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Equal 3-Year Outcomes for Kidney Transplantation Alone in HCV-Positive Patients With Cirrhosis

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Kidney transplantation alone in clinically compensated patients with cirrhosis is not well documented. Current guidelines list cirrhosis as a contraindication for kidney transplantation alone. This is an Institutional Review Board–approved retrospective study. We report our experience with a retrospective comparison between transplants in hepatitis C virus–positive (HCV^+) patients without cirrhosis and HCV^+ patients with cirrhosis. All of the patients were followed for at least a full 3-year period. All of the deaths and graft losses were recorded and analyzed using Kaplan-Meier methodology. One- and three-year cumulative patient survival rates for noncirrhotic patients were 91% and 82%, respectively. For cirrhotic patients, one- and three-year cumulative patient survival rates were 100% and 83%, respectively ($P = NS$). One- and three-year cumulative graft survival rates censored for death were 94% and 81%, and 95% and 82% for the noncirrhosis and cirrhosis groups, respectively ($P = NS$). Comparable patient and allograft survival rates were observed when standard kidney allograft recipients were analyzed separately. This study is the longest follow-up document in the literature showing that HCV^+ clinically ompensated patients with cirrhosis may undergo kidney transplantation alone as a safe and viable practice.

Key words: Kidney – Transplantation – Cirrhotic patients – Safety

Hepatitis C virus (HCV) affects 200 million people.[1] Approximately 85% of people with HCV will develop chronic infection; of those, 10% to 30% will develop cirrhosis. The prevalence of HCV within the dialysis population is as high as 13%.[2] HCV is a negative prognostic indicator for survival

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on dialysis and after kidney transplantation. There is an increased risk of death among long-term hemodialysis patients infected with HCV.[3] Importantly, overall survival in these patients is improved after kidney transplantation compared with dialysis.[4] Liver biopsies are indicated in all HCV-positive candidates considered for kidney transplantation. Up to 12% of asymptomatic patients will have cirrhosis. Those with cirrhosis (while on dialysis) have a 35% higher death rate than their counterparts without cirrhosis.[5]

Established cirrhosis is an important predictor of death after renal transplantation and is considered a relative contraindication to isolated renal transplantation. American Association for Study of Liver Disease (AASLD) guidelines recommend end-stage renal disease patients with cirrhosis be evaluated for dual-organ transplantation. The core curriculum in nephrology and the Kidney Disease: Improving Global Outcomes (KDIGO) initiative consider HCV-related cirrhosis a contraindication to kidney transplantation alone (KTA).[6,7] Some authors consider cirrhosis a relative contraindication for KTA because the prospect of survival for graft and patient is dismal.[8]

The use of KTA in asymptomatic patients with cirrhosis has not been extensively studied. Reports often exclude patients with cirrhosis,[9] are limited by small numbers, or combine clinically compensated patients with cirrhosis with those who have only mild fibrosis.[10] The United Network for Organ Sharing (UNOS) database does not track biopsy results, so registry data cannot be mined.

We performed 18 KTAs on clinically compensated patients with cirrhosis (CCCs) and compared the results to those from a control group of HCV-positive KTA recipients without cirrhosis. We surmised that the results would be equivalent between groups.

Patients and Methods

We performed a retrospective Institutional Review Board–approved review including all deceased-donor HCV^+ kidney transplants from January 2001 to June 2010. All of the patients were followed for 3 years after they underwent kidney transplantation. Data were collected from a computerized database, paper and electronic charts, and UNOS.

A total of 147 HCV^+ kidney transplantations were performed. We excluded 8 combined liver and kidney transplantations (Fig. 1).

Histologic and radiologic assessment

A total of 74 of 139 transplantation patients had histologic assessment of the liver before kidney transplantation. Clear histologic evidence of architectural distortion was considered cirrhosis, consistent with both Batts-Ludwig and Metavir staging/grading systems.

Fifteen patients had cirrhosis. A total of 4 of these 15 patients also had radiologic confirmation of cirrhosis.

Of 139 transplantation patients, 65 lacked histologic assessment of their liver. Of these 65, 47 had imaging studies available. A total of 3 of these 47 demonstrated radiologic changes consistent with cirrhosis.

A total of 18 of 139 transplantation patients lacked the appropriate imaging studies and/or histologic staging of their liver disease, and were excluded.

Ultimately, we identified 18 transplantations performed in 18 HCV^+ patients with cirrhosis. These data were compared to 103 transplantations performed for 95 HCV^+ patients without cirrhosis. This is illustrated in Fig. 1. In total, the study cohort included 121 transplantations ($103 + 18$) for 113 patients ($95 + 18$).

Patient management protocols

All patients were HCV polymerase chain reaction positive. A history and physical examination was performed to delineate CCCs. These were patients without signs of liver failure, such as encephalopathy, ascites, or varices/upper gastrointestinal bleeding history. Patients were evaluated for interferon (IFN) treatment. Because of the difficulty of administering IFN to patients on dialysis and the contraindication against ribavirin in renal failure, very few candidates were actually treated. This information also could not be captured properly because many patients underwent transplantation in a different hospital from where they received their hepatologic care. Candidates underwent biopsies in 5-year intervals unless cirrhosis was present on previous biopsy or abdominal imaging. After 2009, if cirrhosis was present, portal pressures were evaluated. A portal pressure gradient greater than 10 mmHg was considered a contraindication for KTA.

Biopsies were not regularly performed on all patients at our institution throughout the study period, because hepatologists would not routinely

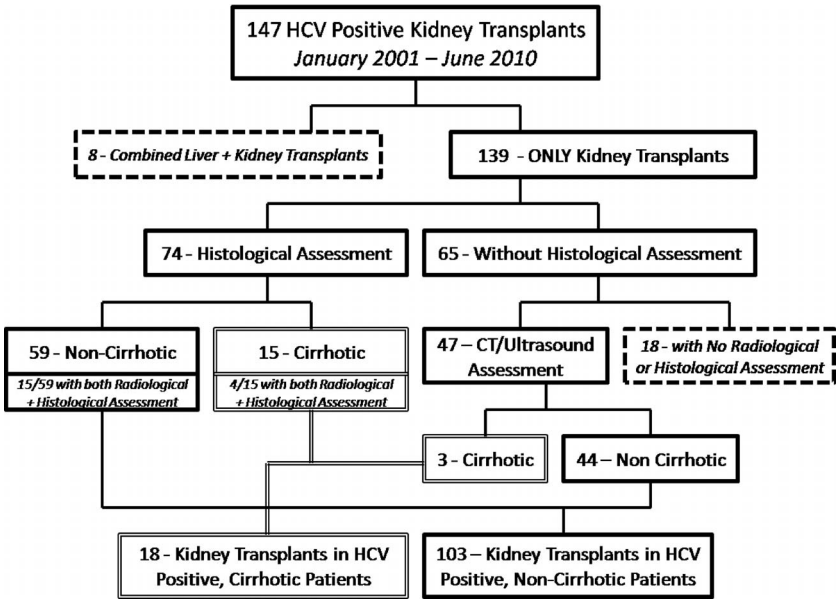

Fig. 1 Outline of patient selection and exclusion.

treat HCV in those patients with renal failure. In addition, kidney transplantation was regularly performed on HCV^+ patients regardless of cirrhosis status, as long as they were clinically compensated.

Induction therapy included antithymocyte globulin (Genzyme, Cambridge, Massachusetts) or interleukin-2 inhibitors. The goal dose of antithymocyte globulin ranged between 5 and 6 mg/kg. Maintenance immunosuppression included tacrolimus (Prograf, Astellas Pharma, Deerfield, Illinois) or cyclosporine. Tacrolimus target trough level was 5 to 12 ng/mL. Cyclosporine target trough level was 150 to 200 ng/mL.

All patients received mycophenolate mofetil (Genentech, Nutley, New Jersey), with doses ranging from 1 to 2 g/d and titrated for gastrointestinal side effects and leukopenia. Patients were administered methylprednisolone 400 to 500 mg IV intraoperatively followed by a prednisone taper to 20 mg by day 7. Our induction and maintenance immunosuppression did not deviate based on age, race, HCV status, cirrhosis, or donor type. Our protocols were standardized in an effort to provide optimum care. Additionally, because high rejection rates have been associated with HCV^+ recipients, we did not aggressively taper steroids.

Statistical analysis

We analyzed 121 HCV^+ transplantation patients: 103 patients without cirrhosis and 18 patients with cirrhosis. There were 8 patients who had 2 transplants within the study period. Because the characteristics of observations within a given sample should not predict the outcomes of the other observations, we removed the first transplant for all 8 of these patients from our analysis of patient presurgery variables and for patient survival outcomes. The sample also included 2 primary nonfunction (PNF) patients: 1 in the cirrhosis group and 1 in the noncirrhosis group (NCG). One PNF kidney was removed from patient survival analysis data because it was a first transplant out of two that were transplanted into the same patient during the same operation. This patient suffered an arterial dissection of his iliac artery. A bypass graft was performed to save the patient's leg. However, the kidney had suffered irreparable damage. Therefore, the second kidney (from the same donor) was implanted. We included both PNF kidney data in graft survival but removed both for comparisons of delayed graft function (DGF), rejections, and 12-month creatinine levels. Between the two groups we compared both presurgery variables and postsurgery outcomes. Quantitative data were tested for independence through a Student t test of means. Categoric variables were compared through a Pearson χ^2 test of independence. Where the criteria were not met for χ^2 tests we used a Fisher exact test of independence.

We measured outcomes with proportions tests and means tests as applicable. Means were com-

Table 1 Donor demographics

Variable	Noncirrhosis (n = 103)	Cirrhosis (n = 18)	*P* value
Age, y, mean (SD)	45.009 (1.195)	36.500 (2.982)	0.0073
Terminal creatinine level, mg/dL, mean (SD)	1.065 (0.436)	1.070 (0.747)	0.9724
BMI, kg/m^2, Mean (SD)	27.594 (0.710)	26.592 (1.904)	0.5938
Donor Type, No. (%)			0.055
ECD	18 (17.48)	0 (0)	
SCD	85 (82.52)	18 (100)	
Anti-HCV, No. (%)			0.655
Positives	74 (71.84)	12 (66.66)	
Negative	29 (28.16)	6 (33.33)	
Sex, No. (%)			0.866
Male	55 (53.98)	10 (55.56)	
Female	48 (46.60)	8 (44.44)	
Ethnicity, No. (%)			0.133
Black	19 (18.45)	5 (27.77)	
Hispanic	7 (6.79)	3 (16.66)	
White	77 (74.75)	10 (55.55)	
Cause of death, No. (%)			0.656
Anoxia	24 (23.30)	7 (25)	
Cerebrovascular/stroke	46 (44.66)	6 (21.43)	
Central nervous system tumor	1 (0.97)	0 (0)	
Head trauma	30 (29.12)	5 (17.85)	
Other	2 (1.94)	0 (0)	

pared using Student *t* tests. We extended the analysis of patient and graft survival through a Kaplan-Meier method and compared outcomes via a log-rank test.

The analysis was performed in Stata 11.2 and SPSS version 20 (StataCorp LP, College Station, TX).

Results

The donor and recipient demographics are in Tables 1 and 2, respectively. The total number of transplants analyzed was 121, as reflected in Table 1. However, because 8 patients received 2 transplants within the study period, the first transplant was removed from analysis of presurgery variables in Table 2 and patient survival outcomes in Table 3. This would alleviate analysis questions about characteristics of observations within a given sample predicting the outcomes of the other observations. Therefore, 95 recipients were in the NCG as mentioned at the bottom of Table 2 ($103 - 8 = 95$). In addition, 2 patients with PNF, although included for patient survival outcomes data in Table 2, were excluded from data analyzing DGF, 12-month creatinine, and graft survival, as seen in Table 3. Therefore, 102 ($103 - 1$) allografts were in the NCG and 17 ($18 - 1$) were in the CCC (as mentioned at the bottom of Table 3). Table 4 demonstrates the characteristics of the 18 patients with cirrhosis in detail. Among all tested variables, only mean donor age ($P = 0.0073$) and cancer rate for the cirrhosis group ($P = 0.002$) were significant, and the rest were nonsignificant. Both groups were followed for 3 years. We collected all of the deaths and graft losses during the long-term follow-up.

Patient demographics

The mean age was 55.801 (±0.916) years for the NCG versus 56.898 (±1.453) years for the CCC. The mean body mass index (BMI) was 27.051 (±0.514) kg/m^2 for the NCG versus 25.207 (±1.017) kg/m^2 for the CCC. Sex distribution was similar (16 of 18 [88.88%] for the NCG versus 73 of 96 [76.84%] for the CCC). African Americans comprised 74 of 96 patients (77.89%) in the NCG versus 14 of 18 patients (77.77%) in the CCC. There were no statistically significant differences for any demographic variables between the two groups.

Laboratory data for the patients with cirrhosis

Platelet and albumin levels for the CCC are listed in Table 5. Of the 18 patients, 2 lacked the time-

Table 2 Recipient demographics

Variable	Group 1, noncirrhosis (n = 95[a])	Group 2, cirrhosis (n = 18)	*P* value
Age, y, mean (SD)	55.801 (0.916)	56.898 (1.453)	0.6194
BMI, kg/m^2, mean (SD)	27.051 (0.514)	25.207 (1.017)	0.5049
Days waited, mean (SD)	567.358 (67.735)	613.444 (136.245)	0.7826
Sex, No. (%)			0.353
Male	73 (76.84)	16 (88.88)	
Female	22 (21.36)	2 (11.11)	
Recipient ethnicity, No. (%)			0.799
Asian	3 (3.16)	0 (0)	
Black	74 (77.89)	14 (77.77)	
Hispanic	2 (2.1)	1 (5.55)	
Multiracial	1 (1.05)	0 (0)	
White	15 (15.78)	3 (16.66)	
Peak panel reactive antibody, No. (%)			0.218
<20	78 (82.98)	16 (88.88)	
20–80	11 (11.70)	0 (0)	
>80	5 (5.32)	2 (11.11)	
Cause of death, No. (%)	31 (100)	7 (100)	0.001
Infection	9 (29.03)	0	0.164
Malignancy	5 (16.12)	3 (42.85)	0.146
Cardiovascular	7 (22.58)	0	0.309
Liver failure	3 (9.67)	1 (14.28)	1.000
Uremia	0 (0)	3 (42.85)	0.004
Unknown	5 (16.12)	0	0.561
Other	2 (6.45)	0	1.000
Cause of graft loss, No. (%)[b]	34 (100)	4 (100)	0.320
Rejection	24 (70.58)	3 (75)	1.000
Infection	3 (8.82)	0 (0)	1.000
PNF	1 (2.94)	1 (25)	0.202
Other	6 (17.64)	0 (0)	1.000
Cancer, No. (%)	95 (100)	18 (100)	0.002
No	90 (94.73)	12 (66.66)	
Yes	5 (5.26)	6 (33.33)	

[a]As mentioned in detail in the methodology, 103 − 8 = 95.

[b]The numbers provided for graft loss are death censored.

appropriate albumin level. The average pretransplantation albumin level for the remaining 16 CCCs was 3.55 (±0.57) mg/dL. The average platelet count at transplantation was 154.72 (±87.18) per microliter. A total of 15 patients had a MELD score of 20, 1 patient had a MELD score of 21, 1 had a MELD score of 22, and 1 had a MELD score of 25. All 18 patients met Child A classification criteria.

Donor demographics

Mean age of donors of the NCG was 45 (±1.195) years, and 36.5 (±2.98) years in the CCC (significant, $P = 0.0073$). Mean donor BMI was similar (27.59 versus 26.59 kg/m^2 for NCG and CCC, respectively; P = not significant [NS]). Donors were mostly male in the NCG (55 of 103 [53.98%]) and the CCC (10 of 18 [55.56%]; P = NS). African Americans comprised 18.45% (19 of 103) of the donors in the NCG versus 27.77% (5 of 18) for the CCC (P = NS). The mean terminal creatinine level was 1.065 mg/dL in the NCG and 1.070 mg/dL in the CCC (P = NS). A total of 74 of 103 donors (71.84%) were HCV$^+$ in the NCG and 66.66% (12 of 18) in the CCC (P = NS).

Comparison of liver decomposition as a cause of death in the entire follow-up period

There were a total of 38 deaths in the NCG over the entire follow-up period. A total of 3 of 31 (9.67%) were due to liver failure. A total of 1 of 7 deaths (14.28%) in the CCC was due to liver failure (P = NS).

Table 3 Outcomes

Variable	Group 1, noncirrhosis (n = 102)[a]	Group 2, cirrhosis (n = 17)[a]	*P* value
12-month creatinine level, mg/dL, mean (SD) [n]	1.55 (0.098) [91]	1.92 (0.126) [15]	0.1374
Follow-up days, mean (SD)	1186.588 (77.735)	966.4706 (210.045)	0.2937
DGF, No. (%)	39 (38.23)	6 (35.29)	0.817
1-year rejections, No. (%)	19 (18.63)	4 (23.53)	0.619
1-year patient survival, No. (%)	95 (100)	18 (100)	0.149
Alive	86 (90.52)	18 (100)	
1-year graft survival, No. (%)	103 (100)	18 (100)	0.837
Functioning	90 (87.38)	15 (88.33)	
Failed	13 (12.62)	3 (16.67)	
Malignancy	5 (7.76)	6 (35.29)	002

[a]As mentioned in the methodology, 1 PNF was removed for each group. Therefore, 18 − 1 = 17 and 103 − 1 = 102.

Comparison of infection as a cause of death and graft loss in the entire follow-up period

In the NCG, 9 of 31 deaths (20.03%) and 3 of 34 graft losses (8.82%) were from infection; there were zero graft losses and deaths from infection in the CCC. The difference was not statistically significant.

Adherence

Nonadherent behavior leading to graft loss or death was seen in 11.6% (12 of 103) of the NCG and 16.6% (3 of 18) of transplantation CCC.

There was no statistically significant difference.

Acute rejection at 1 year

In the NCG, 19 of 102 patients (18.63%) developed acute rejection. In the CCC, 4 of 17 patients (23.53%) developed acute rejection. The difference was not statistically significant.

Delayed graft function

In the NCG, 39 of 102 patients (38.23%) had DGF. In the CCC, 6 of 17 patients (35.29%) experienced DGF ($P = \text{NS}$).

Malignancy in the entire follow-up period

In the NCG, 5 of 95 patients (5.26%) had malignancies. Of these, 1 was hepatocellular carcinoma (HCC) and the other 4 were renal cell carcinoma, lung cancer, prostate cancer, and squamous cell carcinoma.

In the CCC, 6 of 18 patients (33.33%) developed cancer within the follow-up period. Of these, 3 were HCC, 1 was cholangiocarcinoma, and the other 2 were oral and skin cancers. Cancer was more prevalent in the CCC ($P = 0.002$).

A total of 3 of 6 patients with malignancies had undergone a previous transplantation. One patient had undergone a previous orthotopic liver transplantation (OLT) and two patients had received a previous deceased-donor kidney transplant.

KTA after previous liver transplantation

Six patients underwent KTA after a previous OLT. Five were alive with functioning allografts at 1 year. Two patients underwent KTA with biopsy-proven cirrhosis in their liver allografts. Both patients and all allografts were alive and functioning at 1 year. One patient later died of liver decompensation with a functioning kidney. The other died of a malignancy 5 years after KTA. His allograft was functioning.

Of the 4 patients who underwent KTA after OLT in the NCG, 1 died with a functioning allograft at 5 months and 1 lost allograft function at 5 years and died in the sixth year. The remaining 2 patients are alive with functioning allografts 2 and 4 years after KTA, respectively.

Repeat kidney transplantation

A total of 18 transplantations were repeat kidney transplantations: 15 patients in the NCG and 3 in the CCC. Of the 3 patients who underwent retransplantation in the cirrhosis group, all are alive with functioning kidneys. Of these 3 patients, 2 have subsequently developed HCC.

Fibrosing cholestatic hepatitis

No patient in either group suffered from fibrosing cholestatic hepatitis.

Portal pressure

Portal pressure measurement was done for 5 of 18 patients with cirrhosis. Median portal pressure was 3 mmHg, and it ranged from 0 to 8 mmHg.

Table 4 Characteristics of the 18 patients with cirrhosis

Number	DGF	PNF	Rejection	Creatinine level at 1 y, mg/dL	Retransplantation	Cancer	Death	Functional allograft	Graft loss	Cause of death	Cause of graft failure
1	N	N	N	1.1	N	N		Y	N		
2	Y	Y	N	PNF	N	N	Y	N	Y	Nonadherent (uremia)	PNF
3	Y	N	Y	GL	N	N		N	Y		Rejection
4	N	N	N	1.6	N	Cholangiocarcinoma	Y	Y	N	Cholangiocarcinoma	
5	N	N	N	2.6	Y	N	Y	Y	N	Liver decompensation	
6	Y	N	N	2.2	N	Tongue cancer	Y	Y	N	Tongue cancer and infection	
7	N	N	N	1.8	N	N		Y	N		Chronic allograft dysfunction
8	N	N	N	1.5	N	N	Y	N	Y	Uremia	Noncompliance and rejection
9	Y	N	N	1.2	N	N		Y	N		
10	N	N	Y	0.8	N	N		Y	N		
11	Y	N	Y	GL	N	N	Y	N	Y	Uremia	Nonadherence and rejection
12	N	N	N	1.4	Y	HCC	Y	Y	N	Unknown	
13	Y	N	N	1.4	N	N	Y	Y	N	Unknown	
14	N	N	N	1	N	N		Y	N		
15	N	N	N	1.6	Y	N		Y	N		
16	N	N	Y	1.8	N	HCC		Y	N		
17	N	N	N	1.14	Y	HCC		Y	N		
18	Y	N	N	2.1	Y	Skin, squamous cell carcinoma	Y	Y	N	Invasive hidradenocarcinoma	

GL, Graft loss.

Table 5 Recipient demographics (lab data)

Number	Age, y	Sex	LOS, d	Waiting time, d	Ethnicity	BMI, kg/m^2	PRA	MELD	INR	Total bilirubin	Plt	Alb
1	46.8	M	5	1383	White	21.5226	3	20	0.3	1.1	141	Not available
2	48.6	M	5	1175	Black	28.9837	3	21	0.5	1.4	252	Not available
3	63.2	M	36	181	Black	30.1256	0	20	0.4	0.9	133	3.9
4	54.4	M	8	43	Black	29.5347	0	20	0.4	1.0	258	5.1
5	57.7	M	4	194	White	26.66	0	22	0.7	1.9	98	3.1
6	66.9	M	8	815	Black	35.8709	0	20	0.6	1.2	67	2.8
7	52.6	M	9	348	Black	23.96	0	20	0.7	1.0	385	3.2
8	56.6	M	10	158	Black	21.6136	0	20	0.5	0.9	252	3.8
9	50.2	M	11	336	Hispanic	29.8595	0	25	1.5	1.1	123	3.6
10	55.4	F	5	704	Black	28.86	0	20	0.39	1.1	183	3.9
11	58.6	M	11	529	Black	30.7369	0	20	0.6	1.0	158	3.2
12	67.8	M	7	489	Black	20.671	0	20	0.26	1.1	59	3.2
13	61.8	M	15	452	Black	22.3981	0	20	0.3	1.0	87	3.5
14	55.6	F	5	292	Black	23.2284	0	20	0.8	1.1	139	3.1
15	61.8	M	6	1422	Black	29.12	100	20	0.7	1.0	194	4
16	49.4	M	6	122	Black	21.2637	0	20	0.7	1.2	77	2.9
17	54.4	M	8	2186	Black	23.6276	98	20	0.4	1.1	50	3.6
18	62.4	M	9	213	White	23.68	0	20	0.77	1.0	129	4
Mean	56.90	N/A	9.33	613.44	N/A	26.21	11.33	20.4	0.58	1.12	154.72	3.55
SD	6.17	N/A	7.22	578.04	N/A	4.32	31.91	1.24	0.28	0.22	87.18	0.57
Median	56.10	N/A	8.00	400.00	N/A	25.31	0	20	0.55	1.1	136	3.55
Max	67.80	N/A	36.00	2186.00	N/A	35.87	100	25	1.5	1.9	38	5.1
Min	46.80	N/A	4.00	43.00	N/A	20.67	0	20	0.26	0.9	50	2.8

Alb, albumin mg/dl bilirubin mg/dl; INR, international normalized ratio; LOS, length of stay; N/A, not applicable; Plt, platelet ×1000; PRA, panel reactive antibody.

Summary of statistical analysis of donor and recipient demographics

We compared wait time, age, recipient BMI, recipient race, recipient sex, and peak panel reactive antibody (peak panel reactive antibody grouped into <20, 20 to 80, and >80) and found no significant differences.

Donor BMI, donor terminal creatinine level, donor HCV$^+$, donor cause of death, and donor race showed no significant differences. Analyses showed that the donor age of the CCC was significantly lower than that of the NCG (36.5 versus 45 years; $P = 0.007$). There was a larger proportion of standard criteria donor (SCD) kidneys within the cirrhosis group ($P = 0.073$). All donors for the CCC were SCD. Eighteen donors in the NCG were expanded criteria donors. Of the 85 remaining SCDs, 1 was also a donation after cardiac death.

Summary of outcomes analysis

Our outcomes are consistent with the hypothesis that both groups perform similarly. Twelve-month creatinine levels among functioning allografts were lower among the patients with cirrhosis but fell short of significance (1.55 versus 1.92; $P =$ NS). The same situation was observed with 36-month creatinine levels compared between the two groups (2.03 versus 2.16; $P =$ NS). These outcomes were then also assessed among only SCD kidneys, and the same results were found.

The 1- and 3-year cumulative patient survival rates were 91% and 82%, and 100% and 83%, for the noncirrhosis and cirrhosis groups, respectively ($P =$ NS). The 1- and 3-year cumulative graft survival rates censored for death were 94% and 81%, and 95% and 82% for the noncirrhosis and cirrhosis groups, respectively ($P =$ NS). Figs. 2 to 5 show the 1- and 3-year patient and graft survival curves. The median survival time for patients with cirrhosis was 50 months. For additional evidence, we compared only patients with SCD kidneys. The 1- and 3-year patient survival rates were 91% and 84%, and 100% and 84% for the noncirrhosis and cirrhosis groups, respectively ($P =$ NS). Figs. 6 and 7 show the 1-year patient and graft survival rates for the patients with SCD kidneys.

The one- and three-year death-censored graft survival rates were 95% and 81% for noncirrhotic patients, respectively. For cirrhotic patients, the one- and three-year death-censored graft survival rates were 94% and 74%, respectively.

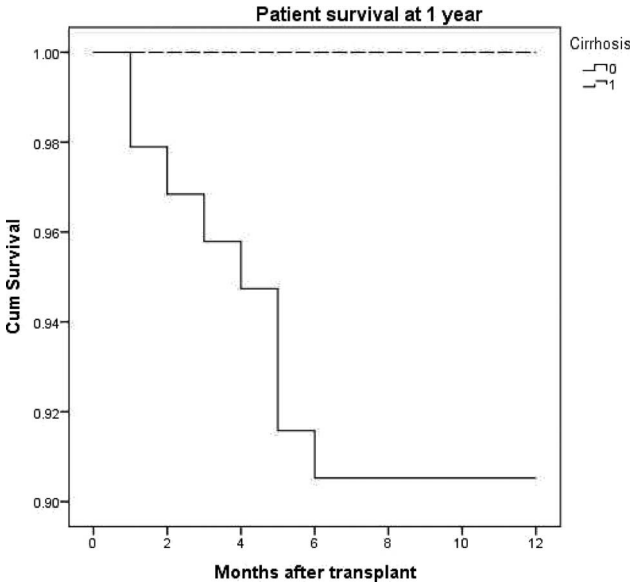

Fig. 2 Patient survival at 1 year.

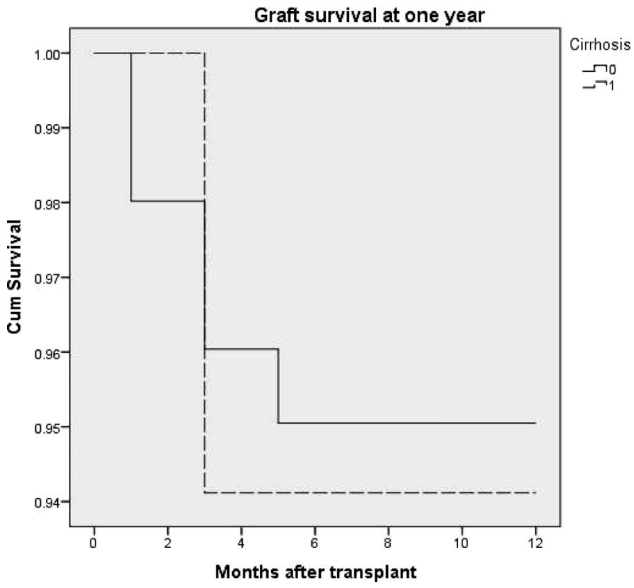

Fig. 4 Graft survival at 1 year.

Discussion

Multiple studies have demonstrated diminished outcomes in patients with cirrhosis undergoing abdominal surgery, thoracotomy, open-heart surgery, and orthopedic surgery.[11–15] The life expectancy of patients with cirrhosis is 40% of that of the general population.[16] The standardized mortality ratio for patients with cirrhosis for all causes of death combined is increased by 12-fold, with a relative 1-year survival rate of 67%. There is a 5- to 22-fold increased risk of dying from infectious diseases.[17] Patients with cirrhosis (while on dialysis) have a 35% higher death rate than their noncirrhosis counterparts.[5]

The median survival time of cirrhotics with a MELD score of 20 or less is 11 months.[18]

The National Kidney Foundation and the AASLD consider cirrhosis a relative contraindication to KTA. It has been suggested that HCV-infected patients with cirrhosis but clinically compensated

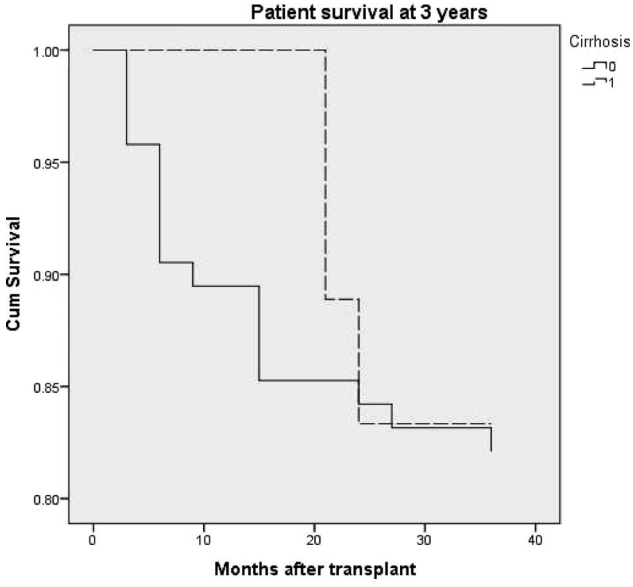

Fig. 3 Patient survival at 3 years.

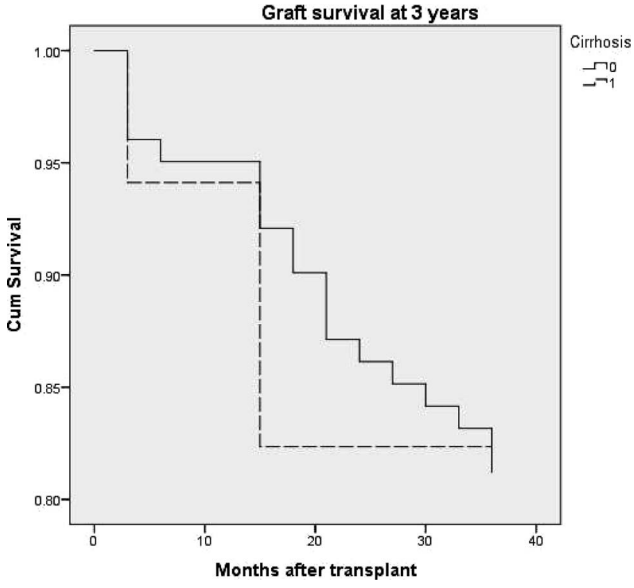

Fig. 5 Graft survival at 3 years.

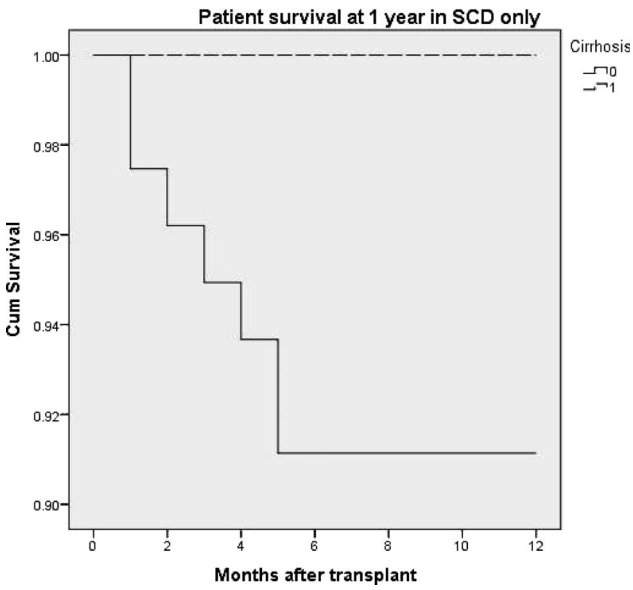

Fig. 6 Patient survival at 1 year in SCD only.

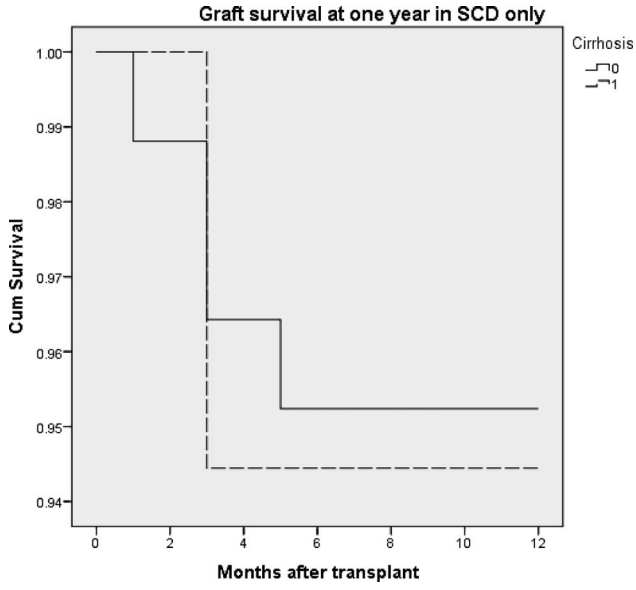

Fig. 7 Graft survival at 1 year in SCD only.

liver disease be considered for kidney transplantation only in an investigational setting.[7] There are minimal data or there is minimal literature to support this.[10,19] Some authors recommend KTA for selected patients with early-stage cirrhosis.[20]

In many large reports of HCV^+ recipients, the liver is not histologically monitored or patients with cirrhosis are excluded outright.[9,21] Current recommendations to evaluate for combined kidney-liver transplantations in CCCs may not be the most appropriate allocation of resources.[6,7] In addition, the benefits of combined (prophylactic) liver and kidney transplantation in CCCs would have to be weighed against the added risk of performing OLT.[22]

A total of 19% of physicians surveyed would perform a KTA on an asymptomatic patient with cirrhosis.[2] Arango *et al*[23] performed KTA on 5 patients with cirrhosis. Of these, 2 were alive at the time of publication and the other 3 died 3, 9, and 10 years later. Paramesh *et al*[24] studied 37 HCV^+ patients who underwent KTA. Their cohort was composed of 9 patients with cirrhosis and 28 patients without cirrhosis. Hepatic portal venous gradient was less than 10 mmHg for all patients. They demonstrated equivalent 1- and 3-year patient and graft survival rates. In their study the negative prognosticators included recipient age and albumin level.[24] They concluded that KTA may be safe in patients with HCV^+ compensated cirrhosis. Their average follow-up was 32 months.

Our larger experience with KTA (a total of 121 KTAs and 18 CCCs) with at least a full 3-year follow-up for all patients confirms this. The 12- and 36-month creatinine levels, incidence of DGF, rejection, and patient and graft survival rates did not differ between patients with cirrhosis and HCV^+ patients without cirrhosis. According to one study, patients with MELD scores lower than 20 had a median survival time of 11 months.[18] We observed a median survival time of 50 months for the cirrhosis group. In fact, all of those patients were alive over a 12-month postoperative period. They had a median MELD score of 20.

Many investigators have found that the increased mortality in KTA for HCV^+ patients appears to be closely related to infectious complications.[9,17,19,25] One study reported a 5- to 22-fold increased risk of dying of infectious diseases.[17] In our experience, the presence of cirrhosis did not lead to an increased likelihood of death or graft loss secondary to infection compared with our HCV^+ controls without cirrhosis (Table 2).

A high proportion of our study patients had cancer, a known risk for organ transplant recipients. Recent evidence suggests that in the next two decades, cancer will surpass cardiovascular disease as the most common cause of death.[26] In one study, the standardized incidence ratio was 2.0.[27] One of the most common cancers showing excess risk (in all solid organ transplant recipients) was liver cancer.[27] The incidence of HCC in individuals with chronic hepatitis is as high as 0.46% per year. The annual

risk of developing HCC in patients with cirrhosis is 1% to 6%.[28] The 5-year cumulative risk of developing HCC in patients with both HCV and cirrhosis is 17%.[11] The combination of a potentially oncogenic virus, cirrhosis, and immunosuppression exposes these patients to significant oncologic risk. In our cirrhosis cohort, 3 of the 6 patients who contracted cancer had undergone transplantation before, thereby increasing their risk because of the increased immunosuppression exposure. Of the 3 patients who developed HCC after KTA, all were listed for OLT. One died while waiting in his seventies with a functioning allograft. Two underwent liver transplantation with functioning renal allografts. It is doubtful that prophylactic liver transplantation for 18 recipients could be justified, because 3 of the cohort subsequently developed HCC. Instead, close surveillance with "salvage" liver transplantation appears to be the more prudent course. It is important to note that in many regions of the country, combined liver and kidney transplantation with a MELD score in the low twenties is simply not realistic. Additionally, if it had been decided to delay transplantation until the development of HCC, many patients in our cohort would have missed out on the potential benefits of a functioning kidney allograft while they gambled on remaining suitable candidates for combined transplantation in the future.

It has been established that liver transplant recipients who experience renal failure due to calcineurin inhibitor toxicity and/or other causes have diminished survival that is improved by KTA.[25] About 40 to 50 of these transplantations are performed annually.[29] Gonwa *et al*[30] reported that patients who suffered from renal failure after liver transplantation had a 6-year survival rate of 27% if they remained on dialysis. For those who received KTA, their 6-year survival rate was 71.4%. It is unknown how many of these patients also suffered from biopsy-proven allograft cirrhosis.

In our experience with 6 patients, 5 were alive with functioning allografts at 1 year. Two patients underwent KTA with biopsy-proven cirrhosis in their liver allograft. Both patients and all allografts were alive and functioning at 1 year. One patient later died from liver decompensation with a functioning kidney. The other died from a malignancy 5 years after KTA. His allograft was functioning. Of the 4 patients who underwent KTA after OLT in the noncirrhosis comparison group, 1 died with a functioning allograft at 5 months, and 1 lost allograft function at 5 years and died in the sixth year. The remaining 2 patients are alive with functioning allografts 2 and 4 years after KTA, respectively. These numbers are too small to address with any statistical relevance. However, the 1-year results appear to be acceptable.

Donor age in the cirrhosis group was significantly lower, and all donors for the cirrhosis group were SCD. Statistical analysis did not reveal that our outcomes were solely based on the use of SCD.

The use of kidneys from HCV^+ donors is associated with worse outcomes than those from HCV^- donors. Kucirka *et al*[31] reported that HCV^+ donor kidneys are 2.5 times more likely to be discarded. However, receiving an HCV^+ donor kidney is associated with improved survival compared with remaining on dialysis.[31–33] The use of HCV^+ donor kidneys is associated with a more than 12-month shorter wait time on dialysis. This shorter wait time may be associated with a 10% to 15% lower rate of death.

In neither of our study groups did we find HCV^+ donor status to be a negative prognosticator for patient or allograft survival. We believe that the aggressive use of HCV^+ donors is appropriate.

Weaknesses of this paper include its retrospective nature and relatively small patient numbers (although it is the largest study ever conducted). We note that cirrhosis was not determined entirely by biopsy, and in some instances was determined entirely radiologically. There is a possibility that abdominal images and biopsies were overread or underread by the radiologists and pathologists. Percutaneous liver biopsy only represents approximately 1/50,000 of the entire liver and may underestimate the degree of fibrosis. There is a false-negative rate of 25% to 30%, along with a discordance rate of nearly 50% on repeated liver biopsy specimens.[34–36] Imaging modalities are exceptionally sensitive and specific for cirrhosis, demonstrating statistical significance in distinguishing between chronic hepatitis and cirrhosis for specific imaging parameters on computed tomography, magnetic resonance imaging, and ultrasound.[35,36] These imaging modalities are specific enough to confirm cirrhosis. In the 19 patients with both imaging and histology, findings were consistent throughout, with no discrepancies identified.

Given the lack of histologic samples from all patients in our cohort, we could not stratify any data by fibrosis staging. Instead, the cohort was stratified by a more definitive means, the presence or absence of cirrhosis.

We did not routinely measure portal gradients.[37,38] Measuring portal pressures is a relatively new practice. Instead, consistent with the practice of this cohort's timeline, compensated hepatic function was determined clinically by the lack of encephalopathy, ascites, varices/upper gastrointestinal bleeding history.

We did not track the viral genotypes in the recipients or in the HCV^+ donors. Genotypes have not been shown to have a prognostic impact in kidney transplantation or renal failure patients. It is a marker of IFN susceptibility, not overall prognosis in the untreated patient. There are no recommendations in the current literature to limit HCV^+ donation to genotype 1 patients.[39] We also could not determine whether patients were treated with IFN before transplantation and what their responses were.

Conclusion

Current recommendations to evaluate for combined kidney-liver transplants in HCV^+ patients with cirrhosis may not be appropriate. We have demonstrated that HCV^+ CCCs with KTA share survival and graft survival rates comparable with their HCV^+ counterparts without cirrhosis, without higher rates of acute rejection or delayed graft function. However, we did note a high rate of malignancy. In order to prevent malignancy we may have to consider avoiding polyclonal antibody induction. The role of active surveillance is important as well. There are no data to support the contention that CCCs should wait on dialysis until they decompensate or develop HCC. Although the numbers of patients we present are small, this study represents the largest documented experience to date with a robust control group and 3-year follow-up with standardized induction and maintenance immunosuppression. At this point we recommend that KTA be considered in CCCs who have no signs or history of ascites, encephalopathy, upper gastrointestinal bleeding, thrombocytopenia, hypoalbuminemia, or HCC. These patients should have a MELD score no higher than 22 and a Child classification no higher than A. Additionally portal pressure measurements should be performed per established guidelines. A pressure gradient higher than 10 mmHg should warrant consideration for dual organ transplantation. Nevertheless, larger multicenter studies with longer follow-up will be necessary.

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