusted analysis excluding IHHD patients with a known contraindication to transplant ^a	1648	270		
IHHD	131	28	1.00 (ref)	
LD	673	97	0.51 (0.33 to 0.78)	0.002
SCD	642	105	0.43 (0.27 to 0.67)	<0.001
ECD	202	40	0.44 (0.26 to 0.74)	0.002
PSM cohort of IHHD patients and deceased donor recipients after exclusion of IHHD patients with a contraindication	174	32		
IHHD	87	19	1.00 (ref)	
Deceased donor KTR	87	13	0.55 (0.27 to 1.11)	0.09
PSM cohort of IHHD patients and LD recipients after exclusion of IHHD patients with a contraindication	254			
IHHD	127	27	1.00 (ref)	
LD	127	21	0.64 (0.36 to 1.14)	0.13

KTR, kidney transplant recipient.

^aAdjusted for age, sex, race, dialysis vintage, era of treatment initiation, cause of ESRD, active smoking status, diabetes, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic lung disease, and non-skin malignancy.

^bAdjusted for sex, dialysis vintage, peripheral vascular disease, and non-skin malignancy.

^cAdjusted for congestive heart failure.

mentioned, the only matched comparison examined United States kidney transplant recipients versus Canadian IHHD patients. Notably, 1-year and 5-year survival for IHHD patients in our cohort (94% and 80%, respectively) was comparable to the study by Pauly *et al.* (96% and 85%, respectively).¹² This underscores that the outcome difference comparing our two studies is likely based on a survival advantage for Canadian versus United States kidney transplant recipients.¹³ It should be acknowledged that there are a number of reasons why this survival advantage exists, including biologic/genetic differences between racial groups in Canada versus the United States, greater access to post-transplant care, and long-term coverage

for immunosuppressive medications in Canada.^{13,25,26} Finally, unlike prior comparisons of transplantation and dialysis, an early survival advantage for dialysis was not appreciated in our study.²⁷ It is likely that our study was underpowered to identify the presence of an early difference in patient/treatment survival. Therefore, a larger, national comparison of outcomes for kidney transplant recipients and IHHD patients would be informative.

This study reaffirms the need to encourage transplantation for potential candidates who are receiving IHHD. However, it is important to acknowledge that the outcomes of IHHD patients were still positive in this study. Patient survival for IHHD

patients was 94% and 80% at 1 year and 5 years, respectively. Patient survival for IHHD patients was further improved after excluding patients with a contraindication to transplantation (96% and 83% at 1 year and 5 years, respectively). In addition, hospitalization rates and length of hospital stay for IHHD

patients remained low even after 1 year of treatment. Therefore, although IHHD may not result in equivalent outcomes to transplantation, its potential role as the best form of bridging dialysis warrants further investigation.²⁸

It should be noted that there was no clear gradation of effect comparing LD, SCD, and ECD kidney transplant recipients to IHHD patients. Treatment/patient survival at 1 year and 5 years was similar for LD kidney transplant recipients and deceased donor kidney transplant recipients in this study (97% and 86% for LD kidney transplant recipients and 96% and 85% for deceased donor kidney transplant recipients, respectively). Although these survival proportions differ only slightly from 2006 national data²⁹ (98% and 88% for LD kidney transplant recipients and 93% and 82% for deceased donor kidney transplant recipients, respectively), there are center-specific variations in outcomes after transplantation within Canada.³⁰ Therefore, it is possible that the advantage of LD recipients was underestimated and that the advantage of SCD/ECD recipients was overestimated because of the case-mix of patients at this center. Specifically, transplantation of higher-risk LD kidney transplant recipients (including LD kidney transplant recipients that require desensitization for HLA and ABO mismatch) and more intensive monitoring of deceased donor kidney transplant recipients may partially explain the comparable outcomes. Alternatively, we acknowledge that a larger

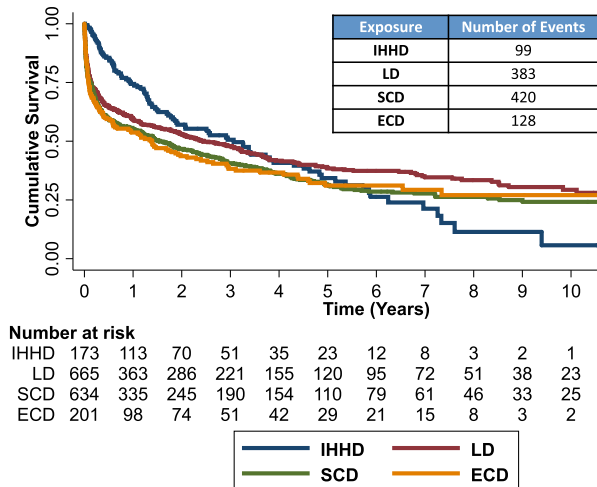


Figure 3. Time to first hospitalization comparing IHHD patients and kidney transplant recipient subtypes (LD, SCD, and ECD recipients). Log-rank $P=0.01$.

Table 3. Rate of admission, duration of admission, and IRRs comparing IHHD patients and kidney transplant recipient subtypes

Admission	<1 mo		1–3 mo		3–12 mo		>12 mo	
	n/yr	IRR (95% CI)	n/yr	IRR (95% CI)	n/yr	IRR (95% CI)	n/yr	IRR (95% CI)
Rate ^a								
Unadjusted								
IHHD	0.21	1.00 (ref)	0.38	1.00 (ref)	0.43	1.00 (ref)	0.35	1.00 (ref)
LD	2.95	15.10 (4.81 to 47.41)	1.28	4.04 (1.78 to 9.14)	0.58	1.39 (0.93 to 2.10)	0.20	0.57 (0.42 to 0.77)
SCD	3.58	19.02 (6.04 to 59.93)	1.68	5.94 (2.59 to 13.65)	0.84	2.27 (1.48 to 3.49)	0.31	0.96 (0.71 to 1.30)
ECD	3.35	18.03 (5.58 to 58.31)	2.03	6.76 (2.82 to 16.19)	0.66	1.76 (1.02 to 3.02)	0.29	0.89 (0.62 to 1.27)
Fully adjusted								
IHHD		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)
LD		15.16 (4.83 to 47.62)		5.31 (2.35 to 11.99)		1.45 (0.93 to 2.25)		0.64 (0.47 to 0.87)
SCD		18.77 (5.86 to 60.12)		7.29 (3.12 to 17.01)		2.07 (1.31 to 3.27)		0.96 (0.69 to 1.34)
ECD		16.39 (4.91 to 54.74)		7.87 (3.10 to 19.99)		1.53 (0.86 to 2.72)		0.80 (0.54 to 1.19)
Duration ^b								
Unadjusted								
IHHD	1	1.00 (ref)	2	1.00 (ref)	2	1.00 (ref)	3	1.00 (ref)
LD	19	18.16 (10.96 to 32.57)	9	4.30 (3.34 to 5.64)	5	2.11 (1.87 to 2.40)	1	0.23 (0.21 to 0.24)
SCD	26	25.42 (15.36 to 45.55)	15	6.78 (5.27 to 8.87)	8	3.59 (3.18 to 4.07)	2	0.47 (0.45 to 0.50)
ECD	31	29.98 (18.01 to 53.96)	17	7.83 (6.03 to 10.33)	7	2.85 (2.50 to 3.27)	1	0.33 (0.30 to 0.36)
Fully adjusted								
IHHD		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)
LD		27.33 (10.08 to 74.13)		6.89 (3.13 to 15.17)		1.86 (1.04 to 3.33)		0.30 (0.16 to 0.58)
SCD		30.43 (11.30 to 81.99)		11.11 (4.95 to 24.94)		2.55 (1.41 to 4.60)		0.51 (0.26 to 1.00)
ECD		32.47 (11.04 to 95.47)		12.33 (5.04 to 30.16)		1.92 (0.92 to 3.98)		0.21 (0.09 to 0.54)

Data are presented by different time periods after treatment initiation, and are adjusted for age, sex, race, dialysis vintage, era of treatment initiation, cause of ESRD, active smoking status, diabetes, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic lung disease, and non-skin malignancy.

^aRate of admission is standardized to number of admissions per year.

^bDuration of admission is standardized to number of days per year.

difference in effect between LD kidney transplant recipients and IHHD patients versus deceased donor kidney transplant recipients and IHHD patients may have been borne out with a larger sample size. However, it is unlikely that a larger sample size would have shifted the relative benefit toward IHHD compared with deceased donor kidney transplant recipients. Furthermore, we feel that the comparison of IHHD patients and kidney transplant recipients from the same tertiary care center is most appropriate because IHHD patients seeking a transplant would typically be referred to the center where they receive their dialysis care.

This study has a number of strengths. It is the first Canadian-only comparison of outcomes for IHHD patients and kidney transplant recipients, and the only study directly comparing hospitalization for these two patient groups. The University Health Network has one of the largest cohorts of IHHD patients worldwide, and is a large tertiary care referral center for kidney transplantation. Therefore, we are uniquely positioned to compare outcomes for IHHD patients and kidney transplant recipients. Access to detailed clinical databases and electronic records minimized missing data. Finally, the findings of the primary analysis were confirmed with detailed sensitivity analyses.

Despite its strengths, there are limitations to this study that deserve note. Although we were able to adjust for many confounding factors, there may have been unmeasured or unknown confounders that could have affected the results of this study. There may be practice patterns with respect to transplantation or IHHD at this center that are different from other centers. However, conducting this study in a large, tertiary care environment improved the consistency of patient data and physician decisions surrounding treatment. Furthermore, both therapies were readily accessible at this institute, a limitation in many other centers. We acknowledge that the sample size of our study is small. However, practice of IHHD is still relatively uncommon in many countries, and this is one of the largest cohorts of IHHD patients internationally. With respect to our outcomes, although differences in early hospitalizations were noted between groups, the nature and severity of those hospitalizations were not captured in this analysis.

In summary, our study shows that kidney transplantation is associated with superior treatment and patient survival compared with IHHD. By contrast, IHHD patients have a lower early hospitalization rate compared with kidney transplant recipients. Overall, this study emphasizes the relative benefit of kidney transplantation over IHHD. However, a future analysis in a larger, more generalizable Canadian cohort of IHHD patients and kidney transplant recipients should be conducted to confirm these results.

CONCISE METHODS

Study Population

We conducted a retrospective cohort study at a large tertiary health sciences center (the University Health Network, Toronto, ON, Canada) of all consecutive, adult patients who started IHHD or

received a kidney transplant from January 1, 2000, and December 31, 2011. Data pertaining to these patients were available in two local electronic databases. We selected a contemporary time frame to ensure data accuracy and availability of relevant demographic, comorbid, and outcome data. Outcomes were collected until July 1, 2012, to allow for at least 6 months of follow-up time. The IHHD cohort included all CKD patients who initiated their first RRT with IHHD, as well as patients who were transferred to IHHD after being on another form of RRT (in-center hemodialysis, peritoneal dialysis, conventional home hemodialysis, or failed kidney transplant before 2000). The kidney transplant cohort included all patients who received a deceased donor or LD kidney transplant during the study period. Approval for this study was received from the research ethics board at the University Health Network.

Exposure Assessment

IHHD was defined as an initial home hemodialysis prescription of ≥ 16 hours per week, and included those performing long hemodialysis (≥ 5.5 hours, three to four sessions per week) and long-frequent hemodialysis (≥ 5.5 hours, five to seven sessions per week).³¹ We selected this dosage as the cut-off, because conventional hemodialysis is typically defined as 3–5 hours per session for 3 days per week.³² Kidney transplant recipients were categorized as LD, SCD, or ECD recipients. The latter was defined based on existing criteria³³: (1) deceased donor age >60 years, or (2) deceased donor age between 50 and 59 years and the presence of at least two of three of the following: history of hypertension, terminal serum creatinine >1.5 mg/dl, or death from a cerebrovascular accident.

Deceased donor kidney transplant recipients with unknown ECD/SCD status were classified as SCD recipients. We made this assumption because the majority of missing ECD/SCD status occurred between 2000 and 2003, when the ECD classification was not well established or widely used in clinical practice.

Primary Outcome Assessment

The primary outcome of this study was time-to-treatment failure or death for IHHD patients compared with kidney transplant recipient subtypes (LD, ECD, and SCD kidney transplant recipients). Treatment failure or death was assessed from the first day of dialysis at home for IHHD patients, and the day of kidney transplantation for kidney transplant recipients. Treatment failure for IHHD patients was defined as a permanent change to peritoneal dialysis or in-center/self-care hemodialysis. Treatment failure for kidney transplant recipients was defined as a permanent change to any dialysis therapy. All patients were censored at last follow-up or at the end of study follow-up (July 1, 2012), whichever occurred first. IHHD patients who received a kidney transplant during follow-up were censored on the date of transplantation. Kidney transplant recipients did not re-enter the IHHD cohort after experiencing treatment (e.g., graft) failure, and IHHD patients who were censored did not re-enter the transplant cohort.

Secondary Outcomes

Prespecified secondary outcomes included hospitalization rate, hospital length of stay, and time to first hospitalization. The hospitalization

rate was calculated as the number of hospitalizations/time at risk, and was assessed within clinically important time periods during follow-up (<1 month, 1–3 months, 3–12 months, and >12 months after transplantation or initiation of IHHD). Hospitalization rates were standardized to number per year within each time period, and time at risk did not include the time in the hospital. Hospital length of stay was calculated as days in hospital/time at risk, and was examined in the same time periods as noted above. Acknowledging that kidney transplant recipients could not be hospitalized during the period of their initial admission for transplantation, hospitalization outcomes for kidney transplant recipients were evaluated from the discharge date of the initial admission for transplantation.

Baseline Characteristics

We collected baseline characteristics including patient age, sex, race, cause of ESRD, active smoking history, medical comorbidity, and pre-exposure dialysis vintage time. Dialysis vintage was calculated as the difference in years between the most recent exposure to any form of dialysis and initiation of IHHD or transplantation. The midpoint of the month of initiation of dialysis or midpoint of the year of initiation of dialysis was used if the exact date was unknown. Missing dialysis vintage times were imputed using the group-specific median values. Cause of ESRD and medical comorbidities were defined based on documentation in the chart and coded using standard International Classification of Diseases–Ninth Revision definitions. Comorbidities of interest included diabetes, coronary artery disease, congestive heart failure, cerebrovascular disease (stroke or transient ischemic attack), peripheral vascular disease, chronic lung disease, and non-skin (excluding melanoma) malignancy. Missing comorbidities were treated as nonexistent.

Statistical Analyses

Results were reported as the mean±SD for normally distributed continuous variables, median and interquartile range for non-normally distributed continuous variables, and counts or percentages for categorical variables. Baseline characteristics of kidney transplant recipients were stratified based on LD, ECD, or SCD status. The time-to-treatment failure or death was analyzed with the Kaplan–Meier product limit method. Survival functions for IHHD patients and LD, ECD, and SCD kidney transplant recipients were compared using the log-rank test. Adjusted HRs and 95% CIs were estimated from multivariable Cox proportional hazard models. The proportionality assumption was visually examined with log-log survival plots and Kaplan–Meier and predicted survival plots. Nonproportionality was addressed by examining survival during several different time periods after initiation of IHHD or transplantation (<1 month, 1–3 months, 3–12 months, and >12 months). Variables were selected *a priori* for inclusion in the adjusted models based on clinical judgment. These variables included age, sex, race, cause of ESRD, dialysis vintage, era of treatment (2000–2003, 2004–2007, and 2008–2011), diabetes, coronary artery disease, congestive heart failure, cerebrovascular disease, chronic lung disease, peripheral vascular disease, and non-skin malignancy (excluding melanoma).

Several prespecified sensitivity analyses were performed to examine the robustness of the main results. First, we performed an analysis excluding patients who received IHHD or were previously transplanted

before January 1, 2000. Second, two 1:1 PSM cohorts were created examining treatment selection to IHHD versus LD transplantation and IHHD versus deceased donor transplantation, using a caliper width of 0.1. Variables chosen for the propensity score were the same as the multivariable model. Differences in baseline characteristics of the PSM cohort(s) were examined using the absolute standardized difference before and after matching. Third, we conducted an analysis excluding IHHD patients who had an absolute contraindication to transplantation at the time of IHHD initiation (generally based on current Canadian guidelines³⁴). Finally, we analyzed two PSM cohorts (IHHD versus deceased donor transplantation and IHHD versus LD transplantation) after exclusion of IHHD patients with an absolute contraindication to transplantation.

Unadjusted incidence rates of hospital admission and days in the hospital were calculated at <1, 1–3, 3–12, and >12 months after exposure to either IHHD or transplantation. Incidence rate ratios were calculated from negative binomial regression models (to account for overdispersion) adjusting for those variables noted above. Finally, time to first hospitalization was analyzed with the Kaplan–Meier product limit method. All statistical analyses were performed using Stata IC software (version 12; StataCorp., College Station, TX). A two-sided *P* value<0.05 was considered statistically significant.

ACKNOWLEDGMENTS

These data were presented in abstract form at the 2013 American Society of Nephrology Annual Meeting, held November 5–10, 2013, in Atlanta, Georgia.

DISCLOSURES

None.

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This article contains supplemental material online at <http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2013111180/-/DCSupplemental>.