Effect of Renal Diagnosis on Survival in Simultaneous Liver-Kidney Transplantation

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BACKGROUND: Simultaneous liver-kidney transplantation is lifesaving, however, the utility of allocating 2 organs to a single recipient remains controversial, particularly in the face of potentially inferior survival. This study aims to determine the effect of renal indication for transplantation on simultaneous liver-kidney transplantation outcomes.

METHODS: All adult recipients of combined whole liver-kidney transplants in the United Network for Organ Sharing database from 2003 to 2016 with a renal diagnosis of hypertension (HTN), diabetes mellitus (DM), acute tubular necrosis (ATN), or hepatorenal syndrome (HRS) were examined. Comparisons were made between the HTN/DM group and the ATN/HRS group using standard statistical methods.

RESULTS: There were 1,204 patients in the HRS/ATN group vs 1,272 patients in the HTN/DM group. The HTN/DM patients were slightly older (58.1 vs 56.4 years; $p < 0.001$), more likely to have liver disease due to chronic viral hepatitis (33.2% vs 21.5%; $p < 0.001$), and less acutely ill (mean Model for End-Stage Liver Disease score of 27.2 vs 33.1; $p < 0.001$) than their HRS/ATN counterparts. The prevalence of nonalcoholic steatohepatitis was 16.8% in both groups. Donor demographics were similar in both groups, although HTN/DM patients were more likely to have a local (81.6% vs 67.7%; $p < 0.001$) rather than regional donor. Patient survival rates at 1, 3, and 5 years were significantly lower in the HTN/DM group (87.4%, 78.2%, and 71.2% vs 90.7%, 84.1%, and 76.6%, respectively). Median survival was 118 months for the HTN/DM group vs 139.7 months for the HRS/ATN ($p < 0.001$). The HTN/DM patients were at significantly higher risk of death (hazard ratio 1.533; $p < 0.001$), liver graft loss (hazard ratio 1.611; $p < 0.001$), and renal graft loss (hazard ratio 1.592; $p < 0.001$) than ATN/HRS patients on multivariable analysis.

CONCLUSIONS: Despite a lower acuity of illness, HTN/DM patients have inferior survival after simultaneous liver-kidney transplantation than those with ATN/HRS. This should be considered in risk adjustment and allocation schemes. (J Am Coll Surg 2019;228:536−546. © 2018 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Disclosure Information: Nothing to disclose.

Support: This work was supported in part by Health Resources and Services Administration contract 234-2005-370011C.

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Presented at the Southern Surgical Association 130th Annual Meeting, Palm Beach, FL, December 2018.

Received December 6, 2018; Accepted December 10, 2018.

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The introduction of the Model for End-Stage Liver Disease (MELD) score as the basis for liver allocation has resulted in a drastic increase in the number of simultaneous liver-kidney transplantations (SLKs) performed annually.[1-4] The survival benefit of SLK compared with liver transplantation alone in patients with combined hepatic and renal failure is supported by numerous studies in the literature.[2,5-7] This benefit is particularly pronounced in patients on dialysis for more than a brief period before transplantation.[8] This benefit does not occur in a vacuum, however. Each kidney allocated to SLK represents an organ removed from the pool available to the kidney transplant waiting list. In addition, there have been concerns that SLK might represent an ineffective or even futile use of a renal allograft if allocated to the wrong recipient.[8-11]

https://doi.org/10.1016/j.jamcollsurg.2018.12.003
ISSN 1072-7515/18

Abbreviations and Acronyms

ATN = acute tubular necrosis
DM = diabetes mellitus
ESRD = end-stage renal disease
HR = hazard ratio
HRS = hepatorenal syndrome
HTN = hypertension
MELD = Model for End-Stage Liver Disease
SLK = simultaneous liver-kidney transplantation

Given these concerns, it is imperative that appropriate selection criteria for SLK be developed that optimally balance benefit to the patient in need of SLK, and making the most effective use of a scarce resource. The recently implemented United Network for Organ Sharing policy outlining which patients qualify for SLK[12] is one such step in that direction. This policy addresses the problem of unnecessary SLK in patients who have significant potential for native renal recovery. Once patients are selected who have little chance of native renal recovery, however, that group must still be scrutinized to determine which ones will have acceptable outcomes after transplantation.

Singal and colleagues[13] have examined the effect of liver disease on outcomes after SLK and determined that recipients with hepatitis C virus or nonalcoholic steatohepatitis-related cirrhosis have poorer survival compared with those receiving transplants for alcohol-related or cholestatic disease.[13] The prevalence of chronic medical conditions, such as hypertension (HTN), diabetes mellitus (DM), and the metabolic syndrome, is increasing in the end-stage liver disease population.[14,15] This increased comorbidity burden presents the challenge of patients with both end-stage liver disease and chronic kidney disease of a separate cause (as opposed to renal failure resulting from hepatic decompensation or from the same cause as the liver disease, such as hepatitis C virus). The effect of the cause of renal disease on outcomes after SLK has yet to be examined. This study was undertaken to determine whether patients undergoing SLK for renal diagnoses related to either liver failure (primarily hepatorenal syndrome [HRS] or prolonged acute tubular necrosis [ATN]) or chronic comorbidities (hypertensive or diabetic nephropathy) have differing outcomes.

METHODS

With an IRB exemption, adult recipients of SLK from 2003 to 2016 in the United Network for Organ Sharing Standard Transplant Analysis and Research file as of September 30, 2017 were analyzed. The study timeframe was selected to correspond to the MELD era, while allowing for adequate follow-up. Recipients of partial/reduced-sized liver grafts and previous transplant recipients were excluded. From this overall study population, recipients listed with HTN, DM, ATN, or HRS as the indication for renal transplantation were selected for comparison.

Continuous covariates were summarized as mean (SD) and compared using Student's *t*-test, and categorical covariates were summarized as count (percentage) and compared using chi-square or Fisher's exact test, where appropriate. Patient survival determined according to the Kaplan-Meier method from transplantation until death. Patients alive at the end of follow-up were censored. Liver graft survival was measured as the time between transplantation and death or relisting, and kidney graft survival (non-death-censored) was measured from transplantation until death, transplantation nephrectomy, or return to dialysis. Patients alive with a functioning graft at the end of follow-up were censored. Univariable comparison between survival curves was made using the log-rank test. Multivariable comparison of the effect of renal indication for transplantation on patient and graft survival was performed using Cox proportional hazards regression. Variables with $p < 0.1$ on univariable analysis were included in the adjusted proportional hazards regression analyses. A p value < 0.05 was considered significant.

RESULTS

There were 5,870 adult recipients of SLK during the study time frame. Selecting only those with a renal diagnosis of HRS/ATN or HTN/DM resulted in a cohort of 2,656 recipients. Removing recipients of earlier transplants yielded the final cohort of 2,476 patients. This included 1,204 recipients in the HRS/ATN group and 1,272 in the HTN/DM group. Mean age was 57.2 years and the majority of patients were Caucasian (59%) and men (66%). The remaining characteristics of the overall cohort are listed in Table 1.

Compared with the ATN/HRS group, recipients in the HTN/DM group were slightly older (58 vs 56 years; $p < 0.001$), more frequently African American (24.8% vs 9.2%; $p < 0.001$), and had a slightly higher BMI (28.4 vs 27.9 kg/m^2; $p = 0.031$). Alcoholic liver disease was more common in the ATN/HRS group than the HTN/DM group (35.8% vs 16.0%; $p < 0.001$), and viral hepatitis was more common in the HTN/DM group (33.2% vs 21.5%; $p < 0.001$). Nonalcoholic steatohepatitis was the indication for liver transplantation in 16.8% of both groups.

The ATN/HRS group had a greater degree of hepatic decompensation than the HTN/DM group, as evidenced by increased prevalence of ascites (90% vs 81.8%; $p < 0.001$), encephalopathy (76.6% vs 64.5%; $p < 0.001$),

Table 1. Overall Cohort Characteristics

Variable	Data
Age, y, mean (SD)	57.2 (8.6)
Sex, male, n (%)	1,633 (66.0)
Race, n (%)	
Caucasian	1,460 (59.0)
African American	426 (17.2)
Hispanic	467 (18.9)
Asian	88 (3.6)
Other	35 (1.4)
BMI, kg/m^2, mean (SD)	28.1 (5.9)
Transjugular intrahepatic portosystemic shunt present, n (%)	235 (9.5)
Ascites, n (%)	
Absent	343 (13.9)
Slight	955 (38.6)
Moderate	1,168 (47.2)
Unknown	10 (0.4)
Encephalopathy, n (%)	
Absent	722 (29.2)
Grade 1−2	1,358 (54.9)
Grade 3−4	386 (15.6)
Unknown	10 (0.4)
Portal vein thrombosis, n (%)	233 (9.4)
Earlier upper abdominal operation, n (%)	1,072 (43.3)
Bilirubin at transplantation, mg/dL, mean (SD)	8.3 (11.3)
Creatinine at transplantation, mg/dL, mean (SD)	3.9 (2.4)
International Normalized Ratio at transplantation, mean (SD)	1.9 (1.0)
Biochemical MELD score at transplantation, mean (SD)	30.1 (8.3)
MELD exception, n (%)	207 (8.4)
On ventilator at transplantation, n (%)	163 (6.6)
Location at transplant offer, n (%)	
Home	1,295 (52.3)
Hospitalized	625 (25.3)
ICU	555 (22.4)
Pretransplantation dialysis, n (%)	1,768 (17.4)
Liver diagnosis, n (%)	
Viral hepatitis	681 (27.5)
Cholestatic disease	87 (3.5)
Alcohol	634 (25.6)
Nonalcoholic steatohepatitis	415 (16.8)
Acute liver failure	46 (1.9)
Other	613 (24.8)
Donor age, y, mean (SD)	36 (1.3)
Donor sex, male, n (%)	1,532 (61.9)
Donor race, n (%)	
Caucasian	1,632 (65.9)
African American	375 (15.2)
Hispanic	377 (15.2)
Asian	67 (2.7)
Other	25 (1.0)
Donor BMI, kg/m^2, mean (SD)	26.8 (5.8)
Donor cause of death, n (%)	
Anoxia	706 (28.5)
CVA	722 (29.2)
Trauma	975 (39.4)
CNS tumor	13 (0.5)
Other	60 (2.4)
Donor terminal aspartate aminotransferase, U/L, mean (SD)	72.6 (101.2)
Donor terminal alanine aminotransferase, U/L, mean (SD)	75.6 (161.1)
Donor terminal bilirubin, mg/dL, mean (SD)	0.9 (0.8)
Donor terminal creatinine, mg/dL, mean (SD)	1.1 (0.6)
Kidney Donor Profile Index	39.5 (26.8)
Share type, n (%)	
Local	1,854 (74.9)
Regional	573 (23.1)
National	49 (2.0)
Liver cold ischemia time, h, mean (SD)	6.6 (3.3)
Renal cold ischemia time, h, mean (SD)	11.8 (7.4)
Renal delayed graft function, n (%)	625 (25.3)
90-day mortality, n (%)	127 (5.1)

MELD, Model for End-Stage Liver Disease.

and portal vein thrombosis (10.9% vs 8%; $p = 0.029$). The increased degree of hepatic decompensation in the ATN/HRS group is reflected by a higher laboratory MELD score at transplantation (33.1 vs 27.2; $p < 0.001$). Patients in the ATN/HRS group were also more likely to be hospitalized or in intensive care (62.5% vs 33.6%; $p < 0.001$), on mechanical ventilation (8.6% vs 4.7%; $p < 0.001$), and on dialysis (74.9% vs 68.1%; $p < 0.001$) at the time of transplantation than their counterparts in the HTN/DM group. Donor characteristics were similar between both groups, with the exception of cause of death and increased use of regional sharing in the ATN/HRS group (Table 2). Hepatic cold ischemia time was also similar between the 2 groups, and renal cold time was slightly longer in the ATN/HRS group (Table 2).

On univariable analysis, patients in the HTN/DM group had significantly lower patient survival (hazard ratio [HR] for death 1.396; 95% CI 1.162 to 1.676; $p < 0.001$), liver graft survival (HR 1.425; 95% CI 1.192 to 1.703; $p < 0.001$), and renal graft survival (HR 1.439; 95% CI 1.213 to 1.707; $p < 0.001$). The respective values for 1-, 3-, and 5-year survival are listed in Table 3 and survival

Table 2. Comparison Between Acute Tubular Necrosis/Hepatorenal Syndrome Group and Diabetes Mellitus/Hypertension Group

Variable	ATN/HRS (n = 1,204)	HTN/DM (n = 1,272)	p Value
Age, y, mean (SD)	56.4 (9.6)	58.1 (7.5)	<0.001*
Sex, male, n (%)	754 (62.6)	879 (69.1)	0.001*
Race, n (%)			<0.001*
Caucasian	823 (68.4)	637 (50.1)	
African American	111 (9.2)	315 (24.8)	
Hispanic	227 (18.9)	240 (18.9)	
Asian	26 (2.2)	62 (4.9)	
Other	17 (1.4)	18 (1.4)	
BMI, kg/m^2, mean (SD)	27.9 (6.1)	28.4 (5.7)	0.031*
Transjugular intrahepatic portosystemic shunt present, n (%)	113 (9.4)	122 (9.6)	0.947
Ascites, n (%)			<0.001*
Absent	118 (9.8)	225 (17.7)	
Slight	385 (32.0)	570 (44.8)	
Moderate	698 (58.0)	470 (37.0)	
Unknown	3 (0.3)	7 (0.6)	
Encephalopathy, n (%)			<0.001*
Absent	278 (23.1)	444 (34.9)	
Grade 1−2	677 (56.2)	681 (53.5)	
Grade 3−4	246 (20.4)	140 (11.0)	
Unknown	3 (0.3)	7 (0.6)	
Portal vein thrombosis, n (%)	131 (10.9)	102 (8.0)	0.029*
Earlier upper abdominal operation, n (%)	515 (42.8)	557 (43.8)	0.741
Bilirubin at transplantation, mg/dL, mean (SD)	11.2 (12.5)	5.5 (9.2)	<0.001*
Creatinine at transplantation, mg/dL, mean (SD)	3.4 (1.9)	4.4 (2.6)	<0.001*
International Normalized Ratio at transplantation, mean (SD)	2.1 (0.9)	1.7 (1.1)	<0.001*
Biochemical MELD score at transplantation, mean (SD)	33.1 (7.8)	27.2 (7.6)	<0.001*
MELD exception, n (%)	48 (4.0)	159 (12.5)	<0.001*
On ventilator at transplantation, n (%)	103 (8.6)	60 (4.7)	<0.001*
Location at transplant offer, n (%)			<0.001*
Home	451 (37.5)	844 (66.4)	
Hospitalized	371 (30.8)	254 (20.0)	
ICU	382 (31.7)	173 (13.6)	
Pre-transplantation dialysis, n (%)	902 (74.9)	866 (68.1)	<0.001*
Liver diagnosis, n (%)			<0.001*
Viral hepatitis	259 (21.5)	422 (33.2)	
Cholestatic disease	48 (4.0)	39 (3.1)	
Alcohol	431 (35.8)	203 (16.0)	
Nonalcoholic steatohepatitis	202 (16.8)	213 (16.8)	
Acute liver failure	20 (1.7)	26 (2.0)	
Other	244 (20.3)	369 (29.0)	
Donor age, y, mean (SD)	36.3 (13.9)	36.0 (14.5)	0.637
Donor sex, male, n (%)	743 (61.7)	789 (62.0)	0.871
Donor race, n (%)			0.702
Caucasian	785 (65.2)	847 (66.6)	
African American	180 (15.0)	195 (15.3)	
Hispanic	188 (15.6)	189 (14.9)	

(Continued)

Table 2. Continued

Variable	ATN/HRS (n = 1,204)	HTN/DM (n = 1,272)	p Value
Asian	37 (3.1)	30 (2.4)	
Other	14 (1.2)	11 (0.9)	
Donor BMI, kg/m^2, mean (SD)	26.9 (5.7)	26.8 (5.8)	0.690
Donor cause of death, n (%)			0.011*
Anoxia	379 (31.5)	327 (25.7)	
CVA	339 (28.2)	383 (30.1)	
Trauma	455 (37.8)	520 (40.9)	
CNS tumor	3 (0.3)	10 (0.8)	
Other	28 (2.3)	32 (2.5)	
Donor terminal aspartate aminotransferase, U/L, mean (SD)	73.4 (97.4)	71.8 (104.7)	0.701
Donor terminal alanine aminotransferase, U/L, mean (SD)	75.7 (125.5)	75.5 (188.8)	0.978
Donor terminal bilirubin, mg/dL, mean (SD)	0.9 (1.0)	0.9 (0.7)	0.459
Donor terminal creatinine, mg/dL, mean (SD)	1.1 (0.6)	1.0 (0.6)	0.334
Kidney Donor Profile Index, mean (SD)	39.3 (26.3)	39.8 (27.3)	0.625
Share type, n (%)			<0.001*
Local	816 (67.8)	1,038 (81.6)	
Regional	374 (31.1)	199 (15.6)	
National	14 (1.2)	35 (2.8)	
Liver cold ischemia time, h, mean (SD)	6.6 (3.2)	6.6 (3.4)	0.734
Renal cold ischemia time, h, mean (SD)	12.5 (8.0)	11.2 (6.7)	<0.001*
Renal delayed graft function, n (%)	354 (29.4)	271 (21.3)	<0.001*
90-day mortality, n (%)	56 (4.7)	71 (5.6)	0.294

*Statistically significant.
ATN, acute tubular necrosis; DM, diabetes mellitus; HRS, hepatorenal syndrome; HTN, hypertension.

curves are presented in Figures 1 to 3. After adjusting for differences in donor and recipient characteristics, HTN/DM remained a significant risk factor for patient death (HR 1.529; p < 0.001), liver graft failure (HR 1.604; p < 0.001), and renal graft failure (HR 1.589; p < 0.001). The full results of the adjusted survival analysis are listed in Tables 4 (patient survival), 5 (liver graft survival), and 6 (renal graft survival).

Table 3. 1-, 2-, and 5-Year Patient, Liver, and Kidney Graft Survival after Simultaneous Liver-Kidney Transplantation with the Renal Diagnosis of Acute Tubular Necrosis/Hepatorenal Syndrome vs Diabetes Mellitus/Hypertension

Variable	1 year, %	3 year, %	5 year, %	p Value
Patient survival				<0.001
ATN/HRS	90.7	84.1	76.6	
DM/HTN	87.4	78.2	71.2	
Liver graft survival				<0.001
ATN/HRS	89.6	82.8	75.8	
DM/HTN	86.2	76.8	70.2	
Liver graft survival				<0.001
ATN/HRS	88.4	81.7	73.5	
DM/HTN	84.2	74.8	67.0	

ATN, acute tubular necrosis; DM, diabetes mellitus; HRS, hepatorenal syndrome; HTN, hypertension.

As a final reference, a cohort of adult first-time recipients of liver transplantation alone during the study period was analyzed. When compared with the liver transplantation alone cohort, the HTN/DM group had significantly inferior 1-, 3-, and 5-year patient survival rates (87.4%, 78.2%, and 71.2% vs 90.0%, 81.8%, 75.4%,

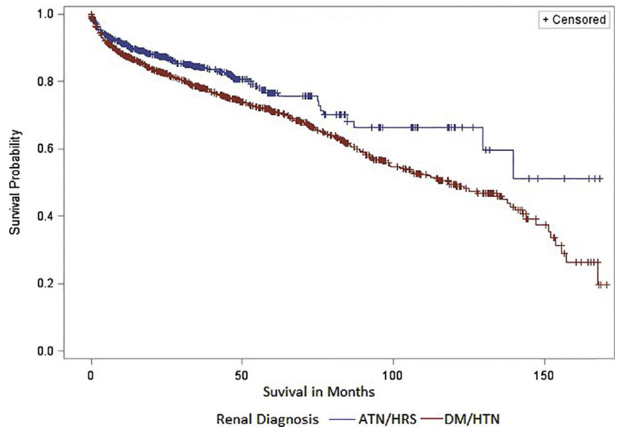

Figure 1. Kaplan-Meier estimated patient survival after simultaneous liver-kidney transplantation with the renal diagnosis of acute tubular necrosis (ATN)/hepatorenal syndrome (HRS) vs diabetes mellitus (DM)/hypertension (HTN).

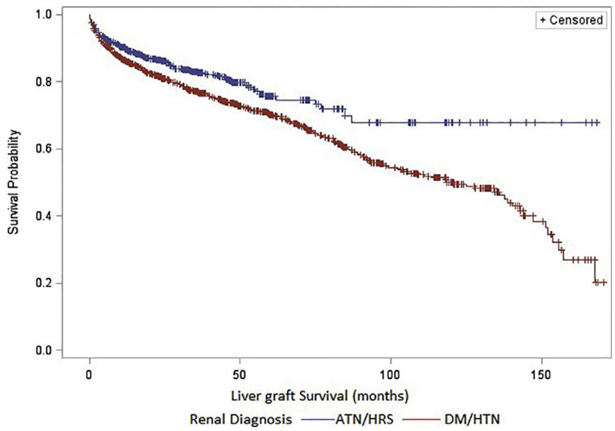

Figure 2. Kaplan-Meier estimated liver graft survival after simultaneous liver-kidney transplantation with the renal diagnosis of acute tubular necrosis (ATN)/hepatorenal syndrome (HRS) vs diabetes mellitus (DM)/hypertension (HTN).

respectively; $p < 0.001$). The HR for death in the HTN/DM group compared with the liver transplantation alone group was 1.312 (95% CI 1.188 to 1.449; $p < 0.001$). Patient survival rates in the HRS/ATN group were actually similar to those in the liver transplantation alone group (90.7%, 84.1%, and 76.6% at 1, 3, and 5 years, respectively; HR 0.895; 95% CI 0.773 to 1.038; $p = 0.142$).

DISCUSSION

This is the first study, to our knowledge, that addresses the effect of the cause of renal disease on outcomes after SLK. Despite being less acutely ill than their counterparts with kidney disease resulting from hepatic decompensation, the patients in this series with hypertensive or diabetic nephropathy actually had significantly worse survival. This is counterintuitive, as many times these patients have generally well-compensated hepatic function, with the majority of their MELD points coming from their renal dysfunction. Often times the primary indication for transplantation will be end-stage renal disease (ESRD), but SLK is judged to be necessary to ameliorate what is thought to be an unacceptable risk profile for kidney transplantation alone in the setting of cirrhosis.

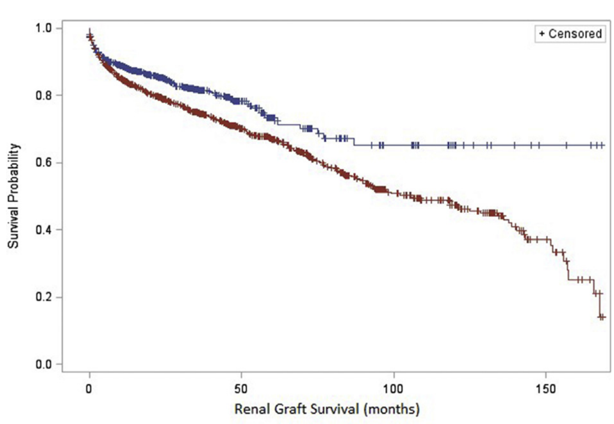

Figure 3. Kaplan-Meier estimated kidney graft survival after simultaneous liver-kidney transplantation with the renal diagnosis of acute tubular necrosis (ATN)/hepatorenal syndrome (HRS) vs diabetes mellitus (DM)/hypertension (HTN).

The findings of this study highlight the inherent risk in such a strategy, and call into question the practice of listing all ESRD patients with concomitant cirrhosis. We have previously demonstrated that kidney transplantation alone in patients with compensated hepatitis C virus cirrhosis and hepatic vein-portal pressure gradients <10 mmHg results in 3-year patient and graft survival rates of 88.9% and 75%, respectively,[16] which compare favorably with the SLK results in the DM/HTN group in the current series. However, many of the patients in the current study cohort might have had significant portal hypertension, as the portal pressure gradient is not reported in the UNOS database, which would have rendered them higher risk for kidney transplantation alone than the patients in our previous study. These findings do highlight the fact that the ESRD patient with compensated cirrhosis should not be taken lightly when deciding on kidney transplantation alone vs SLK.

With the growing epidemic in obesity and the metabolic syndrome, the need to appropriately risk-stratify patients with multiple comorbidities will only become more important going forward. This rise in comorbidities is not just

Table 4. Adjusted Cox Proportional Hazards Model for Patient Survival

Risk factor	Hazard ratio	Lower 95% CI	Upper 95% CI	p Value
Hypertension/diabetes mellitus	1.529	1.232	1.899	<0.001
Race (vs Caucasian)				
Hispanic	0.714	0.557	0.915	0.008
Medical condition (vs at home)				
Intensive care	1.524	1.132	2.052	0.005
Encephalopathy (vs absent)				
Grade 3–4	1.444	1.059	1.968	0.02
Donor cause of death (vs trauma)				
CVA	1.316	1.071	1.618	0.009
Dialysis within 7 d after transplant	1.681	1.374	2.055	<0.001
Recipient International Normalized Ratio	1.107	1.021	1.201	0.014

Only factors significant at $p < 0.05$ are shown. The full model can be found in eTable 1.

Table 5. Adjusted Cox Proportional Hazards Model of Liver Graft Survival

Risk factor	Hazard ratio	Lower 95% CI	Upper 95% CI	p Value
Hypertension/diabetes mellitus	1.604	1.298	1.982	<0.0001
Race (vs Caucasian)				
Hispanic	0.724	0.568	0.922	0.009
Medical condition (vs at home)				
Intensive care	1.51	1.128	2.022	0.006
Encephalopathy (vs absent)				
Grade 3–4	1.487	1.101	2.008	0.01
Donor cause of death (vs trauma)				
CVA	1.242	1.015	1.521	0.036
Dialysis within 7 d after transplant	1.809	1.489	2.198	<0.001
Recipient International Normalized Ratio	1.101	1.015	1.194	0.021

Only factors significant at $p < 0.05$ are shown. The full model can be found in eTable 2.

limited to patients with nonalcoholic steatohepatitis. Up to 25% of patients with chronic hepatitis C cirrhosis and 19% of patients with alcoholic cirrhosis were shown to have pre-existing diabetes at the time of transplantation[17] in an earlier Mayo Clinic series. More recently, diabetes was found to be present in 30% of all patients undergoing liver transplantation between 2006 and 2010 in the UK, up from 17.4% between 1997 and 2000.[14] In another nationwide study in Taiwan, 26.5% of all patients undergoing liver transplantation between 2000 and 2010 had pre-existing diabetes,[18] demonstrating that this problem is not limited to the Western hemisphere.

Hypertension and diabetes have been shown to increase the risk of cardiovascular complications and decrease survival in several studies of liver transplantation alone,[19-23] so it should come as no surprise that diabetes and HTN severe enough to cause end-organ dysfunction (renal failure) would have a significant detrimental impact on outcomes after SLK. Although the outcomes presented in this study are not poor enough to justify making diabetic or hypertensive nephropathy absolute contraindications to SLK, they do illustrate the importance of scrutinizing such patients closely before making listing decisions. Appropriate cardiac risk stratification is particularly important. In a prospective cohort study of patients with 840 patients with diabetes, Valmadrid and colleagues[24] found cardiovascular mortality rates of 36.9, 85.5, and 123 deaths per 1,000 person-years for diabetics without albuminuria, microalbuminuria, and gross proteinuria, respectively. This translates into a roughly 30% 5-year mortality rate for those with diabetes and microalbuminuria and a 50% 5-year mortality rate for those with gross proteinuria based on visual inspection of Kaplan-Meier curves.[24] In a retrospective study of cardiac catheterization in renal transplantation patients, asymptomatic coronary stenosis was found in 48% of type 2 diabetics.[25] Given these findings, invasive cardiac evaluation should be a routine part of the evaluation of this patient population when transplantation is being considered.

Table 6. Adjusted Cox Proportional Hazards Model of Kidney Graft Failure

Risk factor	Hazard ratio	Lower 95% CI	Upper 95% CI	p Value
Hypertension/diabetes mellitus	1.589	1.298	1.944	<0.001
Race (vs Caucasian)				
Hispanic	0.763	0.607	0.96	0.021
Medical condition (vs at home)				
Intensive care	1.468	1.103	1.954	0.008
Encephalopathy (vs absent)				
Grade 3–4	1.265	0.944	1.695	0.116
Donor cause of death (vs trauma)				
Cerebrovascular accident	1.488	1.23	1.801	<0.001
Dialysis within 7 d after transplantation	1.975	1.641	2.376	<0.001
Recipient International Normalized Ratio	1.101	1.02	1.188	0.013
Recipient Model for End-Stage Liver Disease score	0.976	0.954	0.998	0.029

Only factors significant at $p < 0.05$ are shown. The full model can be found in eTable 3.

One of the weaknesses of this study is the lack of granularity available in the data. There likely exists a subset of patients in whom diabetic and/or hypertensive nephropathy truly does represent a contraindication to SLK, but to identify the markers associated with this population will require a level of detailed data collection not available in large databases. For example, peripheral arterial disease and diabetic retinopathy represent significant macro- and microvascular diabetic complications that could potentially indicate prohibitively poor outcomes.[21] Diabetic gastroparesis is another potential marker for severe diabetes that might contraindicate liver transplantation. In a study of the residents of Olmsted County, MN, 5-year mortality in patients with gastroparesis of all causes was 33% compared with only 19% in the population as a whole. Survival was even worse in those with diabetic gastroparesis.[26] Although the current study cannot identify specific groups that should be excluded from SLK, it does identify those with hypertensive and diabetic nephropathy as a risk group that should undergo additional scrutiny in future studies. In the meantime, this indication for transplantation could be incorporated into the risk-adjustment models on which transplantation centers are ultimately judged.

CONCLUSIONS

Patients with diabetic or hypertensive nephropathy represent a high-risk group for SLK, despite a lower overall acuity of illness than their counterparts with liver disease-driven kidney dysfunction. As such, the pretransplantation workup should be particularly vigilant and likely should include invasive cardiac evaluation. When possible, all efforts should be made to list patients with compensated hepatic function and no portal hypertension for kidney transplantation alone. Future studies directed at identifying diabetic and hypertensive complications that would represent a contraindication to transplantation and risk-adjustment models should reflect the increased mortality risk these patients face that is belied by their relatively lower MELD scores.

Author Contributions

Study conception and design: Cannon, Jones
Acquisition of data: Cannon
Analysis and interpretation of data: Cannon, Jones, Davis, Eckhoff
Drafting of manuscript: Cannon, Jones, Davis, Eckhoff
Critical revision: Cannon, Jones, Davis, Eckhoff

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Discussion

DR WILLIAM C CHAPMAN (St Louis, MO): This report investigates the effect of renal diagnosis on survival in patients undergoing simultaneous liver-kidney transplant (SLK). This is a timely and very controversial issue and one that will likely continue to increase.

To put this in context, before 2000, SLK transplantation was only very rarely considered, probably because of case complexity and, also, what has happened with our allocation system that went in place in 2002. Patients with renal insufficiency got increased priority for liver transplant; the higher your creatinine, the higher priority you were for liver transplant.

Currently, more than 10% of patients undergoing liver transplantation also receive a kidney, and this is continuing to increase. This is especially contentious among the renal transplant community where, in many areas, kidney-transplant-listed patients will wait substantially longer than liver patients, in some cases, many years. And as we increase the SLK group, we are pulling kidneys away from patients on the kidney transplant list, which numbers more than 100,000 today.

The authors demonstrate that patients with diabetes and hypertension have worse long-term outcomes than those with hepatorenal or more acute liver-associated causes of renal failure. What you are suggesting is that the former group of patients are essentially those with chronic renal disease, perhaps with cirrhosis but milder liver disease, and perhaps they do not even require a liver transplant. What data do you have to support your view that renal transplant alone would be successful in this cohort? How do you counter the often-made claim that renal transplant alone will result in liver decompensation? Our nephrologists are quite reluctant to consider renal transplant alone in this patient group, but perhaps that fear is misguided.

You suggest that simultaneous liver-kidney transplant should be carefully considered in patients with a diagnosis of hypertension and diabetes, especially those without portal hypertension. Do you have data on the presence or absence of portal hypertension in the United Network for Organ Sharing (UNOS) database? Because I do not think those data are collected, it is a little bit difficult to speculate that liver transplant may or may not be indicated in those patients.

These issues are only going to worsen as we go to broader sharing with longer delays and decreased rates of organ access across the South and Midwest. How do you propose to effect such a change, and would you make this at the policy level? Finally, please comment on your practices at Louisville and the University of Alabama regarding assessment and consideration for SLK. What proportion of your overall transplant volume consists of SLK patients? Do you consider this option in patients with cirrhosis but without portal hypertension, in other words, kidney transplant alone?

DR DAVID SHAFFER (Nashville, TN): As we have heard, the number of SLKs in the US has increased more than 4-fold in the last 15 years. While many studies have shown a survival benefit of SLK in end-stage liver disease patients with concomitant end-stage renal disease (ESRD) on dialysis, the benefit and indication of SLKs vs liver transplant alone in patients with acute kidney injury (AKI) or potentially recoverable renal function is much more controversial.

The steady increase in SLKs over the last 15 years has prompted concern over the misallocation of scarce resources, in this case, the kidney, and whether SLK in such patients is "the best use of donated organs," to use the terminology of the National Organ Transplant Act Final Rule. To address this, UNOS has established more uniform SLK selection criteria in 2016 for patients with either chronic kidney disease or AKI.

In this study, the authors found that patients classified as having diabetes or hypertension had worse patient survival and higher risk of liver graft loss or renal graft loss than patients whose cause of renal dysfunction was acute tubular necrosis or hepatorenal syndrome, despite a lower acuity of illness. This, in and of itself, is not particularly surprising as many of the metrics used to assess acuity of illness reflect hepatic decompensation, which is then ameliorated by a successful liver transplant.

On the other hand, both diabetes and hypertension are chronic medical conditions not improved by liver transplant and are significant risk factors for long-term cardiovascular disease and mortality. They conclude by recommending that the inferior graft survival in patients with diabetes and hypertension should be accounted for in both risk adjustment and allocation schemes, which is imminently reasonable in this era of increasing scarcity and regulatory oversight.

Because of the difficulty in measuring both acute renal dysfunction and the potential for renal recovery in end-stage liver disease patients and ethical concerns over whether multiorgan transplants should have priority over kidney transplant alone, multiple reports in the literature, some of which are referenced in your manuscript, suggest that SLK is overused and scarce kidneys are misallocated or not put to best use.

eTable 1. Full Multivariable Cox Proportional Hazards Model for Patient Survival

Risk factor	Hazard ratio	Lower 95% CI	Upper 95% CI	p Value
Hypertension/diabetes mellitus	1.529	1.232	1.899	<0.001*
Female sex	0.966	0.794	1.175	0.729
Race (vs Caucasian)				
African American	0.948	0.74	1.214	0.672
Hispanic	0.714	0.557	0.915	0.008*
Asian	0.974	0.631	1.503	0.905
Other	0.854	0.399	1.829	0.685
Liver diagnosis (vs viral hepatitis)				
Cholestatic disease	0.737	0.412	1.316	0.302
Alcohol	0.907	0.698	1.177	0.462
Nonalcoholic steatohepatitis	0.933	0.691	1.26	0.653
Acute liver failure	0.874	0.467	1.634	0.672
Other	1.142	0.905	1.44	0.262
Pretransplantation dialysis	1.239	0.985	1.558	0.067
MELD exception	1.061	0.771	1.461	0.716
Medical condition (vs at home)				
Intensive care	1.524	1.132	2.052	0.005*
Hospitalized	1.132	0.883	1.452	0.328
On ventilator	1.048	0.71	1.547	0.812
Ascites (vs absent)				
Slight	1.062	0.797	1.415	0.681
Moderate	0.952	0.702	1.291	0.75
Unknown	0.411	0.099	1.7	0.22
Portal vein thrombus				
Present	0.922	0.407	2.087	0.846
Unknown	1.147	0.845	1.556	0.379
Encephalopathy (vs absent)				
Grade 1–2	0.975	0.779	1.22	0.825
Grade 3–4	1.444	1.059	1.968	0.02*
Donor cause of death (vs trauma)				
Anoxia	1.176	0.934	1.48	0.167
CVA	1.316	1.071	1.618	0.009*
CNS tumor	1.343	0.492	3.665	0.565
Other	1.249	0.693	2.252	0.459
Share type (vs local)				
Regional	1.002	0.798	1.257	0.99
National	0.912	0.507	1.64	0.758
Dialysis within 7 d after transplantation	1.681	1.374	2.055	<0.001*
Recipient age	1.007	0.995	1.018	0.2463
Recipient BMI	0.998	0.982	1.015	0.843
Recipient creatinine	1.009	0.968	1.052	0.682
Recipient bilirubin	0.998	0.986	1.011	0.791
Recipient International Normalized Ratio	1.107	1.021	1.201	0.014*
Recipient MELD	0.98	0.957	1.004	0.098
Renal cold ischemia time (per hour)	1	0.987	1.013	0.994

*Statistically significant at $p < 0.05$.
MELD, Model for End-Stage Liver Disease.

eTable 2. Full Multivariable Cox Proportional Hazards Model for Liver Graft Survival

Risk factor	Hazard ratio	Lower 95% CI	Upper 95% CI	p Value
Hypertension/diabetes mellitus	1.604	1.298	1.982	<0.0001*
Female sex	0.942	0.777	1.142	0.543
Race (vs Caucasian)				
African American	0.944	0.74	1.203	0.64
Hispanic	0.724	0.568	0.922	0.009*
Asian	0.991	0.648	1.515	0.968
Other	0.789	0.369	1.69	0.543
Liver diagnosis (vs viral hepatitis)				
Cholestatic disease	0.778	0.444	1.363	0.381
Alcohol	0.969	0.753	1.248	0.808
Nonalcoholic steatohepatitis	0.923	0.686	1.241	0.596
Acute liver failure	0.89	0.475	1.667	0.716
Other	1.146	0.911	1.442	0.244
Pretransplantation dialysis	1.235	0.985	1.548	0.067
MELD exception	1.043	0.76	1.43	0.796
Medical condition (vs at home)				
Intensive care	1.51	1.128	2.022	0.006*
Hospitalized	1.148	0.9	1.464	0.266
On ventilator	1.047	0.719	1.526	0.811
Ascites (vs absent)				
Slight	1.134	0.854	1.505	0.385
Moderate	0.971	0.719	1.312	0.847
Unknown	0.407	0.098	1.682	0.214
Portal vein thrombus				
Present	0.748	0.307	1.822	0.523
Unknown	1.123	0.833	1.514	0.447
Encephalopathy (vs absent)				
Grade 1–2	0.954	0.766	1.188	0.671
Grade 3–4	1.487	1.101	2.008	0.01*
Donor cause of death (vs trauma)				
Anoxia	1.129	0.902	1.412	0.29
CVA	1.242	1.015	1.521	0.036*
CNS tumor	1.325	0.486	3.61	0.582
Other	1.128	0.626	2.03	0.689
Share type (vs local)				
Regional	1.005	0.805	1.254	0.966
National	0.878	0.489	1.577	0.663
Dialysis within 7 d after transplantation	1.809	1.489	2.198	<0.001*
Recipient age	1	0.989	1.011	0.998
Recipient BMI	1.002	0.987	1.018	0.767
Recipient creatinine	1.007	0.967	1.048	0.746
Recipient bilirubin	0.999	0.987	1.011	0.848
Recipient International Normalized Ratio	1.101	1.015	1.194	0.021*
Recipient MELD	0.98	0.958	1.003	0.089
Renal cold ischemia time (per hour)	0.999	0.987	1.012	0.931

*Statistically significant at $p < 0.05$.
MELD, Model for End-Stage Liver Disease.

eTable 3. Full Multivariable Cox Proportional Hazards Model for Kidney Graft Survival

Risk factor	Hazard ratio	Lower 95% CI	Upper 95% CI	p Value
Hypertension/diabetes mellitus	1.589	1.298	1.944	<0.001*
Female sex	0.967	0.804	1.162	0.720
Race (vs Caucasian)				
African American	0.996	0.791	1.255	0.975
Hispanic	0.763	0.607	0.96	0.021*
Asian	0.994	0.662	1.492	0.976
Other	0.724	0.339	1.547	0.405
Liver diagnosis (vs viral hepatitis)				
Cholestatic disease	0.806	0.468	1.389	0.438
Alcohol	0.937	0.734	1.196	0.601
Nonalcoholic steatohepatitis	1.067	0.812	1.403	0.641
Acute liver failure	0.838	0.449	1.563	0.578
Other	1.105	0.886	1.378	0.374
Pretransplantation dialysis	1.307	1.052	1.624	0.016*
MELD exception	1.057	0.781	1.43	0.721
Medical condition (vs at home)				
Intensive care	1.468	1.103	1.954	0.008*
Hospitalized	1.202	0.955	1.513	0.117
On ventilator	1.154	0.802	1.661	0.441
Ascites (vs absent)				
Slight	1.06	0.81	1.388	0.671
Moderate	1.011	0.761	1.343	0.938
Unknown	0.376	0.091	1.549	0.176
Portal vein thrombus				
Present	0.518	0.192	1.395	0.193
Unknown	1.127	0.843	1.507	0.419
Encephalopathy (vs absent)				
Grade 1–2	0.962	0.781	1.185	0.716
Grade 3–4	1.265	0.944	1.695	0.116
Donor cause of death (vs trauma)				
Anoxia	1.043	0.836	1.3	0.712
CVA	1.488	1.23	1.801	<0.001*
CNS tumor	1.385	0.507	3.785	0.526
Other	1.173	0.667	2.064	0.580
Share type (vs local)				
Regional	1.128	0.915	1.39	0.260
National	1.021	0.594	1.756	0.939
Dialysis within 7 days after transplant	1.975	1.641	2.376	<0.001*
Recipient age	0.999	0.989	1.01	0.911
Recipient BMI	1.005	0.99	1.02	0.533
Recipient creatinine	1.01	0.972	1.05	0.600
Recipient bilirubin	0.999	0.987	1.011	0.896
Recipient International Normalized Ratio	1.101	1.02	1.188	0.013*
Recipient MELD	0.976	0.954	0.998	0.029*
Renal cold ischemia time (per hour)	0.993	0.981	1.006	0.299

*Statistically significant at $p < 0.05$.
MELD, Model for End-Stage Liver Disease.