ORIGINAL ARTICLE

Liver alone or simultaneous liver–kidney transplant? Pretransplant chronic kidney disease and post-transplant outcome – a retrospective study

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SUMMARY

The new Organ Procurement and Transplant Network/United Organ Sharing Network (OPTN/UNOS) simultaneous liver–kidney transplant (SLK) policy has been implemented. The aim of this study was to review liver transplant outcomes utilizing the new SLK policy. Liver transplant alone (LTA) and SLK patients between 2009 and 2015 were reviewed. Graft survival and post-transplant kidney function were investigated among LTA patients meeting the chronic kidney disease (CKD) criteria of the new policy (LTA-CKD group). To validate our findings, we reviewed and applied our analysis to the OPTN/UNOS registry. A total of 535 patients were eligible from our series. The LTA-CKD group (n = 27) showed worse 1-year graft survival, compared with the SLK group (n = 44), but not significant (81% vs. 93%, P = 0.15). The LTA-CKD group significantly increased a risk of post-transplant dialysis (odds ratio = 5.59 [95% CI = 1.27–24.7], P = 0.02 [Ref. normal kidney function]). Post-transplant dialysis was an independent risk factor for graft loss (hazard ratio = 7.25, 95% CI = 3.3–15.91, P < 0.001 [Ref. SLK]). In the validation analysis based on the OPTN/UNOS registry, the hazard of 1-year-graft loss in the LTA-CKD group (n = 751) was 34.8% higher than the SLK group (n = 2856) (hazard ratio = 1.348, 95% CI = 1.157–1.572, P < 0.001). Indicating SLK for patients who meet the CKD criteria may significantly improve transplant outcomes.

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Key words
chronic kidney disease, hepatorenal syndrome, liver–kidney transplantation, Organ Procurement and Transplant Network, United Organ Sharing Network

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Introduction

The fields of both liver and kidney transplant have attempted to confront the controversy surrounding the topic of simultaneous liver–kidney transplantation (SLK) [1–4]. The number of SLK's in the USA has been increasing over the past 10 years. SLK candidates on the waitlist accounted for 2.0% (307/15 728) in 2005, and 6.6% (926/14 047) in 2015. The number of patients who underwent SLK accounted for 5.6% (329/5875) in

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2005 and 9.4% (613/6547) in 2015 of all liver transplants [5]. Previously, the Organ Procurement and Transplant Network (OPTN) Kidney and Liver Intestinal Organ Transplantation Committees set forth a proposal for minimal kidney listing criteria for candidates listed for SLK. However, these recommendations did not become the OPTN policy. Because of the lack of medical criteria, there were concerns about the allocation of high-quality kidneys to liver candidates who may regain renal function after liver transplant and decreased access for kidney-alone candidates who would otherwise be highly prioritized in deceased donor kidney allocation [6].

In 2016, the final proposal was approved, and the current SLK allocation policy by OPTN/United Network Organ Sharing (UNOS) was implemented in August 2017, which requires that the allocation of a kidney is dependent on either (i) the duration of the low glomerular filtration rate (GFR) (chronic kidney disease [CKD] criteria: GFR ≤60 ml/min for >90 consecutive days and ≤30 ml/min at registration), (ii) a sustained acute kidney injury (AKI criteria), or (iii) metabolic disease. Additionally, the policy includes a "safety net" in the post-transplant period for recipients of liver transplant alone (LTA), which gives additional priority for offers of kidney alone in patients where the kidney function does not recover post-LTA (Table 1) [7–9].

Patients listed for liver transplant at our institution were potentially candidates for a SLK primarily based on one of two criteria: (i) any patient, but especially patients with hepatorenal syndrome (HRS) type 1, who had received renal replacement therapy for at least 28 days. (ii) patients with CKD or HRS type 2 with a GFR persistently at or below 30 ml/min without a reversible etiology. We reviewed our recent SLK experience and compared the outcomes of SLK and LTA, specifically in patients with pretransplant renal dysfunction, to investigate the impact of the new OPTN/UNOS SLK policy. The aims of this study were to investigate the impact of pretransplant CKD on liver transplant outcomes and review single-center outcomes of SLK versus LTA alone. In addition, we used the OPTN/UNOS transplant registry as a validation set to confirm our findings.

Methods

Study population

We retrospectively reviewed medical records of patients who underwent LT at our center between January 2009 and December 2015. Patients who received primary deceased donor LT for either LTA or SLK were included. Patients who underwent living donor liver transplant or liver retransplant were excluded. This

Table 1. Current Organ Procurement and Transplant Network/United Organ Sharing Network simultaneous liver–kidney transplant policy.

OPTN Kidney Transplantation Committee Policy 9.7: Liver-Kidney Allocation (2016)*	a. CKD with a measured or calculated GFR less than or equal to 60 ml/min for greater than 90 consecutive days At least *one* of the following: • That the candidate has begun regularly administered dialysis as an end-stage renal disease patient in a hospital-based, independent non-hospital-based, or home setting • At the time of registration on the kidney waiting list, that the candidate's most recent measured or calculated creatinine clearance (CrCl) or GFR is less than or equal to 30 ml/min • On a date after registration on the kidney waiting list, that the candidate's measured or calculated CrCl or GFR is less than or equal to 30 ml/min. b. Sustained acute kidney injury At least *one* of the following, or a combination of both of the following, for the last 6 weeks: • That the candidate has been on dialysis at least once every 7 days. • That the candidate has a measured or calculated CrCl or GFR less than or equal to 25 ml/min at least once every 7 days. c. Metabolic disease

*Ref. #7. Available at https://optn.transplant.hrsa.gov/governance/public-comment/simultaneous-liver-kidney-allocation-2016/.

study was approved by the Institutional Review Board at Henry Ford Hospital (#11068).

Evaluation of pretransplant kidney function

Pretransplant kidney function was assessed by calculating the estimated GFR (eGFR) using the Modifications of Diet in Renal Disease 4 (MDRD 4) study equation [10]. A duration for an eGFR ≤60 ml/min was calculated. The beginning and end dates of pretransplant dialysis were identified. When considering SLK, the patient's pretransplant dialysis requirements and history of CKD were independently evaluated by transplant nephrologists. Considerations for SLK in our center include: (i) any patient, but especially patients with HRS type 1, who had received renal replacement therapy for at least 28 days. (ii) CKD or HRS type 2 with a GFR persistently at or below 30 ml/min without a reversible etiology. The criteria were applied in conjunction with transplant nephrology consultation. The final decision is made at the discretion of our liver and kidney transplant selection committees.

Intra-operative continuous renal replacement therapy

Patients who were on the list for LTA and had marginal kidney function were evaluated by transplant nephrologists and anesthesiologists prior to transplant for indications of intra-operative continuous renal replacement therapy (CRRT). Intra-operative CRRT was typically performed for patients who received SLK and continued until the kidney graft was reperfused. Intra-operative emergency CRRT was considered in cases of intra-operative severe acidosis and/or elevated potassium secondary to acute renal failure during a LT surgery.

Post-transplant management and follow-up

Per our standard practice, rabbit anti-thymocyte globulin (0.5 mg/kg, three doses) was used as our standard induction immunosuppression. An alternative regimen of basiliximab induction (20 mg, two doses) was used for select patients (select patients with liver cirrhosis secondary to hepatitis C infection) [11]. Maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil, and steroids. Tacrolimus was started between postoperative days (POD) 2 and 5, depending on kidney function. The target trough levels were 8–12 ng/ml during the first 3 months, 6–10 ng/ml between months 3 and 12, and 5–8 ng/ml after 12 months. Tacrolimus levels were maintained on the lower side of the range for patients with marginal kidney function. Mycophenolate mofetil was started at 500 mg twice a day and was withdrawn by 1 year, and corticosteroids were tapered off by 3 months, regardless of the type of organ graft(s).

Initiation of early, post-transplant dialysis was made based on clinical findings. Post-transplant kidney function was continuously monitored, and the eGFR at 3, 6, and 12 months was calculated using the MDRD formula and assessed based on the association with transplant type, the status of the pretransplant dialysis requirement, and the pretransplant kidney function. To account for false elevation of eGFR in patients on dialysis, their eGFRs were set at 15 ml/min for the purpose of comparison of eGFR among groups. eGFR of 15 ml/min was chosen as this is equivalent to the cutoff level of eGFR for Stage 5 CKD.

Early post-transplant dialysis: incidence and risk factors

The use of early post-transplant dialysis was examined. Correlation with pretransplant kidney function, recipient and donor characteristics, and surgical factors was assessed. Early post-transplant dialysis was defined as the initiation of dialysis within 30 days after the transplant. If dialysis was discontinued and resumed during a 1-week period, this entire period was included in calculation of the duration of dialysis. The prognostic impact of post-transplant dialysis was evaluated for 1-year graft survival. The impact of post-transplant dialysis on liver allograft dysfunction was assessed using the criteria for early liver allograft dysfunction reported by Olthoff *et al.* [12] (Table S1).

Survival analysis and risk factor analysis for early graft loss

Liver graft survival was compared by graft type (SLK versus LTA) and by pretransplant kidney function. Patients were categorized based on the eGFR at the time of transplant (>60, 31–60, and ≤30 ml/min) and the pretransplant duration of a low eGFR (≤60 ml/min for >90 days or not). Each case that met the sustained AKI and/or CKD criteria was retrospectively evaluated using the new UNOS SLK policy. In addition to SLK group, all LTA patients were classified as follows: (i) LTA-CKD group: patients who met the CKD criteria, (ii) LTA-severe kidney dysfunction group: LTA patients with an eGFR ≤30 ml/min who did not meet the CKD criteria, (iii) LTA-moderate kidney dysfunction group: LTA

patients with an eGFR 31–60 ml/min, and (iv) LTA-normal kidney function group: LTA patients with an eGFR >60 ml/min. Recipient, donor, and perioperative factors were evaluated for association with graft loss within 1 year.

Validation analysis by the OPTN/UNOS registry

To validate the results of this study, we used data from the OPTN/UNOS contained in the Standard Transplant Analysis and Research (STAR) file, which included waitlist and transplant data with the last follow-up date of December 1, 2017. The same inclusion criteria and study period were applied (primary deceased donor LT for either LTA or SLK between January 2009 and December 2015), and transplant outcomes were evaluated. Serum creatinine levels and dialysis requirement were recorded for the purpose of updating MELD scores in the STAR files. We calculated eGFR at all points recorded while patients were on the waitlist and estimated the populations who would have met the UNOS CKD criteria. Similarly, their eGFRs were set at 15 ml/min to account for false elevation of eGFR in patients on dialysis. Patients who met the inclusion criteria were categorized into five groups in the same way: (i) SLK, (ii) LTA-CKD, (iii) LTA-severe kidney dysfunction, (iv) LTA-moderate kidney dysfunction, and (v) LTA-normal kidney function. One-year graft survival rates were compared among these groups. By using this validation set, possible risk factors for 1-year graft loss in the LTA-CKD and SLK groups were investigated.

Statistical analysis

Data were summarized using the median with interquartile range (IQR) for continuous variables and using percentages for discrete variables. Comparisons of continuous variables and discrete variables were performed using the Mann–Whitney *U* test and a chi-square test, respectively. One-year graft survival time distributions were estimated using the Kaplan–Meier method, and differences in the curves were compared using a log-rank test. All graft losses were considered as events in these survival analyses. The analysis of factors associated with survival was performed using Cox's proportional hazards regression model. Association with post-transplant dialysis was evaluated using a logistic regression model. Significant variables with *P*-values <0.1 on the univariate model and ones clinically relevant to events were used to build the multivariable model. In the validation analysis, all variables were included in the multivariable model, because of the large number of patient cohort. The statistical analysis was completed using R (The R Foundation for Statistical Computing, Vienna, Austria), and the level of significance was set at 0.05.

Results

A total of 535 patients underwent primary deceased donor LT during the study period. The median follow-up time was 3.4 years (IQR, 1.9–5.0 years). Forty-four patients (8%) underwent SLK. The remaining 491 patients underwent LTA, with 72, 131 and 288 patients having an eGFR ≤30, 31–60, and >60 ml/min, respectively, at the time of transplant. Pretransplant dialysis was required in 30 of the 44 SLK patients (68%) and in 40 of the 72 patients (56%) with an eGFR ≤30 ml/min. Intra-operative CRRT was indicated for 34 SLK patients (77%), 42 patients with an eGFR ≤30 ml/min (58%), and four patients with an eGFR = 31–60 ml/min (3%). Emergency CRRT was indicated for these four patients with eGFR = 31–60 ml/min because of uncontrolled acidosis and hyperkalemia secondary to acute renal failure during the liver transplant surgery.

Of the 44 patients who underwent SLK, 21 met the sustained AKI criteria and 17 met the CKD criteria of the new UNOS SLK policy. Six SLK patients (14%) did not meet either of these criteria. Of these six patients, two required pretransplant dialysis over 28 days but less than 6 weeks. The rest of four patients were considered to have irreversible kidney function by LTA, and SLK was indicated at discretion of our transplant nephrologist's assessment. Seventy-two patients with a GFR ≤30 ml/min underwent LTA; 27 of them met the CKD criteria (LTA-CKD group). Based on this retrospective analysis, the new UNOS SLK policy, if applied, would increase SLK by 48% (+21/44, increased from 44 to 65 cases, +21 cases [27–6 cases] in 7 years, +3 cases/year) and raise SLK in the entire liver transplant cohort by 4% (21/535) at our center (Fig. S1).

Post-transplant kidney function

The post-transplant eGFRs at 3, 6, and 12 months were significantly worse in the LTA-CKD group than in the SLK group (47 vs. 72 ml/min at 3 months [$P < 0.001$], 52 vs. 62 ml/min at 6 months [$P = 0.006$] and 48 vs. 57 ml/min at 12 months [$P = 0.03$]). The LTA-severe kidney dysfunction group showed comparable eGFRs with those in the SLK group (56 ml/min [$P = 0.08$],

54 ml/min [$P = 0.23$], and 53 ml/min [$P = 0.9$] at 3, 6, and 12 months, respectively).

Post-transplant dialysis was required more frequently in the LTA-CKD group than in the SLK group (59% [16/27] vs. 27% [12/44], $P = 0.01$) (Fig. 1). The median duration of post-transplant dialysis was 8 days (IQR: 3–57 days) in the LTA-CKD group ($n = 16$), 9 days (IQR: 4–25 days) in the LTA-severe kidney dysfunction group ($n = 29$), 9 days (IQR: 2–24 days) in the LTA-moderate kidney dysfunction group ($n = 15$), and 54.5 days (IQR: 39–254 days) in the LTA-normal kidney function group ($n = 13$). Of the 73 LTA patients who required post-transplant dialysis, 17 remained on dialysis until their death or graft loss (14 deaths and three re-transplants). Of these patients, two (7%), four (9%), two (2%), and nine (3%) were in the LTA-CKD, LTA-severe kidney dysfunction, LTA-moderate kidney dysfunction, and LTA-normal kidney function groups, respectively. Liver retransplantation was indicated for liver graft failure in three patients on POD 25, 26, and 53, two of whom died of sepsis 34 and 45 days after the retransplant, respectively. Sepsis followed by multiorgan failure accounted for 76.5% (13/17) of the cause of death. Other causes of death included graft-versus-host disease in one, stroke in one, and unknown etiology in two. Of the 12 SLK patients who required post-transplant dialysis, the median duration of dialysis was 10.5 days (IQR: 6–28 days). Of these 12 patients, two patients had nonfunction of the kidney graft; one required dialysis up until time of death on POD 11, and another required it till the time of retransplant on POD 103. The cause of death of these two patients was sepsis. The remaining 10 patients developed delayed kidney graft function, and their transplant kidney function recovered eventually.

Potential for "safety net" kidney transplant after liver transplant alone

Thirteen LTA patients (3%, 13 of 491) would have met the UNOS criteria of "safety net" (on dialysis or an eGFR at or below 20 ml/min during 2–12 months post-LTA) [8]. Five of these patients died within 1 year and required dialysis until their deaths, and four patients consistently had an eGFR at or below 20 ml/min throughout the first year. The eGFRs at 12 months in the remaining four patients were 24, 25, 44, and 49 ml/min, respectively.

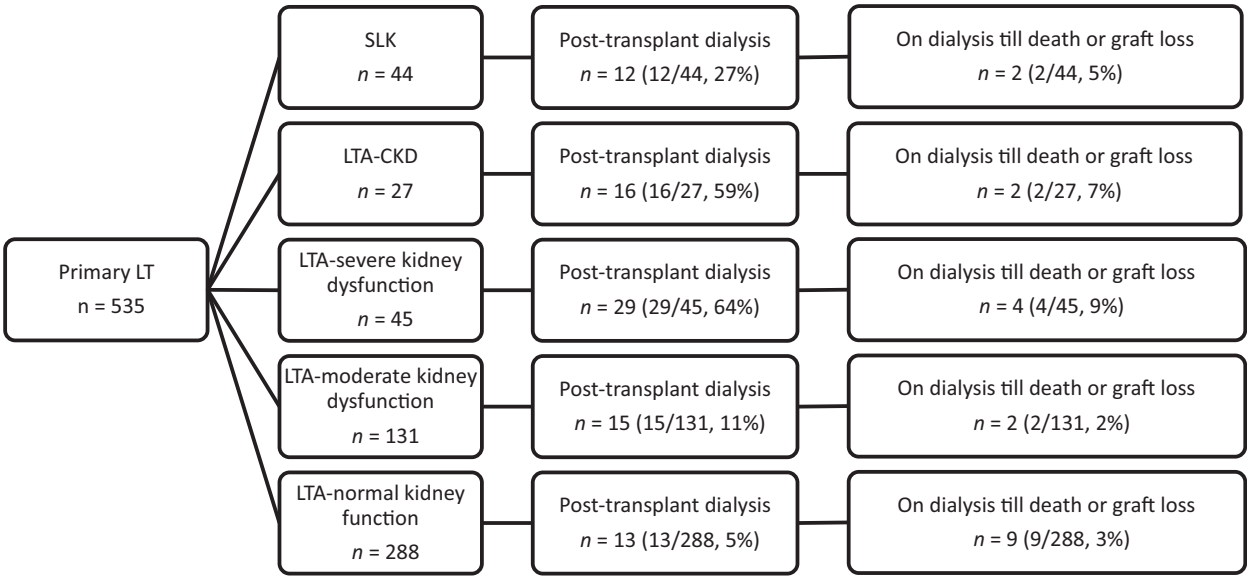

Figure 1 Requirement of post-transplant dialysis and graft loss associated with persistent renal failure. Simultaneous liver–kidney transplant (SLK) and liver transplant alone (LTA) patients classification as follows: (i) SLK group ($n = 44$), (ii) LTA-chronic kidney disease (CKD) group: patients who met the CKD criteria but did not have SLK ($n = 27$), (iii) LTA-severe kidney dysfunction group: LTA patients with an eGFR ≤30 ml/min who did not meet the CKD criteria ($n = 45$), (iv) LTA-moderate kidney dysfunction group: LTA patients with an eGFR 31–60 ml/min ($n = 131$), and (v) LTA-normal kidney function group: LTA patients with an eGFR >60 ml/min ($n = 288$). The LTA-CKD and LTA-severe kidney dysfunction groups showed significantly higher rates of post-transplant dialysis than the SLK group (59% [16/27], 64% [29/45] vs. 27% [12/44], $P = 0.01$ and <0.001, respectively). LTA-moderate kidney dysfunction and LTA-normal kidney function groups showed significantly lower rates of post-transplant dialysis than the SLK group (11% [15/131] and 5% [13/288] vs. 27% [12/44], $P < 0.001$ and <0.001, respectively)

Risk factors for post-transplant dialysis

Pretransplant dialysis was significantly associated with need for post-transplant dialysis ($P < 0.001$). Post-transplant dialysis was required in 90% of the LTA patients who required pretransplant dialysis. Risk factors for post-transplant dialysis were evaluated, specifically in LTA patients without pretransplant dialysis (Table 2). A large volume red blood cell transfusion (>10 units) (odds ratio = 2.85, $P = 0.02$), LTA-CKD (odds ratio = 5.59, $P = 0.02$), and LTA-severe kidney dysfunction (odd ratio = 7.77, $P = 0.01$) remained independent risk factors for post-transplant dialysis in this population. The requirement of post-transplant dialysis was significantly associated with early liver allograft dysfunction ($P = 0.03$).

Risk factors for 1-year graft loss

The LTA-CKD group showed a lower 1-year graft survival rate compared with the SLK group (81% vs. 93%, respectively, $P = 0.15$), but not significant (Fig. 2). When comparing the SLK with CKD group ($n = 17$) and LTA with CKD group ($n = 27$), 1-year graft survival rates were 100% and 81%, respectively ($P = 0.061$). In the LTA-CKD group, sepsis was the cause of death in four of five patients who died in the first year. Patients who required early post-transplant dialysis showed significantly lower graft survival rates compared with those who did not require post-transplant dialysis (69.9% vs. 90.9%, $P < 0.001$). The leading cause of death in patients who required post-transplant dialysis was sepsis (74%, 20 of 27 deaths). Possible risk

Table 2. Logistic regression analysis of possible risk factors for post-transplant dialysis after liver transplant alone without pretransplant dialysis ($n = 448$).

	No. of patients (%)	Odds ratio (95% CI)	Univariate *P**	Adjusted odds ratio (95% CI)	Multivariate *P**
Recipient age					
≥ 60 yo (Ref. <60 yo)	162 (36)	1.19 (0.59–2.42)	0.62		
Recipient sex					
Female (Ref. male)	162 (36)	2.24 (1.12–4.49)	0.02	1.61 (0.69–3.8)	0.27
Recipient race (Ref. Caucasian)					
African-American	70 (16)	1.7 (0.73–3.94)	0.22		
Hispanic	17 (4)	1.75 (0.38–8.11)	0.47		
Middle East	7 (2)	–	–		
Others	15 (3)	2.11 (0.45–9.94)	0.34		
MELD score					
≥30 (Ref. <30)	57 (13)	2.16 (0.93–5.02)	0.07	0.78 (0.24–2.64)	0.7
Primary liver disease					
HCV (Ref. non-HCV)	178 (44)	0.96 (0.48–1.93)	0.9		
Donor age					
≥40 yo (Ref. <40 yo)	253 (57)	1.52 (0.74–3.15)	0.25		
DCD donor (Ref. DBD)	54 (12)	0.23 (0.03–1.78)	0.16	0.59 (0.07–4.71)	0.62
Pretransplant kidney function (Ref. LTA-normal kidney function)					
LTA-CKD	15 (3)	7.69 (2.16–27.5)	0.001	5.59 (1.27–24.7)	0.02
LTA-severe kidney dysfunction	17 (4)	8.81 (2.7–28.8)	<0.001	7.77 (1.54–39.2)	0.01
LTA-moderate kidney dysfunction	128 (29)	2.39 (1.08–5.32)	0.03	1.74 (0.64–4.78)	0.28
CIT					
≥350 min (Ref. <350 min)	154 (43)	2.35 (1.07–5.13)	0.03	1.93 (0.8–4.66)	0.14
WIT					
≥33 min (Ref. <33 min)	269 (70)	4.09 (1.22–13.8)	0.02	3.45 (0.93–12.8)	0.06
Intra-operative PRBC + autologous transfusion					
>10 units (Ref. ≤10 units)	80 (21)	4.35 (2.03–9.35)	<0.001	2.85 (1.21–6.7)	0.02

CI, confidence interval; CIT, cold ischemia time; CKD, chronic kidney disease; DBD, donation after brain death; DCD, donation after cardiac death; LTA, liver transplant alone; MELD score, model for end-stage liver disease–sodium score; PRBC, packed red blood cell transfusion; WIT, warm ischemia time.

*Logistic regression model.

factors for early graft loss within 1-year post-transplant were analyzed (Table 3), revealing that post-transplant dialysis (hazard ratio [HR] = 7.25, $P < 0.001$) and CIT (HR = 1.4 per hour, $P = 0.005$) were considered to be independent risk factors.

Validation analysis with the OPTN/UNOS registry

A total of 38 933 patients met inclusion criteria from the OPTN/UNOS registry. There were 2856 patients (7.3%) in SLK group, 751 patients (1.9%) in LTA-CKD group, 5811 patients (14.9%) in LTA-severe kidney dysfunction, 7796 patients (20.0%) in LTA-moderate kidney dysfunction, and 21 719 patients (55.8%) in LTA-normal kidney function. These 751 patients in the LTA-CKD group would have received SLK, which might have increased SLK by 26.3% (+751/2856). This validation set was unable to assess patients who might or might not meet sustained AKI criteria, because of lack of information regarding pretransplant dialysis duration or pretransplant weekly eGRF.

The LTA-CKD group showed significantly worse 1-year graft survival than all other groups ($P < 0.001$) (Fig. 3a). The hazard of 1-year graft loss in the LTA-CKD group was 34.8% higher than the SLK group (HR = 1.348, 95% CI = 1.157–1.572, $P < 0.001$) (Table 4). Pretransplant kidney function in the SLK population was not associated with 1-year graft survival ($P = 0.484$) (Fig. 3b). When patients showed pretransplant CKD, SLK provided significantly better 1-year graft outcome than LTA. One-year graft survival rate in the LTA-CKD group was 82.0%, whereas 88.4% in the SLK with pretransplant CKD ($P < 0.001$).

A subgroup analysis demonstrated that donor age ≥40 years (HR = 1.447, 95% CI = 1.108–1.889, $P = 0.007$) and donation after cardiac death donor (HR = 2.321, 95% CI = 1.387–3.885, $P = 0.001$) were considered as independent risk factors for 1-year graft loss in the LTA-CKD group. In the SLK group, donor age ≥40 years (HR = 1.657, 95% CI = 1.421–1.932, $P < 0.001$) was regarded as independent risk factors for 1-year graft loss, along with MELD score ≥30 and hepatitis C (Table 5).

Discussion

Our results indicate that the new UNOS SLK policy applied at our center would increase the number of SLKs, decrease the risk of post-transplant dialysis, and potentially improve short-term outcomes in patients undergoing liver transplantation with marginal kidney function. Benefit of SLK would be more prominent, when they meet the CKD criteria in the new policy. Expanding SLK by the new policy could potentially

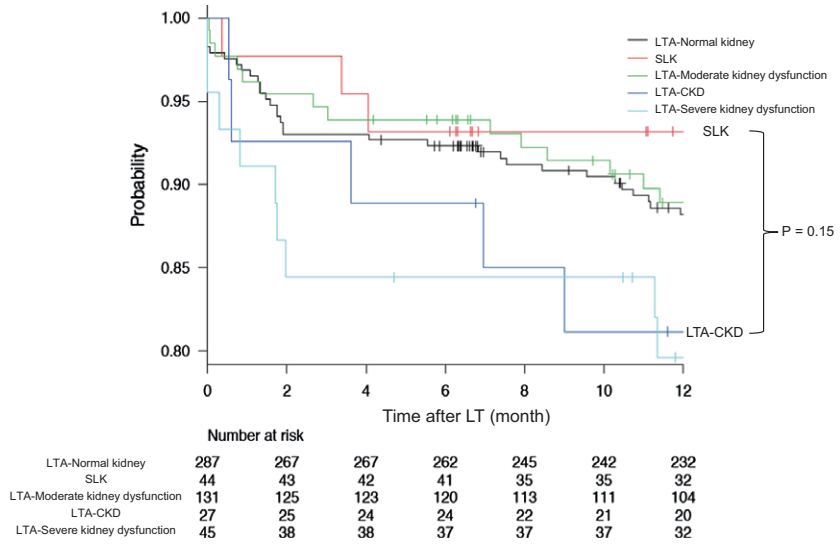

Figure 2 Graft survival up to 1 year according to graft type and pretransplant kidney function (single-center experience). Patients were categorized as follows. (i) Liver transplant alone (LTA)-normal kidney function group: LTA patients with an eGFR >60 ml/min (ii) simultaneous liver–kidney transplant (SLK) group, (iii) LTA-moderate kidney dysfunction group: LTA patients with an eGFR 31–60 ml/min, (iv) and LTA-chronic kidney disease (CKD) group: patients who met the CKD criteria, (v) LTA-severe kidney dysfunction group: LTA patients with an eGFR ≤30 ml/min who did not meet the CKD criteria. LTA-CKD group showed significantly worse 1-year graft survival rate, compared with the SLK group (81.2% vs. 93.2%, $P = 0.15$).

Table 3. Cox's regression analysis of possible risk factors for graft loss in the first year (single center).

	No. of patients (%)	Hazard ratio (95% CI)	Univariate *P**	Adjusted hazard ratio (95% CI)	Multivariate *P**
Recipient age					
≥60 yo (Ref. <60 yo)	196 (37)	0.98 (0.59–1.63)	0.94		
Recipient sex					
Female (Ref. male)	192 (36)	1.24 (0.76–2.05)	0.39		
Recipient race (Ref. Caucasian)					
African-American	88 (16)	0.61 (0.28–1.36)	0.23		
Hispanic	25 (5)	0.57 (0.14–2.34)	0.44		
Middle East	9 (2)	1.81 (0.44–7.43)	0.41		
Others	16 (3)	0.94 (0.23–3.88)	0.94		
MELD score					
≥30 (Ref. <30)	113 (21)	1.25 (0.71–2.19)	0.45		
Primary liver disease					
HCV (Ref. non-HCV)	206 (39)	0.78 (0.46–1.32)	0.36		
Donor age					
≥40 yo (Ref. <40 yo)	296 (55)	1.68 (1.0–2.83)	0.051	1.28 (0.62–2.63)	0.51
DCD donor (Ref. DBD)	58 (11)	0.37 (0.12–1.21)	0.1	1.7 (0.48–5.93)	0.41
Pretransplant dialysis w/o SLK (Ref. no pretransplant dialysis)	43 (7)	2.93 (1.56–5.48)	<0.001	2.23 (0.45–11.1)	0.33
Intra-operative CRRT w/o SLK (Ref. no intra-op CRRT)	47 (9)	2.34 (1.22–4.48)	0.01	0.27 (0.05–1.54)	0.14
Post-transplant dialysis (Ref. no post-transplant dialysis)	85 (16)	3.92 (2.37–6.49)	<0.001	7.25 (3.3–15.91)	<0.001
SLK (Ref.)	44 (8)				
LTA-CKD	27 (5)	2.76 (0.66–11.56)	0.16		
LTA-severe kidney dysfunction	45 (8)	3.05 (0.83–11.28)	0.09		
LTA-moderate kidney dysfunction	131 (24)	1.55 (0.44–5.38)	0.49		
LTA-normal kidney function	288 (54)	1.67 (0.51–5.44)	0.4		
CIT (per hour)	–	1.48 (1.21–1.82)	<0.001	1.4 (1.11–1.76)	0.005
WIT (per 10 min)	–	1.18 (0.9–1.54)	0.23		
Intra-operative PRBC + autologous transfusion (per unit)	–	1.05 (1.03–1.07)	<0.001	1.02 (0.99–1.05)	0.11

CI, confidence interval; CIT, cold ischemia time; CKD, chronic kidney disease; DBD, donation after brain death; DCD, donation after cardiac death; HCV, hepatitis C virus infection; LTA, liver transplant alone; MELD score, model for end-stage liver disease –sodium score; PRBC, packed red blood cell transfusion; SLK, simultaneous liver and kidney transplant; WIT, warm ischemia time.

*Cox's proportional hazards model.

prevent liver graft losses and patient deaths that are directly or indirectly associated with persistent post-transplant renal failure. Of note, the most common reason for death in patients with post-transplant dialysis was sepsis. An association between dialysis and risk of infection has been reported elsewhere [13]. In addition, we observed the adverse impact of immediate post-transplant dialysis on early liver allograft function. Based on our findings, the new UNOS SLK policy will be beneficial for LTA and SLK practice and improve outcomes of LT.

To validate our findings, we reviewed and applied our analysis to the OPTN/UNOS registry. The LTA-CKD group in this validation set showed significantly worse 1-year graft survival and remained as an independent risk factor on the risk adjusted multivariable model. SLK provided significantly better 1-year graft outcome to patients with pretransplant CKD, compared with LTA. The difference in this validation set reached statistical significance, probably because of the larger number of cases. We acknowledge that the LTA-CKD group in this validation set might not be completely meet the CKD criteria, because eGFRs have to be less than or equal to 60 ml/min at any points for 90 consecutive days, whereas this estimation was made based on pretransplant eGFRs reported to OPTN/UONS to

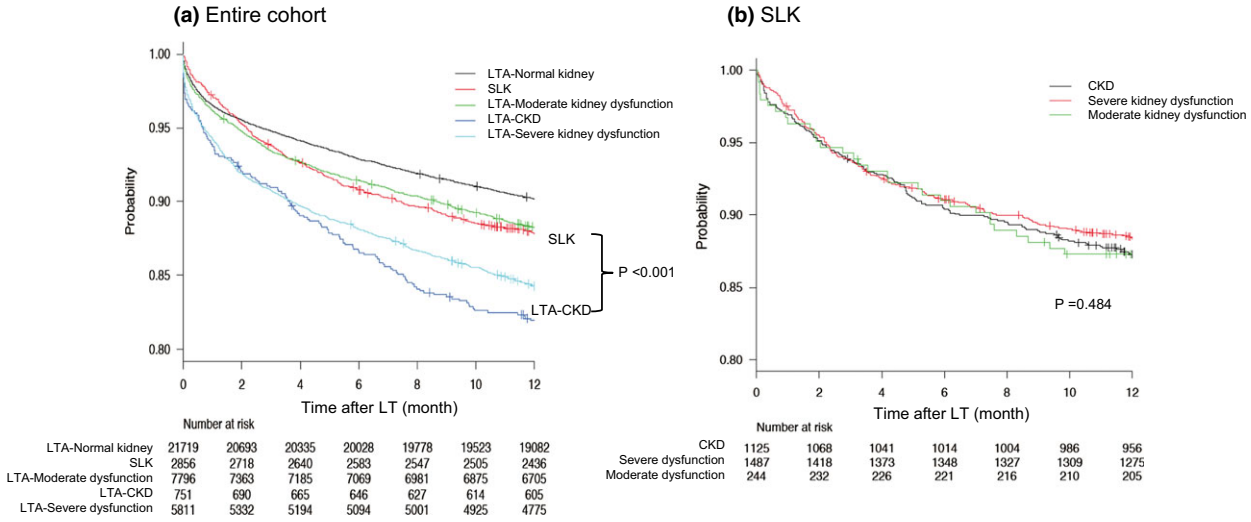

Figure 3 (a) Graft survival up to 1 year according to graft type and pretransplant kidney function Organ Procurement and Transplant Network/United Organ Sharing Network (OPTN/UNOS registry). Patients were categorized in the same way. (i) liver transplant alone (LTA)-normal kidney function group, (ii) simultaneous liver–kidney transplant (SLK) group, (iii) LTA-moderate kidney dysfunction group, (iv) and LTA-chronic kidney disease (CKD) group, (v) LTA-severe kidney dysfunction group. The LTA-CKD group showed significantly worse 1-year graft survival rate (82.0%), compared with the SLK group (87.8%) ($P < 0.001$) and among all groups (90.2%, 88.2%, and 84.3% in LTA-normal kidney, LTA-moderate dysfunction, and LTA-severe kidney dysfunction groups, respectively, $P < 0.001$). (b) Graft survival up to 1 year according to pretransplant kidney function in the SLK group (OPTN/UNOS registry). SLK patients were categorized according to pretransplant kidney function as follows. CKD: SLK patients who met the CKD criteria, Severe kidney dysfunction: SLK patients who showed eGFR ≤30 ml/min at transplant but not meeting the CKD criteria, Moderate kidney dysfunction: SLK patients who showed eGFR 30–60 ml/min. Pretransplant kidney function was not associated with 1-year graft survival rates (87.3%, 88.3%, and 87.3% in the CKD, severe dysfunction, and moderate dysfunction groups, respectively, $P = 0.484$).

update MELD score. However, this would be still the best assumption model based on the review of pretransplant longitudinal kidney function in the OPTN/UNOS registry. The findings of this validation analysis could further support the rationale of the new UNOS SLK policy.

It should be emphasized that the follow-up study is necessary if these outcome trends are still true in the current SLK policy era. More competition among SLK candidates may be occurring after the implementation of the new policy, which potentially prolongs waiting time. If transplant outcome changes in the SLK population in the new era, the findings in this study would not fit the future practice. However, given the fact that the CKD in LTA patients led to a significantly higher risk of post-transplant dialysis and poorer graft outcome, providing an opportunity of SLK to this population should be justified.

In our single-center series, there was no LTA patient who required dialysis for 6 weeks before transplant (defined as sustained AKI). To meet the sustained AKI criteria, a patient needs to be on dialysis or has eGFR ≤25 ml/min at least once a week for the last 6 weeks (Table 1). We were unable to assess association between sustained AKI and post-LTA outcome in the OPTN/UNOS registry, because the registry does not include data of weekly serum creatinine levels (GFRs) or dialysis requirement. In addition, because of the lack of data, we could not estimate possible increase or decrease in the number of SLK by using the OPTN/UNOS registry. Further investigations are warranted to investigate the validity of the sustained AKI criteria and association with transplant outcomes, as well as changes in the number of local, regional, and national SLK.

Reducing the need for post-transplant dialysis improves early post-transplant outcomes [14,15]. Our study demonstrated that LTA, in patients who met the CKD criteria in the new policy, was an independent risk factor for post-transplant dialysis, further justifying the new UNOS SLK policy. Post-transplant dialysis is frequently unavoidable in patients requiring pretransplant dialysis. Based on our risk factor analysis, efforts to reduce intra-operative transfusions and to shorten cold ischemia time may decrease the necessity of post-transplant dialysis, particularly in LTA patients with marginal kidney function [16].

Wadei *et al.* [7] reported that the incidence rate of delayed graft function (DGF) of kidney graft (defined as

Table 4. Cox's regression analysis of possible risk factors for graft loss in the first year (validation analysis based on the Organ Procurement and Transplant Network/United Organ Sharing Network registry).

	No. of patients (%)	Adjusted hazard ratio (95% CI)	*P* value*
Recipient age			
≥60 yo (Ref. <60 yo)	14 568 (37.4)	1.152 (1.103–1.203)	<0.001
Recipient sex			
Female (Ref. male)	12 956 (33.3)	0.976 (0.932–1.022)	0.295
Recipient race (Ref. Caucasian)	27 608 (70.9)		
African-American	3835 (9.9)	1.241 (1.161–1.327)	<0.001
Hispanic	5248 (13.5)	0.931 (0.873–0.993)	0.03
Asian	1714 (4.4)	0.860 (0.769–0.962)	0.008
Others	528 (1.4)	0.955 (0.792–1.152)	0.631
MELD score			
≥30 (Ref. <30)	10 467 (26.9)	0.992 (0.931–1.056)	0.796
Primary liver disease			
HCV (Ref. non-HCV)	15 813 (40.6)	1.225 (1.173–1.280)	<0.001
Donor age			
≥40 yo (Ref. <40 yo)	21 027 (54.0)	1.349 (1.291–1.490)	<0.001
DCD donor (Ref. DBD)	2098 (5.4)	1.368 (1.256–1.491)	<0.001
Pretransplant dialysis w/o SLK (Ref. no pretransplant dialysis)	3383 (8.7)	1.191 (1.083–1.310)	<0.001
SLK (Ref.)	2856 (7.3)		
LTA-CKD	751 (1.9)	1.348 (1.157–1.572)	<0.001
LTA-severe kidney dysfunction	5811 (14.9)	1.087 (0.976–1.212)	0.129
LTA-moderate kidney dysfunction	7796 (20.0)	0.963 (0.879–1.054)	0.413
LTA-normal kidney function	21 719 (55.8)	0.881 (0.809–0.960)	0.004
CIT (per hour)	–	1.023 (1.017–1.03)	<0.001

CIT, cold ischemia time; CKD, chronic kidney disease; DBD, donation after brain death; DCD, donation after cardiac death; HCV, hepatitis C virus infection; LTA, liver transplant alone; MELD score, model for end-stage liver disease–sodium score; SLK, simultaneous liver and kidney transplant.

*Cox's proportional hazards model.

the need for dialysis in the 1 week after SLK) was 26%; and that use of donation after cardiac death (DCD) donor graft was associated with an increased risk of DGF, compared with brain death donor graft (42% vs. 22%). In our series, there were 12 SLK patients (12/44, 27%) who developed delayed graft function and required dialysis post-transplant, and one of them received liver and kidney grafts from a DCD donor. In the subgroup analysis of the OPTN/UNOS registry, older donor age and DCD increased risk of 1-year graft loss in the SLK and LTA-CKD groups. Given the association between donor factors and transplant outcomes observed, careful donor selection is crucial for success in the SLK for LTA-CKD populations.

Trend of post-transplant kidney function in LTA-CKD group was significantly worse than those in the SLK group. These findings also support the new criteria in that increased use of SLK could help to avoid the poor outcome associated with persistent kidney dysfunction after LTA. In fact, a previous research study reported that kidney function had not fully recovered 1 year after LTA, which concurred with our findings [17,18]. On the other hand, post-transplant eGFR gradually declined in the SLK group, which was probably associated with nephrotoxicity because of calcineurin inhibitor. It could be argued that the difference of eGFR at 12 months observed (48 vs. 57 ml/min) would not be clinically relevant; therefore argue that SLK for this population might not be necessary. The eGFR values need careful interpretation, and it should be noted that 19% of patients in the LTA-CKD group died in the first year, whereas the first year mortality in the SLK group was only 7%. Their outcomes were not included in the comparison of GFRs at 12 months, which created selection bias. These results suggest that LTA patients with CKD could not expect the same outcomes as SLK patients.

Another important aspect in the new UNOS SLK policy is the provision of a "safety net" [8]. It remains unclear if kidney transplant alone after LTA would provide acceptable or equivalent kidney and liver graft

Table 5. Cox's regression analysis of possible risk factors for graft loss in the first year in the liver transplant alone-chronic kidney disease and simultaneous liver–kidney transplant groups (Organ Procurement and Transplant Network/United Organ Sharing Network registry)

	LTA-CKD group			SLK group		
	No. of patients (%)	Adjusted hazard ratio (95% CI)	*P* value*	No. of patients (%)	Adjusted hazard ratio (95% CI)	*P* value*
Recipient age						
≥60 yo (Ref. <60 yo)	384 (51)	1.237 (0.955–1.604)	0.108	1211 (42)	1.022 (0.875–1.194)	0.782
Recipient sex						
Female (Ref. male)	425 (57)	1.055 (0.815–1.365)	0.684	1004 (35)	0.883 (0.747–1.043)	0.142
Recipient race (Ref. Caucasian)	563 (75)			1823 (64)		
African-American	36 (5)	1.055 (0.593–1.877)	0.855	422 (15)	1.002 (0.803–1.250)	0.987
Hispanic	117 (16)	1.022 (0.715–1.461)	0.905	482 (17)	0.711 (0.565–0.895)	0.004
Asian	22 (3)	1.608 (0.847–3.051)	0.146	97 (3)	1.115 (0.744–1.671)	0.598
Others	13 (2)	0.512 (0.126–2.069)	0.347	32 (1)	0.793 (0.354–1.779)	0.574
MELD score						
≥30 (Ref. <30)	431 (57)	0.883 (0.666–1.170)	0.387	1367 (48)	1.239 (1.048–1.466)	0.012
Primary liver disease						
HCV (Ref. non-HCV)	269 (36)	1.246 (0.953–1.032)	0.683	1035 (36)	1.189 (1.010–1.399)	0.038
Donor age						
≥40yo (Ref. <40yo)	418 (56)	1.447 (1.108–1.889)	0.007	1149 (40)	1.657 (1.421–1.932)	<0.001
DCD donor (Ref. DBD)	29 (4)	2.321 (1.387–3.885)	0.001	131 (5)	1.357 (0.961–1.917)	0.083
Pretransplant dialysis w/o SLK (Ref. no pretransplant dialysis)	271 (36)	1.321 (0.993–1.756)	0.056		–	
Pretransplant kidney function		–				
Meeting the CKD criteria (Ref.)				1125 (39)		
Severe dysfunction (GFR <30)				1148 (52)	0.906 (0.764–1.075)	0.259
Moderate dysfunction (31–60)				244 (9)	0.826 (0.596–1.144)	0.250
CIT (per hour)	–	1.321 (0.993–1.756)	0.683	–	1.000 (0.979–1.021)	0.998

CIT, cold ischemia time; CKD, chronic kidney disease; DBD, donation after brain death; DCD, donation after cardiac death; HCV, hepatitis C virus infection; LTA, liver transplant alone; MELD score, model for end-stage liver disease–sodium score; SLK, simultaneous liver and kidney transplant.

*Cox's proportional hazards model.

outcomes, compared with those in SLK [19]. Considerations include; sensitization developing after LTA, leading to a potentially increased risk of rejection because of no immunologically protective effect of the liver graft from the same donor, or patients becoming too ill to undergo subsequent kidney transplantation because of the significant comorbidity after LTA [20]. Recognizing these challenges, our results might support for this aspect, too. In our series, 13 patients met the safety net criteria, five of whom died in the first year. While it is difficult to definitively attribute their death to renal failure, knowing that renal failure is associated mortality, it is reasonable to consider it as a contributory factor. Therefore, "safety net kidney transplant" may have prevented their mortality. The safety net can be applied to any LTA patients meeting the criteria. This is reasonable, given the worse outcomes with persistent dialysis and the difficulty in predicting which patients will require prolonged dialysis. The OPTN/UNOS registry used in this study does not contain data for post-transplant kidney function, and we could not estimate the number of patients who would have met the safety net criteria. Future studies will provide exact incidence and outcomes of safety net kidney transplant for liver transplant recipients.

The present study is retrospective and was performed at a single center. The relatively small number of patients in each group is a limitation of this study. To resolve this issue, we conducted the validation analysis by using the OPTN/UNOS registry. Transplant centers which aggressively indicated SLK would need to limit their criteria, because the policy does not allow centers to exceed the criteria. The impact of the new policy among these centers remains to be elucidated. Contrarily, limiting SLK indication is still left to the discretion of each center. Our assessments in this study would help them (conservative centers) estimate anticipated

impacts of the new UNOS SLK policy on their LTA and SLK practice, and decide whether or not they should expand their SLK criteria accordingly. In addition, because SLK practice varies worldwide, the results of our study would be helpful for centers in other countries to consider expansion of SLK criteria. The new UNOS SLK policy contains more aggressive indication criteria than other countries' or regions' policies [21–23]. To confirm the validity and applicability of the new UNOS SLK policy, additional national or international surveys and/or multisite studies are needed [24].

In conclusion, as more LT candidates present with marginal kidney function, continued discussion is required regarding the SLK criteria to maintain and improve LT outcomes [25]. The new UNOS SLK policy can potentially improve LT outcomes, which was validated by the analysis of the OPTN/UNOS registry. It would be worthwhile for transplant centers not only in the USA but also in other countries taking these findings into account, when they consider expanding their SLK criteria. Further discussion and evaluation are warranted in the new SLK policy era with adequate follow-up period to determine the clinical impact on both liver and kidney transplant patients and candidates.

Authorship

SN, MS, KC, AP, DM and MA: participated in research design. SN, MS, KC and RES: participated in the writing of the paper. SN, KC, MR, DM, AP, KB, AY and MA: participated in the performance of the research. SN, MS, RES, AP, KB, AY and MA: participated in data analysis. MR, DM, AP, KB, AY and MA: critical review of the paper.

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Conflicts of interest

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SUPPORTING INFORMATION

Additional supplemental material may be found online in the Supporting Information section at the end of the article

Figure S1. Retrospective review of possible change in the SLK and LTA populations by the new UNOS SLK policy (single center).

Table S1. Definition of early allograft dysfunction.

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