Open Access

OBM Transplantation

LIDSEN Publishing Inc.

Original Research

Non-Renal Factors Associated with Simultaneous Liver-Kidney Transplant in Patients with End-Stage Liver Disease and Stage 3-5 Chronic Kidney Disease Not Requiring Dialysis

Alfonso H. Santos *, Amer Belal, Hisham Ibrahim, Muhannad A. Leghrouz

Division of Nephrology, Hypertension and Renal Transplantation, Department of Medicine, College of Medicine, University of Florida, Gainesville, FL, USA; E-Mails: Alfonso.Santos@medicine.ufl.edu; Amer.Belal@medicine.ufl.edu; Hisham.Ibrahim@medicine.ufl.edu; Muhannad.Leghrouz@medicine.ufl.edu

* **Correspondence:** Alfonso H. Santos; E-Mail: Alfonso.Santos@medicine.ufl.edu

Academic Editor: Tatsuya Kin

Special Issue: Evaluations for Organ Transplantation: Liver, Kidney and Pancreas in the 21st Century

OBM Transplantation
2023, volume 7, issue 1
doi:10.21926/obm.transplant.2301175

Received: August 19, 2022
Accepted: February 03, 2023
Published: February 21, 2023

Abstract

We aimed to identify the non-renal risk factors for simultaneous liver-kidney transplantation (SLKT) vs. liver transplantation alone (LTA) in end-stage liver disease (ESLD) patients with estimated glomerular filtration rate (eGFR) <60 ml/min, not on dialysis. Using organ procurement and transplantation network data, we studied adult ESLD patients who received deceased-donor SLKT or LTA in July 2002-Mar 2016 with a 4-point modification of renal disease (MDRD) equation-estimated glomerular filtration rate (eGFR) stratified into chronic kidney disease stage 3 (CKD-3): 30-59 ml/min, CKD stage 4 (CKD-4): 15-29 ml/min, and CKD stage 5 (CKD-5): <15 ml/min) and not on maintenance dialysis (NOD). The outcome of the study was identification of non-renal risk factors predicting likelihood of SLKT vs. LTA. We reported the odds ratio (OR) and 95% confidence interval (CI) for SLKT vs. LTA associated with important clinical variables. Strong non-renal (non-creatinine-associated) risk factors for SLKT were WL-time >2 yrs. and 1-2 yrs. (OR = 3.80, CI = 2.94-4.91; OR = 3.20, CI = 2.58-3.97; respectively), African American or Hispanic recipient race/ethnicity (OR = 2.93, CI = 2.45-3.51;

OR = 1.46, CI = 1.24-1.72; respectively), liver repeat transplant (OR = 1.66, CI = 1.39-1.99), and diabetes (OR = 1.53, CI = 1.36-1.72). Factors associated with lower likelihood of SLKT were donor age >60 years (OR = 0.25, CI = 0.19-0.32), female recipient sex (OR = 0.48, CI = 0.43-0.54), hepatocellular carcinoma (OR = 0.53, CI = 0.35-0.81), and transplant center procedure volume tercile ranks 3rd (OR = 0.74, CI = 0.62-0.89) and 2nd (OR = 0.78, CI = 0.64-0.95). Model for end-stage liver disease scores have varying associations with SLKT vs. LTA, depending on calculation time: at wait listing or transplant. CKD-5 and -4 at wait listing (WL) and transplant were the risk factors with highest point estimates for SLKT vs. LTA. In patients with ESLD and CKD stage 3-5, not on dialysis, strong non-renal risk factors favoring SLKT versus LTA include: prolonged waitlist time, African American or Hispanic race/ethnicity, previous liver transplant, and diabetes. Some novel associations found between risk factors and likelihood of SLKT need further study for confirmation. Lack of uniform criteria for SLK allocation during the period studied is a major limitation of the study.

Keywords
Risk factors; renal failure; liver failure; simultaneous transplantation

1. Introduction

Simultaneous liver and kidney transplantation have been shown to provide a survival benefit to end-stage liver transplant patients who are dialysis-dependent or with advanced chronic kidney disease [1]. In the US, there were 11,143 simultaneous liver and kidney transplants (SLKTs) versus 191,212 liver-alone transplants (LTAs) and 587,247 kidney-alone transplants between 1988 and 2021 [2]. In patients with end-stage liver disease (ESLD) or cirrhosis and end-stage renal disease (ESRD), the decision to allocate kidney and liver from the same deceased donor is straightforward [3]. In liver transplant candidates with CKD, not on dialysis (CKD-NOD), the decision to perform a SLKT versus LTA has not been straightforward until the implementation of the United Network Organ System (UNOS) allocation criteria for SLK transplant in August 2017 [1, 4]. Prior to that period, there was no uniform national guidelines for SLK transplantation, and prevailing expert opinion on who should receive an SLK transplantation included: 1) an acute kidney injury criterion variably defined as estimated glomerular filtration rate (eGFR) ≤30 ml/min; creatinine ≥2 mg/dl and dialysis requirement ≥8 weeks; sustained acute kidney injury (AKI) requiring ≥6 weeks dialysis; eGFR ≤25 ml/min for ≥4 or 6 weeks ; increase creatinine >3-fold from baseline or dialysis >4; 2) a chronic kidney disease (CKD) criterion defined as dialysis need; CKD (GFR <30 ml/min and proteinuria >3 g/day); CKD with GFR ≤30 ml/min only; creatine clearance ≤30 ml/min for > 3 months; and 3) a pathologic criterion based on kidney biopsy showing >30% glomerulosclerosis or >30% interstitial fibrosis; evidence of irreversible damage; and 4) a proteinuria criterion of >2 gram/day combined with 1 or more of the other preceding criteria above [5-7].

Despite the predominant use of renal function indicators (estimated glomerular filtration rate, dialysis status, and duration of acute or chronic kidney injury in making listing decision for SLKT versus LTA in ESLD patients [8-12]; non-renal risk factors are likely to indirectly influence the likelihood that a patient with ESLD and non-dialysis dependent CKD will receive a SLKT [7]. However,

the association of non-renal factors on the propensity of receiving a SLKT versus LTA in patients with non-dialysis dependent CKD has not been well studied and these risk factors to SLKT or LTA have just been typically mentioned perfunctorily in enumeration of baseline variables in transplant studies [9-10, 13-17].

A formal analysis to determine the independent association of non-renal risk factors with the likelihood of SLKT or LTA in ESLD patients with CKD stage 3-5, NOD has been lacking. The purpose of this study was to determine the non-renal factors significantly associated with increased likelihood of SLKT vs. LTA in ESLD patients with CKD stage 3-5, NOD, Therefore, a retrospective observational study of SLKT and LTA between 2002-2016 was performed. Results of multivariable statistical analyses on the risk factors associated with CLK or LTA recipients with CKD stage 3-5 NOD both at waitlisting and transplant are presented. This study presents the strength of associations between non-renal risk factors and SLKT in ESLD patients with CKD stage 3-5, NOD, the identification of these associations would provide broader insight into the non-renal determinants of receiving an SLK transplant.

2. Methods

This research was conducted in accordance with both the Declarations of Helsinki and Istanbul. This study with approval from the University of Florida Institutional Review Board used data from the Organ Procurement and Transplantation Network Transplant Recipients (OPTN) for transplants between July 2002 and March 2016, based on OPTN data as of 17 June 2016. The study was granted an exempt approved status because the research involved the collection or study of existing data, documents, and records, and the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

The study period included the period when the model for end-stage liver disease (MELD) score has been in use [18] and the period shortly before the OPTN/UNOS Board approved a change to the way liver-kidney transplant combinations were allocated [18]. Using a retrospective design, we studied adult recipients of SLKT and LTA with estimated GFR <60 ml/min (based on the MDRD-4 equation) and NOD both at the time of liver transplant listing and surgery [19, 20]. We excluded patients who received organ transplant/s other than liver-alone of simultaneous liver-kidney, had a previous non-liver organ transplant, had an estimated GFR of ≥60 ml/min, or were on maintenance dialysis at the time of liver transplant listing and surgery. The outcome of the study was identification of non-renal risk factors predicting likelihood of a simultaneous liver and kidney transplant (SLKT) from the same deceased donor or liver transplant alone (LTA).

3. Statistical Analysis

Baseline cohort characteristics are presented using means with standard deviations for continuous variables and percentages for categorical variables. Differences in means and proportions were compared with the Student's t-test and Chi-square test, respectively. The odds ratio for the outcome of SLKT vs. LTA was assessed by univariable and multivariable logistic regressions followed by the purposeful selection of variables for the final models as previously described [21]. Covariates in the logistic regression analysis included the following: 1. recipient citizenship, non-US citizen (vs. US citizen), [22]; 2. repeat liver transplant; 3. wait-list duration >2 yrs. ,1 yr. – 2 yrs., 0.5-1 yr.; vs. (vs. 0.5 yr.); 4. donor age 40-60 yrs., >60 yrs.; (vs. <40); 5. estimated

MDRD-4 equation GFR at the time of transplant listing: <15 ml/min, 15-29 ml/min; vs. (30-59 ml./min), [18].; 6. estimated MDRD-4 equation eGFR at transplant: <15 ml/min, 15-29 ml/min; (vs. 30-59 ml./min); 7. model for end-stage liver disease (MELD) score [17] at transplant listing: 21-30, 31-35, >35 (vs. <21); 8. MELD score at transplant [17]: 21-30, 31-35, >35 (vs. <21); 9.primary Insurance private (vs. other); 10. recipient age at transplant 50-64 years, > = 65 years; (vs. <50 years); 11. recipient on life support at transplant; 12. recipient race and ethnicity African American, Hispanic, Other/unknown; (vs. White); 13. Recipient diabetes mellitus history; 14. year of transplant 2009-2016 (vs. 2002-2015); 15. end-stage liver disease diagnosis, HCV (hepatitis C virus), ALD (alcoholic liver disease), and HCC (hepatocellular carcinoma) vs. other diseases (primary biliary cirrhosis, primary sclerosing cholangitis, non-alcoholic steatohepatitis; hepatitis B; non-A non-B hepatitis; chronic active hepatitis, and autoimmune hepatitis); 16. liver transplant procedure partial or split (vs. whole); 17. recipient sex: male or female; 18. recipient history of previous abdominal surgery; 19. recipient body mass index (BMI) at wait-listing <21 kg/m^2, 26-29 kg/m^2, or ≥30 kg/m^2; (vs. 21-25 kg/m^2); 20. donor race, African American (vs. other); 21. organ from donation after cardiac death (DCD) donor; 22. liver cold ischemia time (CIT), 6-10 hr., ≥11 hr. (vs. <6 hr.); and 23. transplant center total liver transplant volume tercile rank, 2nd tercile or 3rd tercile; [vs. 1st tercile]. For the preceding variable, transplant centers were ranked based on total liver transplant volumes per year and stratified into terciles as high-volume centers (≥67th percentile of observations), middle volume (mid-volume) centers (34th-66th percentile of observations), and low volume centers (≤33rd percentile of observations). To account for variation in yearly volumes per center, transplant volume stratifications were determined for 12 months (January 1 to December 31) of each year during the study period, except for the year 2002, the year when the MELD classification system was first introduced, for which only the July to December data were included [19], and for the year 2016; only data from January 1 through March 31 were used (to avoid anticipatory bias from the announcement of the impending change in the SLKT allocation system approved by the UNOS in June 2016) [4, 17]. Results of logistic regression models are reported as odds ratio (OR), with the 95% confidence interval (CI) for each covariate. Statistical significance was based on a p-value <0.05 and all confidence intervals used a 95% threshold. All analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC, USA).

4. Results

We studied 15,604 end-stage liver disease patients with eGFR of <60 ml/min and not requiring dialysis who received a deceased-donor liver transplant from July 2002 through March 2016; 13 588 (87.08%) received a liver transplant alone (LTA) and 2016 (12.92%) received a simultaneous liver and kidney transplant (SLKT). The most frequent specific ESLD diagnoses in both the LTA and SLKT recipient groups were hepatitis C, alcoholic liver disease, and non-alcoholic steatohepatitis (Table 1). Race/ethnicity distribution of overall liver (LTA and SLKT) vs. SLKT-only recipients were: White 76.39% vs. 66.9%, African American 7.72% vs. 13.54%, and Hispanic 11.94 % vs. 15.53%. More than two-thirds of all transplant recipients were overweight or obese: 41.18 % and 26.75% of LTA vs. 37.30 % and 25.20% of SLKT recipients were obese and overweight, respectively. Diabetes afflicted 27.55% of LTA vs. and 41.27% of SLKT recipients. The MELD scores at waitlisting were >35 in 14.2% and 9.2% of LTA and SLKT recipients, respectively; and at transplant were >35 in 23% and 24.1% of LTA and SLKT recipients, respectively. CKD stage 5 (eGFR <15 ml/min) was present at waitlisting in

5.8% and 17.1% of LTA and SLKT recipients, respectively; and at transplant in 9.1% and 32.8% of LTA and SLKT recipients, respectively.

Table 1 Demographic and Clinical Characteristics of US Adults with CKD Stage 3-5 &Not on Dialysis at Liver-Alone or Liver-Kidney Transplant (July 20002-March 2016).

Variables	**Total** **N = 15604**	**Liver Alone Transplant** **N = 13588** **-87.08%**	**Simultaneous Liver-Kidney Transplant** **N = 2016 (12.92%)**
Recipient Age (Years)			
18-49	3254 (20.85)	2888 (21.25)	366 (18.15)
50-65	9898 (63.43)	8585 (63.18)	1313 (65.13)
65+	2452 (15.71)	2115 (15.57)	337 (16.72)
Recipient Sex			
Female	6360 (40.76)	5619 (41.35)	741 (36.76)
Male	9244 (59.24)	7969 (58.65)	1275 (63.24)
Recipient Ethnicity			
White	11920 (76.39)	10570 (77.79)	1350 (66.96)
Black	1205 (7.72)	932 (6.86)	273 (13.54)
Hispanic	1863 (11.94)	1550 (11.41)	313 (15.53)
Other/unknown	616 (3.95)	536 (3.94)	80 (3.97)
Donor Ethnicity			
African America	2593 (16.62)	2263 (16.65)	330 (16.37)
Other (non-African American)	13011 (83.38)	11325 (83.35)	1686 (83.63)
Donor Age			
>60 yr.	2101 (13.46)	2015 (14.83)	86 (4.27)
40-60 yr.	6161 (39.48)	5414 (39.84)	747 (37.05)
<40 yr.	7342 (47.05)	6159 (45.33)	1183 (58.68)
MELD score at liver wait-listing			
>35	2114 (13.55)	1928 (14.19)	186 (9.23)
31-34	1975 (12.66)	1752 (12.89)	223 (11.06)
21-30	5435 (34.83)	4634 (34.10)	801 (39.73)
≤20	5946 (38.11)	5163 (38.00)	783 (38.84)
Unknown	134 (0.86)	111 (0.82)	23 (1.14)
MELD score at transplant			
>35	3606 (23.11)	3121 (22.97)	485 (24.06)
31-34	2615 (16.76)	2220 (16.34)	395 (19.59)
21-30	5771 (36.98)	4893 (36.01)	878 (43.55)
≤20	3599 (23.06)	3341 (24.59)	258 (12.80)
Unknown	13 (0.08)	13 (0.10)	0 (0.00)
Recipient BMI at listing			
≥30 kg/sq. m.	6348 (40.68)	5596 (41.18)	752 (37.30)
26- <30 kg/sq m	4143 (26.55)	3635 (26.75)	508 (25.20)

21-25 kg/sq m	4157 (26.64)	3562 (26.21)	595 (29.51)
<21 kg/sq m	891 (5.71)	736 (5.42)	155 (7.69)
Unknown	65 (0.42)	59 (0.43)	6 (0.30)
Recipient Citizenship			
US	15118 (96.89)	13185 (97.03)	1933 (95.88)
Non-US	486 (3.11)	403 (2.97)	83 (4.12)
Recipient Diabetes History			
Yes	4575 (29.32)	3743 (27.55)	832 (41.27)
No	10767 (98.32)	9602 (70.67)	1165 (57.79)
Unknown	262 (1.68)	243 (1.79)	19 (0.94)
Cold Ischemia Time, Liver			
0-5 Hours	5870 (37.62)	5049 (37.16)	821 (40.72)
6-10 Hours	7948 (50.94)	6978 (51.35)	970 (48.12)
≥11 hours	1062 (6.81)	932 (6.86)	130 (6.45)
Unknown	724 (4.64)	629 (4.63)	95 (4.71)
Pre-transplant Wait list duration			
0- ≤ 6 months	12781 (81.91)	11421 (84.05)	1360 (67.46)
6 months- ≤ 1 yr	1379 (8.84)	1072 (7.89)	307 (15.23)
1 yr.- ≤ 2 years	891 (5.71)	678 (4.99)	213 (10.57)
> 2 years	553 (3.54)	417 (3.07)	136 (6.75)
Recipient on life support			
Yes	14254 (91.35)	12408 (91.32)	1846 (91.57)
No	1350 (8.65)	1180 (8.68)	170 (8.43)
GFR at wait-listing (MDRD, ml/min)			
0-14	1128 (7.23)	783 (5.76)	345 (17.11)
15-29	3838 (24.60)	2990 (22.00)	848 (42.06)
30-59	10638 (68.17)	9815 (72.23)	823 (40.82)
GFR, transplant (MDRD, ml/min)			
0-14	1891 (12.12)	1230 (9.05)	661 (32.79)
15-29	4916 (31.50)	3985 (29.33)	931 (46.18)
30-59	8784 (56.29)	8360 (61.52)	424 (21.03)
Missing	13 (0.08)	13 (0.10)	0 (0.00)
Previous Liver Transplant			
Yes	1697 (10.88)	1386 (10.20)	311 (15.43)
No	13907 (89.12)	12202 (89.80)	1705 (84.57)
Primary liver disease [b]			
1. Hepatitis C virus	4111 (26.35)	3560 (26.21)	551 (27.33)
2. Alcoholic liver disease	3017 (19.34)	2665 (19.62)	352 (17.46)
3. Hepatocellular Carcinoma	380 (2.44)	347 (2.55)	33 (1.64)
4. Other Diagnoses	6881 (44.11)	5964 (43.91)	917 (45.49)
5. Missing/Unknown	1210 (7.76)	1047 (7.71)	163 (8.09)
Transplant year			
2002-2008	6914 (44.31)	6119 (45.03)	795 (39.43)
2009-2016	8690 (55.69)	7469 (54.97)	1221 (60.57)

Partial or Split liver transplant	149 (0.96)	125 (0.92)	24 (1.19)
Whole liver transplant	15454 (99.05)	13462 (99.08)	1992 (98.81)
Unknown	1 (0.01)		
Donation after cardiac death (DCD)	665 (4.26)	581 (4.28)	84 (4.17)
Non-DCD Donor	14939 (95.74)	13007 (95.72)	1932 (95.83)

[a] Based-on Organ Procurement Transplantation Network Data.

[b] **Other diagnoses include:** PBC, Primary Biliary Cirrhosis; PSC, Primary Sclerosing Cholangitis, Non-alcoholic Steatohepatitis; hepatitis B; Non-A Non-B hepatitis; chronic active hepatitis, autoimmune hepatitis.

Abbreviations: MELD, model of end stage liver disease: BMI, body mass index; US, United States; GFR, glomerular filtration rate MDRD, modification of diet in renal disease.

Annual SLKTs as a percent of total liver transplants are depicted in Figure 1. Transplant centers in the lowest tercile had the highest percentage of SLKTs in 11 of the 14 years studied. Mid-tercile centers had the highest percentage of SLKTs in three (2006, 2010, and 2011) and the highest tercile centers had the highest percentage of SLKTs in one (2014) year. Linear trend analysis showed that mid-tercile centers are 22% less likely, and high tercile centers 28% less likely to perform SLKT vs. LTA than low tercile centers, respectively (Mantel-Haenszel Chi-square for linear trend $p < 0.0001$, Figure 1). Univariable and multivariable regression analyses consistently showed that (relative to low-tercile centers) mid-and high-tercile centers were associated with lower odds of SLKT in ESLD patients with CKD stage 3-5, NOD (Figure 2 and Figure 3).

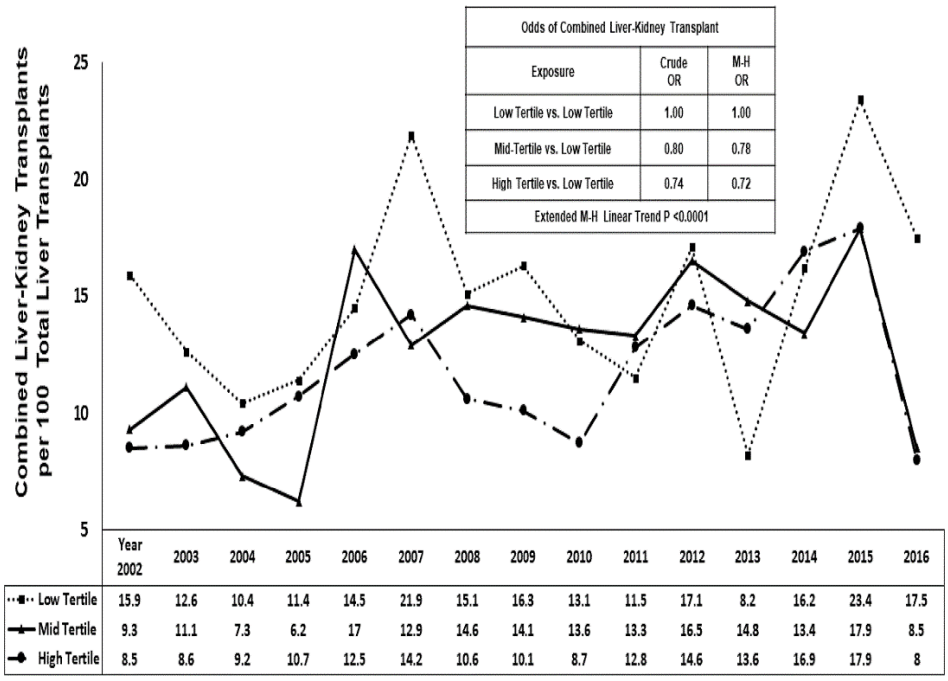

Figure 1 Annual Simultaneous Liver-Kidney Transplant Rates Depicted as Percent of Total Liver Transplants in Surgical Volume Terciles.

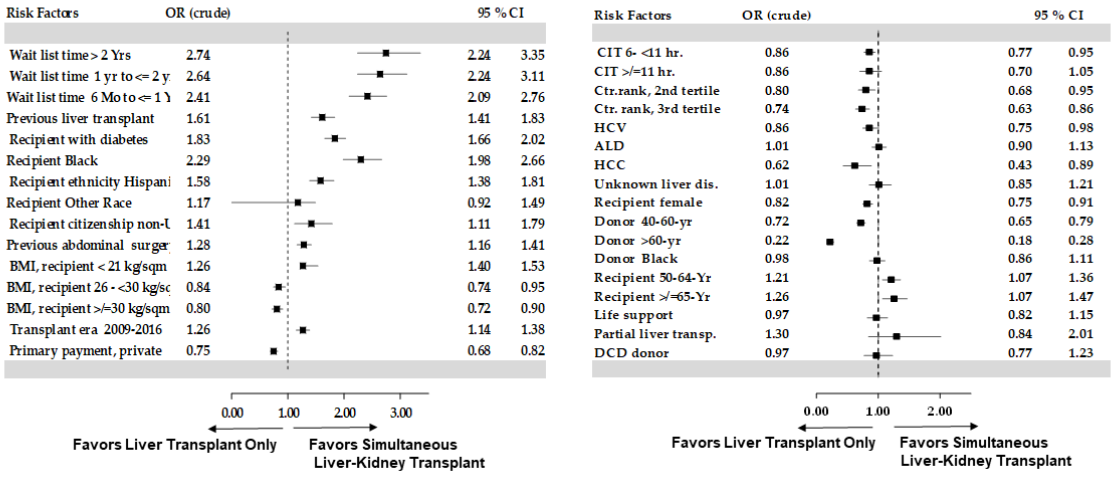

Figure 2 Crude Association of Risk Factors with Odds of Simultaneous Liver and Kidney Transplantation. OR, odds ratio; CI, confidence interval Liver and Kidney Transplantation; CIT, cold ischemia time; HCV, hepatitis C virus; ALD, alcoholic liver disease; HCC, hepatocellular carcinoma; DCD, donation after cardiac death.

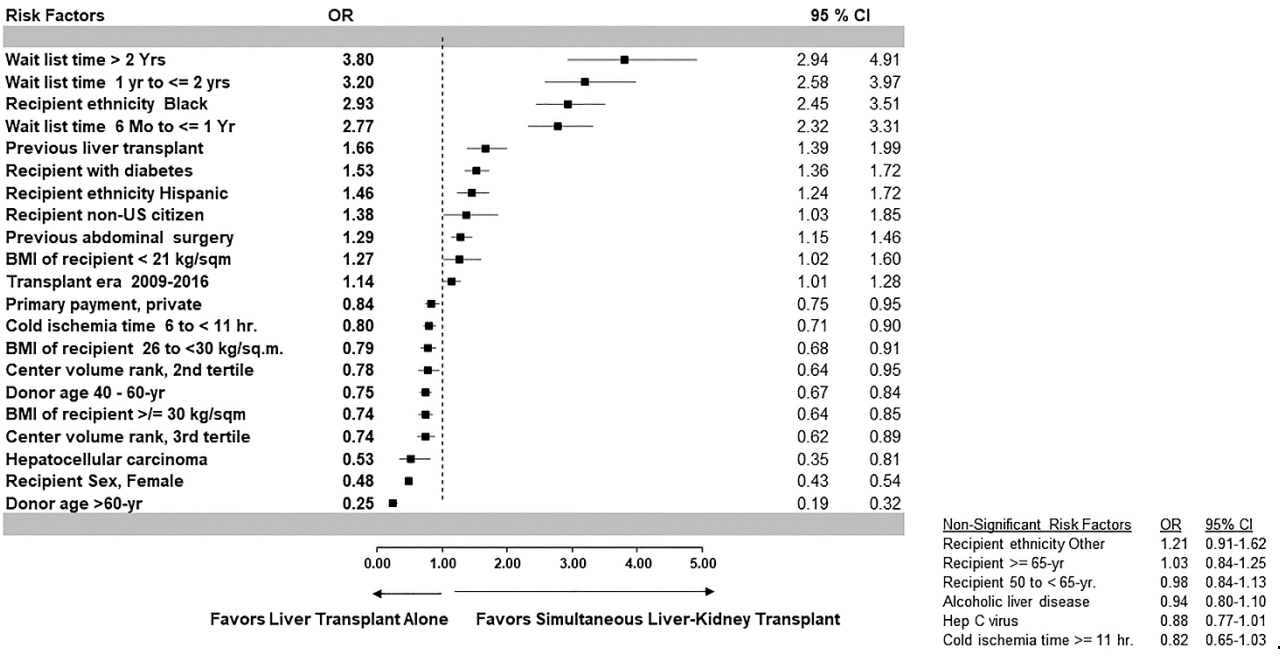

Figure 3 Adjusted Association of Non-Renal Factors with Odds of Simultaneous Liver and Kidney Transplantation. OR, odds ratio; CI, confidence interval Liver and Kidney Transplantation; BMI, body mass index.

Factors not significantly associated with SLKT or LTA on univariable analysis (Figure 2) included repeat transplant, life support, other recipient race/ethnicity, partial or split liver transplant, donor race/ethnicity, DCD donor, liver cold ischemia time ≥11 hours (vs. <6 hours), and ESLD due to alcoholic liver disease or unknown cause. Factors with significant association with SLKT or LTA on

univariable but not on multivariable analysis were recipient age and ESLD due to hepatitis C virus (Figure 2 and Figure 3).

Significant predictors of SLKT vs LTA based on a single multivariable logistic regression analysis are separately presented as 1. renal (creatinine-related) risk factors (Figure 4), and 2. non-renal risk factors (Figure 3). The renal (creatinine-related) risk factor associated with a higher likelihood of SLKT vs. LTA were eGFRs at wait listing and transplant of <15 ml/min *(OR = 8.25, 95% CI = 6.59-10.32 and OR = 6.60, 95% CI = 5.50-7.93; respectively)* and 15-29 ml/min *(OR = 4.78, 95% CI = 4.11-5.51 and OR = 3.26, 95% CI = 2.82-3.77; respectively),* (Figure 4). The association of the MELD score (also a creatinine-related risk factor) with SLKT or LTA depended on the time of its determination. MELD score categories equal or above 21 at liver transplant waitlisting were associated with a lower likelihood of SLKT, while the same (MELD ≥ 21) score categories at the time of liver transplant were associated with a higher likelihood of SLKT (Figure 4).

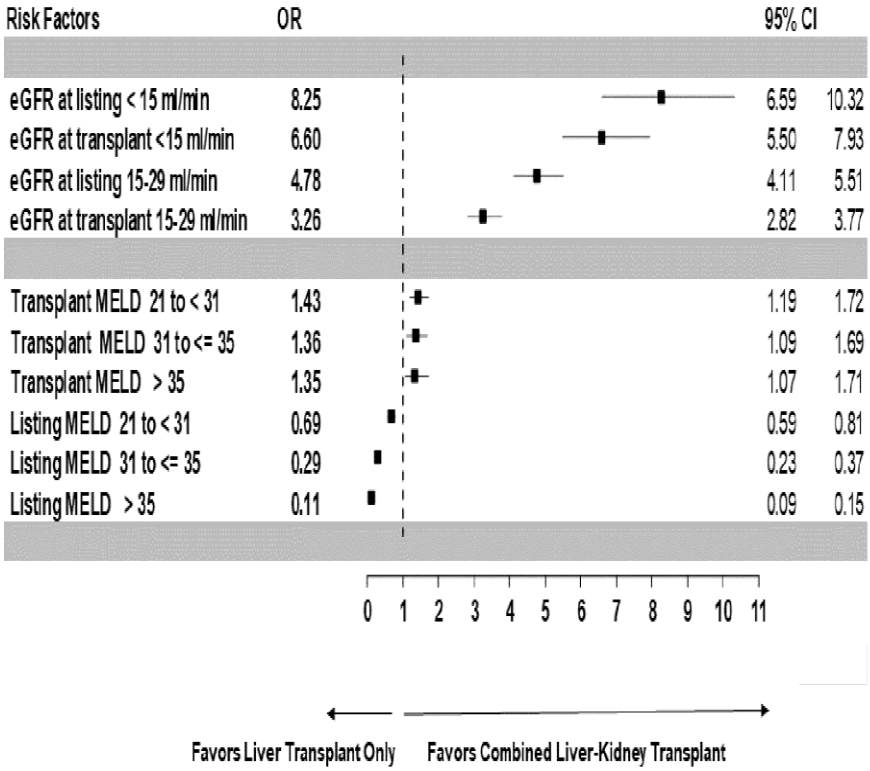

Figure 4 Adjusted Association of Renal Factors with Odds of Simultaneous Liver and Kidney Transplantation. OR, odds ratio; CI, confidence interval Liver, and Kidney Transplantation; eGFR, estimated glomerular filtration rate; MELD, model of end-stage liver disease score.

Non-renal risk factors with strong association to SLKT were time spent on the transplant waitlist [>2 years (*OR = 3.80, 95% CI = 2.94-4.91*), 1-2 years (*OR = 3.20, 95% CI = 2.58-3.97*) and 0.5-1-year (*OR = 2.77, 95% CI = 2.32-3.10*)]; recipient's African American or Hispanic (vs. White) race/ethnicity (OR = 2.93, 95% CI = 2.45-3.51 and OR = 1.46, 95% CI = 1.24-1.72; respectively); previous liver transplant (OR = 1.66, 95% CI = 1.39-1.99); and history of diabetes (OR = 1.53, 95% CI = 1.36-1.72). Other non-renal risk factors associated with SLKT were non-US citizen status, BMI <21 kg/sq. m.; and transplantation during the 2009-2016 (vs. 2000-2015) inclusive period (Figure 3).

Non-renal risk factors associated with a lower likelihood of SLKT (and conversely, higher likelihood of LTA) included donors aged 40-60 years and >60 years; female recipient sex, obese or overweight recipient BMI, and ESLD due to hepatocellular carcinoma; private insurance payer; and high-or mid-tercile liver transplant volume of transplant center (Figure 3).

5. Discussion

The number of SLKTs performed in the USA has been increasing and the relative proportion of liver transplants performed as part of an SLKT has increased steadily, from 2.7% in 2000 to 9.3% in 2016 [4]. This study was conducted to identify non-renal risk factors associated with increased likelihood of SLKT vs. LTA in liver transplant recipients with CKD stage 3-5 and not on maintenance dialysis (NOD) at the time of waitlisting and transplant. Non-renal risk factors associated with increased likelihood of SLKT were duration of time on the transplant waitlist; recipient's African American or Hispanic race /ethnicity, previous liver transplant, diabetes, non-US citizenship, low BMI (<21 kg/sq. m.); and later transplantation era (Figure 3). The renal (creatinine-related) risk factors associated with a higher likelihood of SLKT vs. LTA were eGFR categories <30 ml/min at wat-listing and transplant and high MELD score at transplant (Figure 4).

The higher likelihood of SLKT vs. LTA in African American and Hispanic vs. White liver transplant candidates with CKD stage 3-5, not on dialysis could be due to the higher incidence of advanced kidney disease [23-25], uncontrolled hypertension [26], diabetes [27], and obesity [28] in the former vs latter racial/ethnic groups. Non-Hispanic African American and Hispanic patients were more likely to receive a SLKT than non-Hispanic White patients due to their listing at more advanced liver disease stages stemming from barriers to early referral as well as lower eGFR [29]. In a study where, African American race/ethnicity was associated with higher rates of SLKT vs. LTA, the authors raised the concern of potential bias towards African American patients due to the perception that they have a faster decline of renal function and progression of CKD following LTA [30]. Consistent with findings in other studies, the current study also found that diabetes, male sex, or previous liver transplant were associated with a higher likelihood of a SLKT vs. LTA [15, 16, 30, 31]. The findings may be explained by the association of diabetes with chronic kidney disease [28], male sex with faster decline of GFR and progression in CKD [30], and previous liver transplant with calcineurin-inhibitor associated nephrotoxicity [32].

A previous study encompassing the period 1992-2005 found that non-US citizen liver transplant recipients (LTRs) had superior outcomes compared to US citizen LTRs [22]. A novel finding of the current study is the association of non-US citizen status of LT candidates with a higher likelihood of SLKT than US citizens. In the 14-year study period, 3.1% of the overall LT recipients were non-US citizens while 96.9% were US citizens. However, SLKT was proportionally higher in non-US citizens (17.1%) compared with US citizens (12.8%), (Table 1). Crude and adjusted analyses showed that non-US citizens had 41% and 38% higher odds, respectively than US citizens to receive SLKT (Figure 2 and Figure 3, respectively). The results could be related to the higher prevalence of comorbid advanced CKD in non-US citizens with ESLD due to higher incidence of diabetes [33], lower private insurance coverage rates [34-36], and delayed access to dialysis [37].

Characteristics associated with decreased likelihood of an SLK transplant on adjusted multivariable analyses including donor age >60-year, female recipient sex, HCC diagnosis,

overweight or obese BMI, private payer, and prolonged cold liver ischemia time were present in a higher proportion of LTA recipients (Figure 3).

Time on the waitlist ≤6 months or a high MELD score (>35) was associated with an increased likelihood of LTA, while time on the waitlist longer than 6 months or a lower MELD score was associated with an increased likelihood of SLKT. Taken together, these findings suggest that sicker and more acutely ill patients who received life-saving liver transplants might have been deemed too decompensated to be able to tolerate a prolonged and complicated dual-organ transplant surgery. Additionally, the decision to proceed with LTA rather than SLKT could have been biased by previously reported increased risks of both post-transplant mortality and need for renal replacement therapy in high MELD SLKT recipients [23].

The association of transplant recipient's obesity with a reduced likelihood of SLKT may be related to clinicians' concerns regarding post-transplant complications of infections, wound dehiscence, biliary leak, and metabolic syndrome [38]. Similarly, a history of hepatocellular carcinoma reduced the likelihood of SLKT probably due to considerations of projected decreased recipient longevity and ability to tolerate immunosuppression [39, 40]. This study also confirmed that gender and racial disparities negatively impact access to SLKT as seen by other authors [29, 41, 42]. The lower likelihood of SLKT in female versus male ESLD patients correlated with the higher proportion (63.2%) of male SLKT recipients. This finding is consistent with a UNOS OPTN analysis showing that 54%-64% of SLKT recipients were male [42]. Unfavorable donor and organ characteristics of older age and cold ischemic time respectively were also associated with a lower likelihood of SLKT in the current study.

The association of the transplant center's high overall liver transplant volumes with a lower likelihood of SLKT in non-dialysis dependent CKD stage 3-5 patients while a novel finding was not inconsistent with the findings of Nadim et. al [7] that high-volume liver transplant centers were not lenient in using a shorter acute kidney injury duration or higher CKD eGFR threshold for SLKT.

Although not the focus of this study, it must be mentioned for completeness of study analysis that renal function reflected by eGFR of liver transplant candidates was the strongest risk factor associated with SLKT. Indeed, compared with CKD stage 3, CKD stage 5 at transplant listing and transplant surgery was associated with 8.25-and 6.60-times as high likelihood of SLKT compared with LTA, respectively; while CKD stage 4 at transplant listing and transplant surgery were associated with 4.78-and 3.26-times as high likelihood of SLKT compared with LTA respectively.

On the other hand, the MELD score, a combination of renal and liver-related laboratory test results, had disparate associations with the likelihood of SLKT or LTA depending on the time when it was derived. A higher MELD score at the time of listing for liver transplant was associated with a lower likelihood of SLKT in LT candidates not on dialysis probably because the high MELD score reflected poorer health and more debility that made a prolonged surgery untenable. However, the results may have been biased by study design as LT candidates requiring dialysis were excluded from the analyses so that potentially in the patients included in the analysis, the major drivers of their high MELD score at waitlisting were liver-rather than kidney-related parameters.

Limitations inherent on a database analysis apply to our study including incomplete data reporting and non-uniform definitions of clinical conditions including diagnoses. Some of our findings are novel and would require validation by future studies to be generalizable to transplants under the SLK allocation system implemented since late 2017. Due to the retrospective nature of

our study, our findings can only establish associations and not causality, can only be considered as hypothesis generating, and cannot be the basis for changing clinical practice.

In conclusion, in patients with ESLD and CKD stage 3-5, not on dialysis, strong non-renal predictors of SLKT were candidate's longer waitlist time, previous liver transplant, diabetes mellitus, African American or Hispanic race/ethnicity, non-US citizenship, and low BMI. The unexpected association of the center's overall liver transplant volume and recipient's citizenship status to the likelihood of SLKT need further study for confirmation.

Acknowledgments

The data reported here have been supplied by the United Network for Organ Sharing as the contractor for the Organ Procurement and Transplantation Network. This work was supported in part by Health Resources and Services Administration contract HHSH250-2019-00001C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. We would like to thank Mr. Jon Gregg for his assistance in data management and statistical analyses.

Author Contributions

Dr. A Santos- conceived and designed the study; drafted and revised the manuscript. Dr. A. Belal- revised the manuscript. Dr. H. Ibrahim- revised the manuscript. Dr. M. Leghrouz-revised the manuscript.

Competing Interests

The authors report no conflict of interest.

References

1. Formica RN, Aeder M, Boyle G, Kucheryavaya A, Stewart D, Hirose R, et al. Simultaneous liver-kidney allocation policy: A proposal to optimize appropriate utilization of scarce resources. Am J Transplant. 2016; 16: 758-766.
2. Organ Procurement & Transplantation Network. National data [Internet]. Available from: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/.
3. Singal AK, Ong S, Satapathy SK, Kamath PS, Wiesner RH. Simultaneous liver-kidney transplantation. Transpl Int. 2019; 32: 343-352.
4. Miles CD, Westphal S, Liapakis A, Formica R. Simultaneous liver-kidney transplantation: Impact on liver transplant patients and the kidney transplant waiting list. Curr Transplant Rep. 2018; 5: 1-6.
5. Davis CL, Feng S, Sung R, Wong F, Goodrich NP, Melton LB, et al. Simultaneous liver-kidney transplantation: Evaluation to decision making. Am J Transplant. 2007; 7: 1702-1709.
6. Eason JD, Gonwa TA, Davis CL, Sung RS, Gerber D, Bloom RD. Proceedings of consensus conference on simultaneous liver kidney transplantation (SLK). Am J Transplant. 2008; 8: 2243-2251.

7. Nadim MK, Davis CL, Sung R, Kellum JA, Genyk YS. Simultaneous liver-kidney transplantation: A survey of US transplant centers. Am J Transplant. 2012; 12: 3119-3127.
8. Asch WS, Bia MJ. New organ allocation system for combined liver-kidney transplants and the availability of kidneys for transplant to patients with stage 4–5 CKD. Clin J Am Soc Nephrol. 2017; 12: 848-852.
9. Organ Procurement & Transplantation Network. Simultaneous Liver Kidney (SLK) Allocation. Available from: https://optn.transplant.hrsa.gov/media/1888/kidney_policynotice_slk_201606.pdf.
10. Tanriover B, MacConmara MP, Parekh J, Arce C, Zhang S, Gao A, et al. Simultaneous liver-kidney transplantation in liver transplant candidates with renal dysfunction: Importance of creatinine levels, dialysis, and organ quality in survival. Kidney Int Rep. 2016; 1: 221-229.
11. Enestvedt CK. PRO: Simultaneous liver-kidney transplantation in the current era: Still the best option. Clin Liver Dis. 2020; 16: 266-271.
12. Cullaro G, Hirose R, Lai JC. Changes in simultaneous liver kidney transplant allocation policy may impact post liver transplant outcomes. Transplantation. 2019; 103: 959-964.
13. Baccaro ME, Pépin MN, Guevara M, Colmenero J, Torregrosa JV, Martín-Llahí M, et al. Combined liver–kidney transplantation in patients with cirrhosis and chronic kidney disease. Nephrol Dial Transplant. 2010; 25: 2356-2363.
14. Modi RM, Tumin D, Kruger AJ, Beal EW, Hayes Jr D, Hanje J, et al. Effect of transplant center volume on post-transplant survival in patients listed for simultaneous liver and kidney transplantation. World J Hepatol. 2018; 10: 134-141.
15. Yadav K, Serrano OK, Peterson KJ, Pruett TL, Kandaswamy R, Bangdiwala A, et al. The liver recipient with acute renal dysfunction: A single institution evaluation of the simultaneous liver-kidney transplant candidate. Clin Transplant. 2018; 32: e13148.
16. Mindikoglu AL, Raufman JP, Seliger SL, Howell CD, Magder LS. Simultaneous liver-kidney versus liver transplantation alone in patients with end-stage liver disease and kidney dysfunction not on dialysis. Transplant Proc. 2011; 43: 2669-2677.
17. Cullaro G, Sharma P, Jo J, Rassiwala J, VanWagner LB, Wong R, et al. Temporal trends and evolving outcomes after simultaneous liver-kidney transplantation: Results from the US SLKT Consortium. Liver Transplant. 2021; 27: 1613-1622.
18. UNOS. Simultaneous liver-kidney allocation (SLK) policy changes now in effect [Internet]. Available from: https://unos.org/news/simultaneous-liver-kidney-allocation-slk-policy-changes-now-in.
19. Bittermann T, Hubbard RA, Lewis JD, Goldberg DS. The proportion of model for end-stage liver disease sodium score attributable to creatinine independently predicts post-transplant survival and renal complications. Clin Transplant. 2020; 34: e13817.
20. Skluzacek PA, Szewc RG, Nolan III CR, Riley DJ, Lee S, Pergola PE. Prediction of GFR in liver transplant candidates. Am J Kidney Dis. 2003; 42: 1169-1176.
21. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. Source Code Biol Med. 2008; 3: 17.
22. Butler T, Rana A, Garfinkel M. Non-US citizen liver transplant recipients (LTR) have superior outcomes compared to US citizen LTR: A retrospective study of 50,422 subjects using the Organ Procurement and Transplant Network (OPTN) from 1992-2015. Am J Transplant. 2018; 18: 569.

23. Lunsford KE, Bodzin AS, Markovic D, Zarrinpar A, Kaldas FM, Gritsch HA, et al. Avoiding futility in simultaneous liver-kidney transplantation. Ann Surg. 2017; 265: 1016-1024.
24. Nee R, Agodoa L. Chapter 8-Racial differences in kidney disease and end-stage kidney disease in the USA. In: Chronic kidney disease in disadvantaged populations. Academic Press; 2017. pp. 65-75.
25. United States Renal Data System. 2021 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2021. Available from: https://www.ajkd.org/article/S0272-6386(22)00453-X/fulltext.
26. Aggarwal R, Chiu N, Wadhera RK, Moran AE, Raber I, Shen C, et al. Racial/ethnic disparities in hypertension prevalence, awareness, treatment, and control in the United States, 2013 to 2018. Hypertension. 2021; 78: 1719-1726.
27. Canedo JR, Miller ST, Schlundt D, Fadden MK, Sanderson M. Racial/ethnic disparities in diabetes quality of care: The role of healthcare access and socioeconomic status. J Racial Ethn Health Disparities. 2018; 5: 7-14.
28. Petersen R, Pan L, Blanck HM. Racial and ethnic disparities in adult obesity in the United States: CDC's tracking to inform state and local action. Prev Chronic Dis. 2019; 16: E46.
29. Chang SH, Wang M, Liu X, Alhamad T, Lentine KL, Schnitzler MA, et al. Racial/ethnic disparities in access and outcomes of simultaneous liver-kidney transplant among liver transplant candidates with renal dysfunction in the United States. Transplantation. 2019; 103: 1663-1674.
30. Luo X, Massie AB, Haugen CE, Choudhury R, Ruck JM, Shaffer AA, et al. Baseline and center-level variation in simultaneous liver-kidney listing in the United States. Transplantation. 2018; 102: 609-615.
31. Sharma P, Shu X, Schaubel DE, Sung RS, Magee JC. Propensity score-based survival benefit of simultaneous liver-kidney transplant over liver transplant alone for recipients with pretransplant renal dysfunction. Liver Transplant. 2016; 22: 71-79.
32. Pillebout E, Nochy D, Hill G, Conti F, Antoine C, Calmus Y, et al. Renal histopathological lesions after orthotopic liver transplantation (OLT). Am J Transplant. 2005; 5: 1120-1129.
33. Hsueh L, Wu W, Hirsh AT, de Groot M, Mather KJ, Stewart JC. Undiagnosed diabetes among immigrant and racial/ethnic minority adults in the United States: National health and nutrition examination survey 2011-2018. Ann Epidemiol. 2020; 51: 14-19.
34. Kaiser Family Foundation. Health coverage of immigrants [Internet]. San Francisco: Kaiser Family Foundation; 2022. Available from: https://www.kff.org/racial-equity-and-health-policy/fact-sheet/health-coverage-of-immigrants.
35. Ku L, Jewers M. Health care for immigrant families: Current policies and issues. Washington, DC: Migration Policy Institute; 2013.
36. Lee BP, Terrault NA. Liver transplantation in unauthorized immigrants in the United States. Hepatology. 2020; 71: 1802-1812.
37. Cervantes L, Johnson T, Hill A, Earnest M. Offering better standards of dialysis care for immigrants: The Colorado example. Clin J Am Soc Nephrol. 2020; 15: 1516-1518.
38. Spengler EK, O'Leary JG, Te HS, Rogal S, Pillai AA, Al-Osaimi A, et al. Liver transplantation in the obese cirrhotic patient. Transplantation. 2017; 101: 2288-2296.
39. Singal AK, Salameh H, Kuo YF, Wiesner RH. Evolving frequency and outcomes of simultaneous liver-kidney transplants based on liver disease etiology. Transplantation. 2014; 98: 216-221.

40. Khorsandi SE, Heaton N. Optimization of immunosuppressive medication upon liver transplantation against HCC recurrence. Transl Gastroenterol Hepatol. 2016; 1: 25.
41. Peschard G, Wang M, Al-Hosni Y, Lentine K, Chang S, Alhamad T. Simultaneous liver and kidney transplantation and gender disparities in transplant access and outcomes. Am J Transplant. 2022; 22: 867-868.
42. Goyes D, Nsubuga JP, Medina-Morales E, Patwardhan V, Bonder A. New OPTN simultaneous liver-kidney transplant (SLKT) policy improves racial and ethnic disparities. J Clin Med. 2020; 9: 3901.