

A Novel Approach in Combined Liver and Kidney Transplantation With Long-term Outcomes

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Objective: The aim of this study was to compare the outcomes of simultaneous and delayed implantation of kidney grafts in combined liver-kidney transplantation (CLKT).

Background Data: Delayed function of the renal graft (DGF), which can result from hypotension and pressor use related to the liver transplantation (LT), may cause worse outcomes in CLKT.

Methods: A total of 130 CLKTs were performed at Indiana University between 2002 and 2015 and studied in an observational cohort study. All kidneys underwent continuous hypothermic pulsatile machine perfusion until transplant: 69 with simultaneous kidney transplantation (KT) (at time of LT, group 1) and 61 with delayed KT (performed at a later time as a second operation, group 2). All patients received continuous veno-venous hemodialysis during the LT. Propensity score match analysis in a 1:1 case-match was performed.

Results: Mean kidney cold ischemia time was 10 ± 3 and 50 ± 15 hours, for groups 1 and 2 ($P < 0.0001$), respectively. The rate of DGF was 7.3% in group 1, but no DGF was seen in group 2 ($P = 0.0600$). Kidney function was significantly better in group 2, if the implantation of kidneys was delayed >48 hours ($P < 0.01$). Patient survival was greater in group 2 at 1 year (91%), and 5 year (87%) post-transplantation ($P = 0.0019$). On multivariate analysis, DGF [hazard ratio (HR), 165.7; 95% confidence interval (CI), 9.4–2926], extended criteria donor kidneys (HR, 15.9; 95% CI 1.8–145.2), and recipient hepatitis C (HR, 5.5; 95% CI 1.7–17.8) were significant independent risk factors for patient survival.

Conclusions: Delayed KT in CLKT (especially if delayed >48 h) is associated with improved kidney function with no DGF post-KT, and improved patient and graft survival.

Keywords: cold ischemia time, combined liver and kidney transplantation, delayed graft function, kidney transplantation, liver transplantation, pulsatile perfusion
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Liver allocation according to the model for end-stage liver disease (MELD) system was introduced in 2002. As a direct consequence, there was a rapid increase in the yearly number of combined liver-kidney transplants (CLKTs), as patients with renal failure had a consistently high MELD score.¹ As many as 30% of liver transplant (LT) patients have renal insufficiency at the time of transplant, contributing significantly to their overall MELD score.^{1,2} The selection of candidates for CLKT, however, is complex because renal disease associated with liver failure may be acute or chronic in nature. As a consequence, there is no well-defined allocation policy for patients listed for CLKT.^{3,4} Despite “proposed” listing criteria for CLKT, several transplant centers use more liberal selection criteria to minimize post-LT kidney failure.^{5,6} Nadim et al⁷ conducted a survey of 88 transplant centers that perform CLKT in the United States to determine practice patterns. The majority of centers in this study (73%) used dialysis duration for acute renal failure as a cutoff for CLKT listing, with duration varying between >4 and >8 weeks. There were 30% of centers that used any acute kidney injury alone as adequate criterion for determining the need for CLKT.⁷

Given the increased use of deceased donor kidney grafts in the LT population, there is a need to optimize outcomes for these transplants. Unfortunately, because of the severity of disease for patients with combined liver and kidney failure, and the complexity of multiorgan transplant, patient survival in CLKT is inferior to that for LT alone. The survival for CLKT, however, is superior to kidney transplant (KT) after LT or LT after KT.^{8,9} The complexity of CLKT derives not only from the surgical procedure itself, but also from postoperative management. Recipients of LT are frequently coagulopathic and often require pressors to correct perioperative hypotension. Liver allograft function is optimized with a low central venous pressure and even fluid balance to minimize graft congestion. In contrast, the kidney allograft performs poorly in the face of low central venous and systolic pressures, or when vasopressors are required to maintain blood pressure. Additionally, the kidney allograft is compromised by significant hepatic reperfusion injury and elevated bilirubin levels, both of which damage renal tubules, creating acute tubular necrosis. This phenomenon results in a decrease of 15% to 20% of glomerular filtration rate (GFR) in the first 2 to 3 days post-LT.¹⁰

Historically, the CLKT procedure is performed as a single contiguous procedure in which the KT immediately follows the LT.

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Hibi et al¹¹ reported on 74 adult CLKTs with overall patient survival of 77%, 66%, and 64% at 1, 3, and 5 years, respectively. Overall, 24 patients died (32%), with 16 (22%) of the deaths in the first year. At their center, this compares to a 4% 1-year patient death rate in patients receiving only KT. In their analysis, delayed graft function (DGF) of the renal allograft was found to be the strongest negative predictor of diminished survival with a hazard ratio (HR) of 8.3 [95% confidence interval (CI) 2.5–27.9].¹¹

The present study reports on a novel management approach in a cohort of patients undergoing CLKt. To optimize the physiologic environment for KT, the LT is first performed while the kidney graft is placed on a hypothermic pulsatile perfusion machine. Implantation of the kidney graft is delayed for 2 to 3 days post-LT. This approach allows stabilization of LT patient's hemodynamics and coagulopathy in the post-LT period, before implantation of the renal allograft. This delay also permits decompression of varices to minimize blood loss during KT, which may directly impact renal allograft outcome. Finally, planned delayed implantation of the kidney frequently provides time to completely wean vasopressors before the implantation of the renal allograft, thus lowering risk of pressor-related DGF. Use of continuous hypothermic pulsatile machine perfusion has been shown to be associated with 20% lower risk of DGF than cold storage in recipients of KT alone.^{12–14}

The aim of this study was to determine the impact of delayed implantation of the kidney allograft in the CLKt procedure. The primary outcome for this study is patient and graft survival. Secondary outcomes include the incidence of DGF, length of hospital stay, and long-term kidney graft function. Subgroup analysis is performed to determine whether a prolonged time delay to KT negatively affects kidney graft outcomes when compared with a shorter time delay.^{15,16}

MATERIALS AND METHODS

Medical records were reviewed of an observational cohort (n = 130) of all adult (≥ 18 years' old) recipients of CLKt, performed at Indiana University Hospital from March 2002 to October 2015. Inclusion criteria for the data analysis included all adult transplant recipients undergoing CLKt, including kidney or liver re-transplants. There were no exclusions for intraoperative or perioperative mortality or graft loss, for non-transplant-related deaths, or for noncompliance. There was a single case in which the LT recipient died 1-day post-LT, while the kidney graft was being maintained on the pulsatile perfusion machine. The kidney allograft was allocated as a KT alone, and the case was excluded from the analysis. The first "delayed" implantation of a kidney allograft in CLKt was performed in June 2007. Over the subsequent 2 years, delayed implantation of the kidney allograft gradually became standard practice. Since January 2010, all CLKts were performed with a delayed KT approach. Retrospective review and analysis of data from the transplant center database were approved by the institutional review board of Indiana University School of Medicine.

Indications and Definitions

Recipient listing for LT was according to standard criteria and protocols as established by our center and the United Network for Organ Sharing (UNOS). Patients who required CLKt were listed according to their estimated GFR (eGFR) <30 mL/min/1.73 m² calculated by the modification of diet in renal disease (MDRD) formula before transplant for chronic renal failure, or their need for dialysis for >8 weeks for acute renal failure, as proposed by the UNOS.^{2,7} Post-KT DGF was defined as the need for dialysis within the first 7 days after KT, in both the simultaneous or delayed approach. Kidney graft failure was defined as removal of the graft or complete loss of graft function requiring retransplantation or

permanent dialysis. Graft function was monitored clinically and by laboratory values (serum creatinine and eGFR by MDRD formula). Allograft biopsies were only performed for indication.

In the simultaneous CLKt procedure, KT was performed immediately post-LT at the same operation [group 1 (n = 69)]. In the delayed CLKt approach, KT was delayed up to 81 hours and performed as a separate operation [group 2 (n = 61)]. Although there were 2 separate transplants in group 2, the procedure was considered as CLKt in the Scientific Registry of Transplant Recipient registry, as both organs came from the same donor and were transplanted into the same recipient. Statistical analysis of outcomes included a direct comparison of groups 1 and 2. Subgroup analysis was performed for group 2 only, dividing patients according to kidney cold ischemia time (CIT) [<48 hours (group 2a, n = 26) and >48 hours (group 2b, n = 35)]. This subgroup analysis was conducted to answer 2 questions: whether it was safe to extend CIT to >48 hours in CLKt, allowing more time for stabilization of LT recipient, and whether CIT >48 hours was associated with lower kidney allograft and patient survival. The rationale of choosing a 48-hour cutoff for CIT analysis was based on 2 main reasons: our clinical observations over 2000 LT recipients who generally become hemodynamically stable within 48 hours post-LT and there is evidence from the literature of worse outcomes (33%) for kidney allograft CIT >36 hours.^{15–16}

Surgical Technique

Procurement and cold preservation of deceased donor livers and kidneys were accomplished using standard techniques. At our center, all deceased donor kidney grafts are maintained on continuous hypothermic pulsatile machine perfusion until the time of transplant. All LT recipients (LT alone or CLKt) routinely undergo a second post-transplant operation. At the time of the initial LT, the skin is closed only. A second-look operation is performed between postoperative days 2 and 5, during which the liver is evaluated, a biopsy is obtained, and the abdomen is formally closed. More than 95% of LT cases were performed using a piggyback hepatectomy technique. Details of this approach have been reported previously.¹⁷ Briefly, delayed closure of the abdomen aims to minimize the risk of abdominal compartment syndrome (and its stress on the native kidneys); prevent graft congestion in the critical postreperfusion period; re-assess for early duct necrosis and bile leak, unrecognized bowel injuries, and bowel obstructions; and wash-out the abdomen to evacuate any fluid collection or hematoma. In the case of delayed KT (group 2), the second-look operation was performed as usual, followed by KT through a separate incision. In both groups 1 and 2, the kidney allograft was implanted extraperitoneally using a separate Gibson incision in the left iliac fossa for technical reasons related to the extended right-side subcostal LT incision. In groups 1 and 2, all recipients were supported by continuous veno-venous hemodialysis (CVVH) started at the time of LT, and continued until the KT was complete. In group 2, CVVH was included in the intensive care unit in the delay period between LT and KT.

Continuous Hypothermic Pulsatile Machine Perfusion

Details of continuous hypothermic pulsatile machine perfusion of kidney allografts have been reported previously.¹² All kidney allografts in group 1 and group 2 were pumped in the same manner. Kidney grafts were flushed with Waters IGL perfusion solution (Waters Medical Systems, Rochester, MN) after the procurement, and before they were supported by the perfusion machine (Waters Medical Systems). Initially, kidneys were perfused at systolic and diastolic pressures of 60 and 40 mmHg, respectively. Systolic pressures gradually declined during perfusion to an

TABLE 1. Donor and Recipient Demographics With Univariate and Multivariate Analysis

	Total (n = 130)	Group 1 (n = 69)	Group 2 (n = 61)	Univariate P	Multivariate P	Hazard Ratio (95% CI)
Recipient demographics						
Age, y (mean ± SD)	56.4 ± 10.9	54.7 ± 10.6	58.3 ± 11.2	0.0161	0.9436	1.00 (0.95–1.06)
Age >60 y, (n, %)	54, 42%	23, 33%	31, 51%	0.0510		
Sex (n, %)				0.4488		
Male	90, 69%	50, 72%	40, 66%			
Female	40, 31%	19, 28%	21, 34%			
Race (n, %)				0.3867		
White	110, 85%	56, 81%	54, 89%			
African-American	14, 11%	10, 15%	4, 6%			
Other	6, 4%	3, 4%	3, 5%			
Blood Type (n, %)				0.1525		
A	57, 45%	33, 48%	24, 39%			
B	14, 10%	4, 6%	10, 16%			
AB	5, 4%	4, 6%	1, 2%			
O	54, 41%	28, 40%	26, 43%			
Body mass index, kg/m ² , (mean ± SD)	27.6 ± 4.9	27.9 ± 4.7	27.1 ± 5.1	0.4156	0.3465	0.95 (0.86–1.06)
Primary indication for transplant (n, %)				0.6112		
ETOH	25, 19%	11, 16%	14, 23%			
Hepatitis C	41, 31%	21, 30%	20, 33%			
Autoimmune liver disease	17, 13%	11, 16%	6, 10%			
NASH	19, 15%	12, 18%	7, 11%			
Other	28, 22%	14, 20%	14, 23%			
Hepatitis C positivity (%)	42%	41%	44%	0.6715	0.0043	5.52 (1.71–17.83)
PRA (%; mean ± SD)						
Class I	15%, 34.3 ± 27.9	14%, 40.1 ± 26.3	15%, 27.8 ± 29.9	0.9664		
Class II	13%, 56.3 ± 24.8	16%, 57.4 ± 24.1	10%, 54.3 ± 28.3	0.3028		
Cytomegalovirus status (%)				0.2461		
D–/R–	9%	10%	7%			
D–/R+	26%	25%	30%			
D+/R–	20%	14%	25%			
D+/R+	45%	51%	38%			
MELD (mean ± SD)	26.8 ± 8.0	26.5 ± 8.9	27.1 ± 6.9	0.6219	0.6592	1.01 (0.95–1.08)
D-MELD (mean ± SD)	938 ± 443	921 ± 412	956 ± 478	0.9424		
Previous kidney transplant (%)	3%	4%	2%	0.3899	0.6613	1.84 (0.12–28.51)
Previous liver transplant (%)	12%	16%	7%	0.1082	0.0660	0.19 (0.03–1.12)
Dialysis before transplant (n, %)	81, 62%	47, 68%	34, 56%	0.1461	0.2641	0.55 (0.19–1.57)
Dialysis before transplant >3 months (n, %)	72, 55%	39, 56%	33, 54%	0.9198		
Duration of dialysis before transplant (days) (median, IQR)	360, 180–360	360, 180–360	270, 120–360	0.2543		
Duration of eGFR <30 mL/ min/1.73 m ² for patients who were not on dialysis, days (median, IQR)	120, 90–180	90, 56–165	120, 90–180	0.2225		
Donor demographics						
Age, y, (mean ± SD)	35.8 ± 14.1	36.6 ± 14.7	34.9 ± 13.5	0.5061	0.4532	1.03 (0.95–1.12)
Sex (%)				0.3048		
Male	59%	55%	64%			
Female	41%	45%	36%			
Body mass index, kg/m ² , (mean ± SD)	26.4 ± 6.0	26.1 ± 6.4	26.8 ± 5.6	0.2296		
Cause of death (%)				0.0295		
Stroke	31%	39%	22%			
Trauma	44%	43%	44%			
Anoxia/other	25%	18%	34%			
Donor hepatitis C positivity (%)	5%	3%	8%	0.2520		
Extended criteria donor kidneys (%)	10%	6%	15%	0.1413	0.0140	15.95 (1.75–145.15)

TABLE 1. (Continued)

	Total (n = 130)	Group 1 (n = 69)	Group 2 (n = 61)	Univariate P	Multivariate P	Hazard Ratio (95% CI)
Donation after circulatory death kidneys (%)	6%	1%	11%	0.0255	0.3569	2.19 (0.41–11.60)
Donor KDPI (mean ± SD) (median, IQR)	(33.7 ± 24.4) (29.5, 14–48)	(30.8 ± 24.0) (25, 12–48)	(37.0 ± 24.6) (34, 19–44)	0.1043	0.0905	1.17 (0.98–1.41)
Donor KDRI (mean ± SD) (median, IQR)	(0.88 ± 0.24) (0.82, 0.69–0.98)	(0.85 ± 0.23) (0.80, 0.68–0.98)	(0.91 ± 0.25) (0.86, 0.75–0.94)	0.1000	0.0957	0.00 (0.00–21.04)

D indicates donor; eGFR, estimated glomerular filtration rate; ETOH, alcoholic liver disease; IQR, interquartile range; KDPI, kidney donor profile index; KDRI, kidney donor risk index; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; PRA, panel reactive antibody; R, recipient; SD, standard deviation.

approximate nadir of 40 mmHg, with the goal of achieving a perfusion rate of >100 mL/min. The kidneys were maintained under these conditions at 4°C until transplantation.¹²

Immunosuppressive Therapy and Infection Prophylaxis

Details of the immunosuppressive regimen and prophylaxis against cytomegalovirus and *Pneumocystis jiroveci* pneumonia in LT recipients have been reported previously.¹⁷ All patients received induction therapy using rabbit antithymocyte globulin (rATG) (2 mg/kg for 3 doses), and anti-CD20 monoclonal antibody (Rituximab, single dose 1.5 mg/m², maximum 300 mg). The only immunosuppression difference between groups 1 and 2 was the administration of the first dose of rATG on postoperative days 1 and 2, respectively. In group 2, rATG was administered before the implantation of the kidney allograft. A methylprednisolone bolus was administered as premedication for each of the 3 rATG infusions, and then was discontinued completely. Maintenance immunosuppressive therapy for CLKT patients started on postoperative day 2 and included tacrolimus (target trough levels of 7–10 ng/dL for the first 3 months post-transplant, and 6–8 ng/mL, thereafter), and mycophenolate mofetil (1000 mg twice daily).¹⁷

End-Points

The primary end-point was patient survival after CLKT. Secondary end-points included DGF, kidney allograft function (measured by serum creatinine and eGFR), and kidney allograft loss.

Statistical Analysis

The data were summarized using means with standard deviations, or medians with interquartile ranges for continuous variables, and percentages for discrete variables. Continuous variables were analyzed using Wilcoxon-Mann-Whitney test. For discrete variables, the χ^2 analysis was performed unless the event number for the given group was ≤ 5 , in which case Fisher exact test was performed. Patient and graft survival probability was estimated using the Kaplan-Meier method, and differences in the curves were analyzed using a log-rank test. Any independent variables with P value <0.10 were used to build the multivariate model, and clinically relevant factors likely affecting patient survival were also included in the multivariate analysis. The multivariate analysis was performed using Cox proportional-hazards regression model. Images were created using GraphPad Prism 6 for MAC OS X (La Jolla, CA).

Owing to the observational nature of this study, and the differences in the 2 groups, a case-control matched analysis on propensity score was performed to reduce selection bias and approximate a randomized trial. The propensity score was estimated with the use of a multivariable logistic-regression model. Matching was performed with the use of a 1:1 matching protocol without replacement. All statistical tests, including propensity score-matched

analysis, were performed using the SAS v9.4 (SAS Institute Inc, Cary, NC).¹⁸ All graft survival curves were calculated as non-death censored. A P value of <0.05 was considered statistically significant.

RESULTS

Primary indications for LT, and recipient and donor demographics, are listed in Table 1. All recipient and donor variables were comparable in the 2 groups, except that recipients were older in group 2 (58 ± 11 in group 2 vs 55 ± 11 years in group 1, $P = 0.02$). In group 2, there were significantly more donation after circulatory death (DCD) donors ($P = 0.03$), which also correlated with a significantly higher number of anoxic deaths in group 2 ($P = 0.03$).

Transplant clinical outcomes are shown in Table 2. The mean kidney CIT was 9.9 ± 2.9 hours in group 1, compared with 50.2 ± 14.9 hours in group 2 ($P < 0.0001$). Kidney warm ischemia time (WIT) was shorter in group 1 (33 minutes in group 1 vs 38 minutes in group 2, $P < 0.001$), whereas liver WIT was longer in group 1 (22 minutes in group 1 vs 18 minutes in group 2, $P < 0.0001$). The rate of kidney DGF was 7.3% (5/69) in group 1, but no DGF was seen in group 2 ($P = 0.06$). Intensive care unit stay, hospital stay, kidney loss, and death rate within 7 days, 90 days, and 1 year post-transplant were comparable in groups 1 and 2. Serum creatinine was lower in group 2 at 6 months ($P < 0.01$) and 1 year ($P = 0.03$) post-CLKT. However, serum creatinine did not differ statistically between the 2 groups at 2, 3, 4, and 5 years post-transplant. Graphically, a comparison of eGFR in groups 1 and 2 follows a pattern similar to serum creatinine (Figs. 1A and B). Perioperative clinical data demonstrate a greater requirement for PRBCs and FFP in group 1. More group 2 patients required pressors at the completion of LT (66% vs 30% in group 1, $P < 0.0001$). The mean central venous pressure at the end of LT, and at 48 hours post-transplant, was higher in group 1 (11 mmHg in group 1 vs 4 mmHg in group 2, $P < 0.0001$, and 9 mmHg in group 1 vs 7 mmHg in group 2, $P = 0.0002$), respectively (Table 2).

Patient survival was significantly better for group 2 (Fig. 2A, $P = 0.01$). Within group 2, there was higher survival for those patients in which the KT was performed at least 48 hours post-LT. On multivariate analysis, DGF of kidney allografts [HR, 165.7 (95% CI 9.4–2926.5)], the use kidneys from extended criteria donors (ECDs) [HR, 15.9 (95% CI 1.8–145.2)], recipient hepatitis C [HR, 5.5 (95% CI 1.7–17.8)], and increased requirement of packed red blood cell (PRBC) transfusion at the time of LT [HR, 0.03 (95% CI 0.01–0.86)] were significant independent risk factors associated with patient survival (Tables 1 and 2). Cause of death analysis for both study groups is shown in Table 3.

Non-death-censored kidney allograft survival was higher in group 2 and mirrored the patient survival difference between groups 1 and 2. Details are shown in Figure 3. In the subgroup analysis [kidney CIT <48 hours (group 2a, $n = 26$) or >48 hours (group 2b, $n = 35$)], all variables in the recipient and donor demographics were comparable

TABLE 2. Outcomes of Combined Liver and Kidney Transplants With Univariate and Multivariate Analysis

	Total (n = 130)	Group 1 (n = 69)	Group 2 (n = 61)	Univariate P	Multivariate P	Hazard Ratio (95% CI)
Transplant Outcomes						
Cold ischemia time, h (mean ± SD)						
Kidney	28.8 ± 22.7	9.9 ± 2.9	50.2 ± 14.9	<0.0001	0.3337	0.96 (0.89–1.04)
Liver	6.4 ± 1.9	6.7 ± 2.2	6.0 ± 1.2	0.1300	0.1422	1.18 (0.95–1.47)
Warm ischemia time, min (mean ± SD)						
Kidney	35.1 ± 7.9	32.7 ± 6.9	37.9 ± 8.5	0.0006	0.8873	1.01 (0.92–1.09)
Liver	20.3 ± 4.9	22.2 ± 4.9	18.2 ± 4.1	<0.0001	0.4680	0.96 (0.86–1.07)
Delayed graft function of renal grafts (%)	3.9%	7.3%	0%	0.0600	0.0005	165.66 (9.38–2926.45)
UOP <40 mL within 24 h post-kidney transplant (%)	0.8%	1.5%	0%	1.0000		
Transfusion requirements during liver transplantation, unit (%), (median, IQR)						
Packed RBCs	97%, (7, 4–11)	100%, (9, 6–14)	93%, (5, 2–9)	0.0556	0.0403	0.03 (0.01–0.86)
Fresh frozen plasma	80%, (5, 2–10)	87%, (9, 5–12)	62%, (2, 0–4)	<0.0001	0.3752	3.15 (0.25–39.87)
Platelets	55%, (1, 0–5)	54%, (1, 0–8)	56%, (1, 0–3)	0.8431		
Cryoprecipitate	11%, (0, 0–0)	10%, (0, 0–0)	11%, (0, 0–0)	0.9489		
Pressor requirements at the end of liver transplantation (%)	49%	33%	66%	0.0003	0.3505	0.57 (0.17–1.87)
Central venous pressure at the end of liver transplantation (mean ± SD)	7.1 ± 4.4	10.8 ± 2.3	3.6 ± 2.6	<0.0001	0.5563	1.08 (0.85–1.37)
Central venous pressure at 48 h post-transplant (group 1) or at the end of kidney transplantation (group 2) (mean ± SD)	8.1 ± 2.4	8.9 ± 1.9	7.4 ± 2.6	0.0002	0.4562	1.10 (0.86–1.41)
Intensive care unit stay, days (median, IQR), (mean ± SD)*	(5, 3–17) (13.0 ± 18.94)	(6, 4–17), (13.8 ± 17.9)	(5, 3–12), (12.0 ± 20.2)	0.3127	0.4036	1.04 (0.96–1.12)
Hospital stay, days (median, IQR) (mean ± SD)*	(17, 10–29) (28.2 ± 40.9)	(14, 10–28), (23.7 ± 23.3)	(19, 11–32), (33.3 ± 54.3)	0.1161	0.4603	0.98 (0.92–1.04)
Kidney loss within 7 days post-transplantation (%)	2%	3%	0%	0.4980		
Kidney loss within 90 days post-transplantation (%)	8%	9%	7%	0.7520		
Kidney loss within 1 year post-transplantation (%)	15%	17%	11%	0.4249		
Death within 7 days post-transplantation (%)	2%	3%	0%	0.4980		
Death within 90 days post-transplantation (%)	7%	9%	5%	0.5000		
Death within 1 year post-transplantation (%)	13%	17%	8%	0.1915		
Serum creatinine, mg/dL (mean ± SD)						
1 Month	1.22 ± 0.63	1.33 ± 0.77	1.09 ± 0.40	0.1731		
6 Month	1.23 ± 0.40	1.33 ± 0.44	1.12 ± 0.31	0.0058		
1 Year	1.25 ± 0.40	1.33 ± 0.44	1.15 ± 0.32	0.0265		
2 Year	1.41 ± 0.64	1.49 ± 0.73	1.25 ± 0.40	0.1077		
3 Year	1.37 ± 0.49	1.40 ± 0.51	1.30 ± 0.43	0.4108		
4 Year	1.47 ± 0.73	1.48 ± 0.71	1.45 ± 0.82	0.2750		
5 Year	1.54 ± 0.93	1.49 ± 0.84	1.83 ± 1.44	0.8643		

CI indicates confidence interval; HR, hazard ratio; IQR, interquartile range; SD, standard deviation; RBC, red blood cells; UOP, urine output.

*Median value was used for statistical calculation.

between the 2 groups except that the mean body mass index of recipients was higher in group 2a (29 kg/m² in group 2a vs 26 kg/m² in group 2b, $P = 0.03$), which also correlated with a significantly higher number of patients with nonalcoholic steatohepatitis in group 2a ($P = 0.05$) (Table, Supplemental Digital Content 1 <http://links.lww.com/SLA/B9>). The mean kidney CIT in group 2a was 35 ± 8 hours versus 61 ± 8 hours in group 2b ($P < 0.0001$). Although kidney

WIT was longer in group 2b (40 minutes in group 2b vs 35 minutes in group 2a, $P = 0.02$), liver WIT was shorter (17 minutes in group 2b vs 20 minutes in group 2a, $P = 0.02$). During KT, more patients required PRBC transfusion in group 2b (89% in group 2b vs 58% in group 2a, $P < 0.01$); however, fewer patients required FFP (6% in group 2b vs 27% in group 2a, $P = 0.03$), and no patient required platelet transfusion (0% in group 2b vs 15% in group 2a, $P = 0.03$). There was a significant

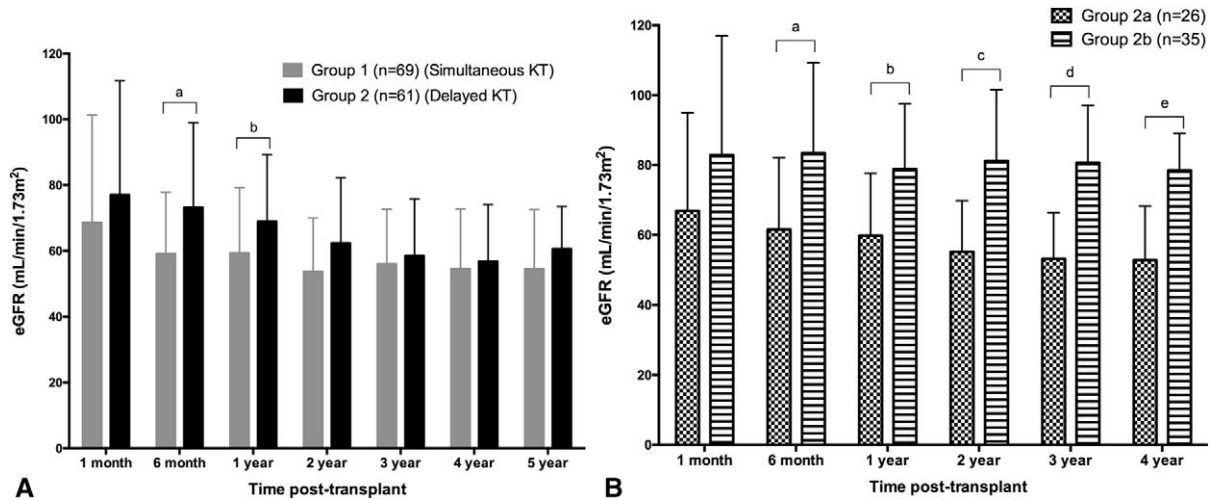


FIGURE 1. Estimated glomerular filtration rates in combined liver-kidney transplantation. (A) = Comparison of group 1 (simultaneous KT) (gray bar) and group 2 (delayed KT) (black bar). (a) $P = 0.0053$; (b) $P = 0.0236$. (B) Comparison of subgroups, group 2a (kidney cold ischemia time <48 h) (dotted bar) and group 2b (kidney cold ischemia time >48 h) (solid line bar). (a): $P = 0.0040$; (b): $P = 0.0023$; (c): $P = 0.0102$; (d): $P = 0.0156$; (e): $P = 0.0302$. eGFR, estimated glomerular filtration rate, KT, kidney transplant.

reduction in the percentage of patients requiring pressors at the time of KT in group 2b [83%–51% (32% change) vs 42%–27% (15% change) in group 2a, $P = 0.05$] (Table, Supplemental Digital Content 2 <http://links.lww.com/SLA/B9>). Kidney function (serum creatinine and eGFR) was significantly better when KT was delayed >48 hours (group 2b) starting from 6 months post-CLKT throughout the study

follow-up period (Fig. 1). Patient and kidney allograft survivals were better in group 2b (Figs. 2 and 3).

Propensity score-matched analysis identified 24 cases matched 1:1 between groups 1 and 2. Nineteen different variables were included in a logistic-regression model (Table, Supplemental Digital Content 3 <http://links.lww.com/SLA/B9>). After propensity

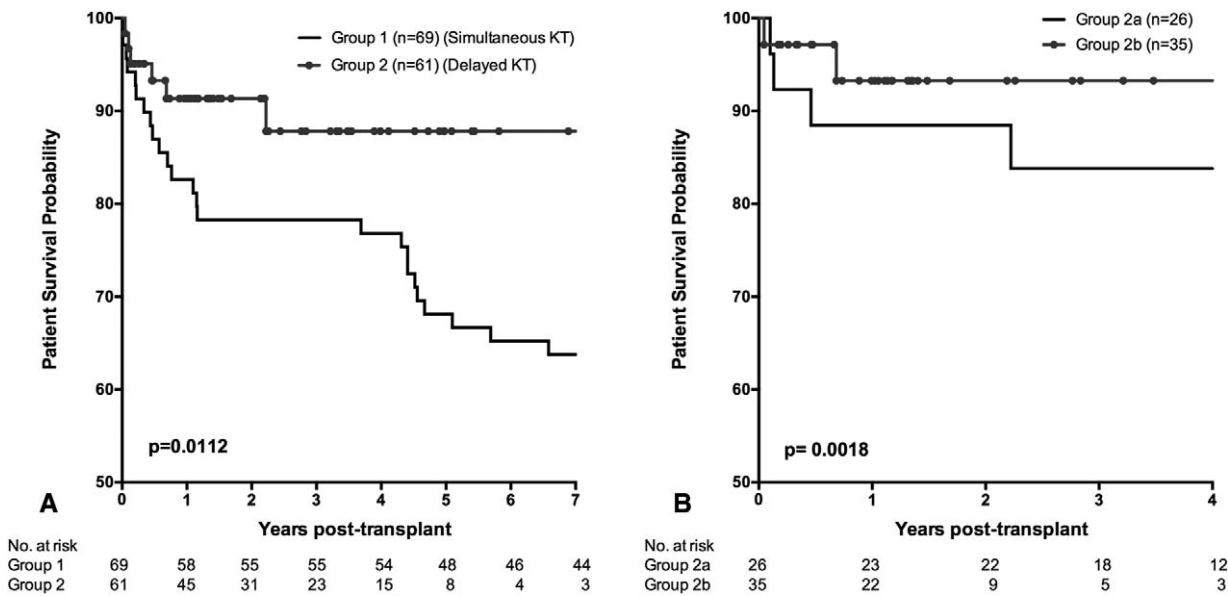


FIGURE 2. Patient survival curves in combined liver-kidney transplantation. (A) Cox-regression patient survival probability in group 1 and group 2. Patient survival was significantly greater in group 2 at 1 year (91% vs 83% in group 1), 3 years (87% vs 78% in group 1), and 5 years (87% vs 63% in group 1) post-transplantation, $P = 0.0112$. Covariates included in the regression model are shown in Tables 1 and 2. (B) Cox regression patient survival probability in subgroups group 2a and group 2b. In subgroup analysis, patient survival was significantly improved in group 2b when the implantation of kidney was delayed >48 h, which was 93% at 1 year and 3 years (vs 88% and 83% in group 2a, respectively, $P = 0.0018$). There was no significant independent variable in the multivariate analysis. Covariates included in the regression model are shown in supplementary tables (Supplemental Digital Content Table 2 and Table 3 <http://links.lww.com/SLA/B9>). KT, kidney transplant.

TABLE 3. Causes of Death

	Group 1 (n = 69)		Group 2 (n = 61)	
			Group 2a (n = 26)	Group 2b (n = 35)
Sepsis	6		1	1
Malignancies	5		1	
Multiorgan failure	3			1
Liver failure	4			
Cardiovascular causes	2		1	
Renal failure	2			
Other, unknown	9		2	
Total	31		7	

In group 1, the deaths (n = 31) occurred at a median 1291 days post-transplantation (range 1–4667). In group 2, the deaths (n = 7) occurred at a median 161 days post-transplantation (range 16–2686).

score matching, patient survival was 75% and 82% at 5 years post-transplant in groups 1 and 2, respectively ($P = 0.79$). Survival curves are shown in Figure 4.

DISCUSSION

This article reports a novel approach to the CLKT, with the goal of optimizing kidney allograft function and long-term graft and patient survival. Results from this 14-year clinical experience suggest that patient and graft survival was improved during the second time period, during which implantation of the kidney was

delayed by up to 81 hours post-LT. The incidence of kidney DGF was lower in the delayed KT group, with a higher eGFR throughout the 4-year follow-up period for the delayed group. The simultaneous and delayed groups had a statistically similar intensive care unit and hospital length of stay, risk of graft loss, and death rate up to 1-year post-transplant. Subgroup analysis for all patients undergoing delayed implantation of the kidney did not show any negative effects related to a delay of >48 hours compared with <48 hours post-LT. At the very least, these results demonstrate that delayed implantation of the kidney is associated with no deleterious effects, whereas the kidney graft is maintained on hypothermic pulsatile perfusion. At best, they suggest superior outcomes for the delayed KT approach.

There are several unique factors to this approach that may be associated with improved outcomes. The severity of underlying disease and the complexity of the surgical procedure render the kidney allograft more susceptible to DGF when it is simultaneously transplanted at the time of LT. Wadei et al²¹ reported an overall DGF rate of 26% in simultaneous CLKT, which was higher when DCD donors were used (42%). In our series of simultaneous CLKT (group 1), DGF rate was 7%. First, the lower rate of DGF may be related to hypothermic pulsatile machine perfusion, which was utilized for all kidney grafts in this study (both in groups 1 and 2). Even for the short time between organ procurement and kidney implantation in simultaneous CLKT, several hours on the machine may benefit the graft by clearance of the products of anaerobic metabolism and minimizing vasospasm.^{13–16} Delayed closure of the abdomen minimizes the effects of increased pressure in the abdominal compartment. Implantation of the kidney as a separate procedure, through a separate incision, and by a fresh surgeon, optimizes operative conditions for

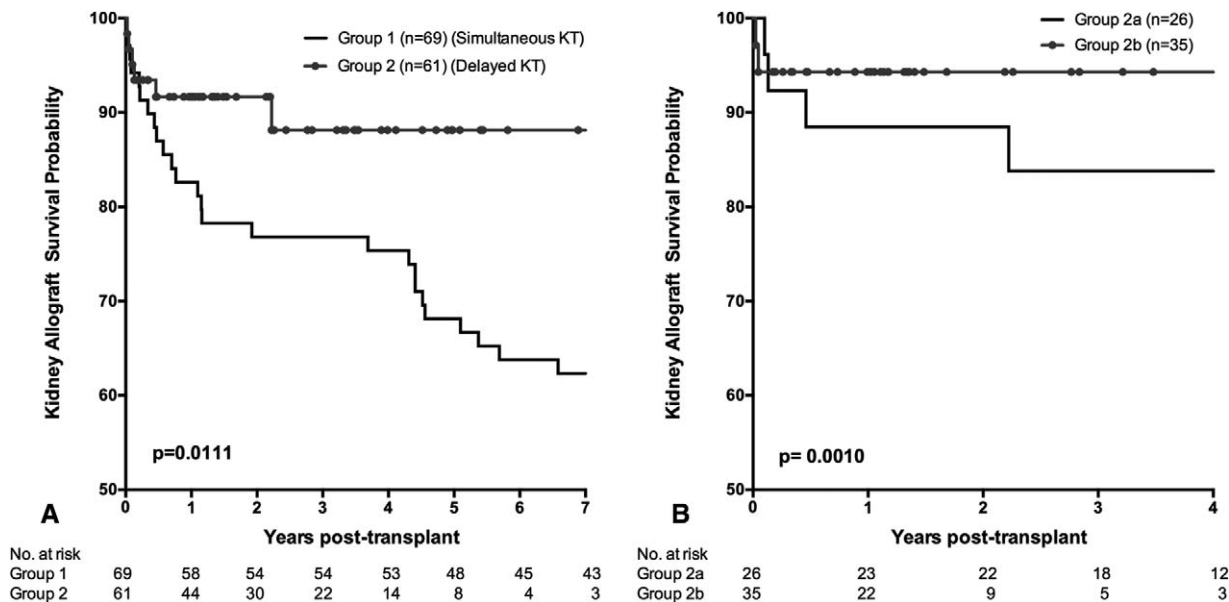


FIGURE 3. Non-death censored kidney allograft survival curves in combined liver-kidney transplantation. (A) non-death-censored Cox regression kidney allograft survival probability in group 1 and group 2. Kidney survival was better in group 2 at 1 year (92% vs 83% in group 1), 3 years (88% vs 77% in group 1), and 5 years (88% vs 66% in group 1) ($P = 0.0111$). Multivariate analysis showed that DGF of the kidney allograft [hazard ratio (HR), 204.7; 95% confidence interval (CI) 12.9–3233.8], the use of kidneys from ECD donors (HR 11.8; 95% CI 1.4–96.7), and recipient hepatitis C (HR 4.9; 95% CI 1.7–14.2) were significant independent risk factors for kidney allograft survival (see Table, Supplemental Digital Content 4 <http://links.lww.com/SLA/B9>). (B) non-death-censored Cox regression kidney allograft survival probability in group 2a and group 2b. Kidney survival was better in group 2b (when KT was delayed >48 h) at 1 year (94% vs 88% in group 1), and 3 and 4 years (94% vs 84% in group 1), $P = 0.0010$. Multivariate analysis did not identify any significant independent risk factors (not shown). KT, kidney transplant.

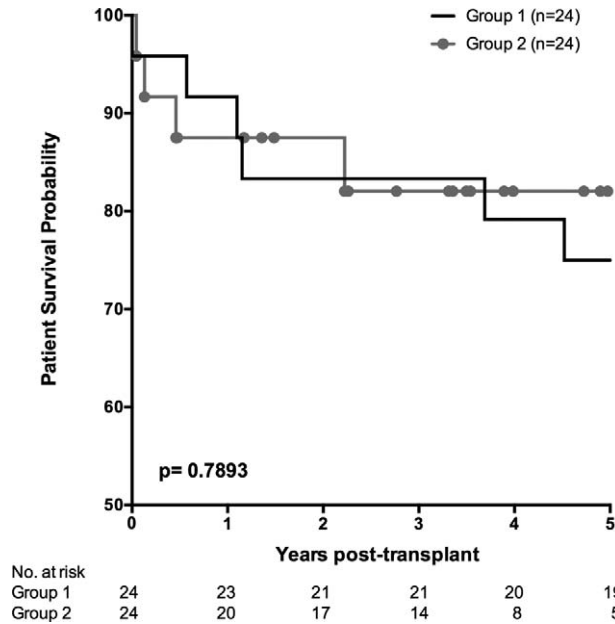


FIGURE 4. Kaplan-Meier patient survival probability between propensity score-matched groups 1 and 2 ($n = 24$). Patient survival in groups 1 and 2 at 1 year was 88% vs 88%, respectively, at 3 years was 83% and 82%, respectively, and at 5 years was 75% vs 82%, respectively, $P = 0.7893$. Variables used in logistic-regression model are shown in a supplemental digital content (see Table, Supplemental Digital Content 3 <http://links.lww.com/SLA/B9>).

the kidney transplant surgeon, which lowers the risks associated with varying the procedure. Finally, the delay allows the post-LT patient a period to resolve coagulopathy, reduce or stop pressor support, resolve any early liver DGF, decompress varices, and to clear post-liver reperfusion debris that could compromise kidney function. CVVH maintenance throughout this period provides the surgeon with total control of fluid status to optimize conditions for early recovery for the liver graft and establish favorable conditions for implantation of the kidney graft. In this study, a delay of up to 3 days to achieve these conditions did not negatively impact the kidney graft.

Subgroup analysis from this study indicated that recipients of LT may have further benefited when the implantation of kidney allograft was delayed >48 hours (mean 61 ± 8 hours) (group 2b). Recipients in this group became more hemodynamically stable when compared with the <48 hours' group as evidence by less need at KT for pressors, FFP and platelets. The group delayed >48 hours actually had a higher eGFR at all time periods in the post-transplant follow-up period ($P < 0.05$ at all times from 6 months to 4 years). Kidney graft survival for this group was also superior by Cox-regression multivariate analysis ($P < 0.01$).

Important pre-transplant risk factors for the function of the kidney allograft and patient and graft survival, such as frequency of recipients on dialysis and the duration of pre-transplant dialysis, were similar in the 2 study groups and did not negatively affect patient and graft survival. Locke et al previously analyzed the data from the UNOS database between 1987 and 2006 comparing pre-MELD and MELD eras. They showed that recipients of CLKT who were on pre-transplant dialysis >3 months had 43% lower risk of liver graft failure in the MELD era.²³ In the present series, recipients of CLKT in both groups 1 and 2 had pre-transplant

dialysis >3 months (group 1, median 12 months and group 2, median 9 months). The impact of the duration of pre-transplant dialysis ($>$ or <3 months) was not included in this report because the small numbers of patients receiving short-term dialysis prevented valid analysis.

Outcomes of KT alone from DCD¹⁹ and ECD²⁰ donors are worse than KT alone from standard criteria brain-dead donors. The negative impact of DCD donors in simultaneous CLKT was also recently demonstrated in a single center and UNOS database analysis with a patient survival of 72% at 1 year (83% in CLKT from brain-dead donors, $P = 0.01$) and 58% at 5 years (69% in CLKT from brain-dead donors, $P = 0.06$).²¹ A recent propensity score-based UNOS database analysis showed similar patient survival between simultaneous CLKT and LT alone recipients who had pre-transplant renal dysfunction. However, the patient survival was significantly better in CLKT recipients if the donor kidney was of sufficient quality, which was calculated by the kidney donor risk index.²² In the present study, patient survival in group 1 (simultaneous KT) was similar to the UNOS CLKT survival rate ($\sim 64\%$ – 68% at 5 years).²¹ However, in group 2 (delayed KT), patient survival was significantly better at 5 years post-transplant (87%, $P = 0.01$). This higher patient survival rate was achieved despite significantly older recipients, a worse kidney donor profile index, more ECD donors, and more DCD donors compared with group 1. A carefully matched propensity score analysis demonstrated similar patient survival between the simultaneous and delayed groups, for the 24 matched patients from each group ($P = 0.79$).

Broader Implications

This single-center analysis of 130 CLKT in adult patients over a 14-year period represents one of the largest experiences of CLKT, and the only experience to date with a novel approach of delaying the implantation of the kidney allograft with long-term follow-up. In light of these findings, a delayed approach to KT may also be considered for other multiorgan transplants, such as combined heart-kidney, as the opposing needs of heart and kidney allografts immediately post-reperfusion are similar to those of liver and kidney allografts.^{24–26} Unlike many clinical surgery studies, the findings reported in this article should be reproducible because there are no unique surgical techniques described. Many centers now routinely place kidney grafts on pulsatile perfusion machines, and delaying implantation of the kidney makes the entire transplant process technically and logistically easier. With the delay, the patient can be stabilized post LT, and the kidney transplant can be performed electively as a scheduled case.

In 2015, the number of CLKT exceeded 600 in the United States ($\sim 10\%$ of all LT) (Figure, Supplemental Digital Content 5 <http://links.lww.com/SLA/B9>). More concerning is the fact that 50% of the kidneys used in these transplants come from donors with kidney donor profile index (KDPI) of $\leq 35\%$, and would have otherwise been allocated to children.^{1,22,27} Results from this study demonstrate that, after careful selection, ECD and DCD kidneys can be safely used for CLKT, which may help to achieve the goal of further expanding the donor pool with comparable or even better results. Moreover, the delayed KT approach may avoid the wastage of kidneys in high-risk patients. If the LT recipient dies within 48 hours, while the kidney allograft is being pumped, the kidney allograft can be re-allocated as KT alone.

Study Limitations

The primary limitation of this study is that it is simply a retrospective cohort study. The nonrandomized design weakens its ability to demonstrate causation between delayed KT and improved patient survival. It is very easy to argue an “era effect” because group 1

was primarily transplanted before 2007 and group 2 was primarily after 2010. There is a benefit, though, to being a single-center study that is there was no substantial change in the primary surgical team during the entire study period. Factors such as transplant technique, usage of continuous hypothermic pulsatile machine perfusion, usage of CVVH during the LT until the KT, patient management post-CLKT (though we might have become more adept at managing such complex cases), or immunosuppressive therapy introduced during the observation period were similar throughout the observation period. However, these approaches could vary from center to center. Because of small numbers, this study could not compare the specific impact of pressors and blood product transfusions post-LT between groups 1 and 2. The positive impact of delayed KT on the use of pressors and especially on blood-product usage was observed in subgroup analysis for group 2. As with any nonrandomized study, all confounding factors could not be controlled for in this analysis. This study attempts to approximate a randomized study by matched propensity score analysis, which demonstrated similar patient survival for groups 1 and 2. This finding suggests that, at the very least, there is no detrimental effect to delayed implantation of the kidney. Additionally, it is unknown whether there is some immunologic benefit provided by the liver, to protect other organs from the same donor (ie, kidney), which may be amplified by allowing more time for the liver to “embed” before implanting the kidney. This can be further studied with serial blood draws and immunologic analysis during the delay and post-KT periods.

CONCLUSIONS

In conclusion, this study demonstrates that CLKLT, with a delayed approach to implantation of the kidney, is associated with improved patient and graft survival, especially if the KT is delayed >48 hours; low DGF rates; higher GFR after 6 months post-KT; and successful use of ECD and DCD donor kidneys with outcomes comparable or better than simultaneous CLKLT performed with low-risk donor kidneys. Delayed KT after LT allows the transplant recipient to become more hemodynamically stable before KT, resulting in less use of pressors and blood products.

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