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Factors predicting kidney delayed graft function among recipients of simultaneous liver-kidney transplantation: A single-center experience

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Abstract

Background: Kidney delayed graft function (KDGF) remains a challenging problem following simultaneous liver and kidney transplantation (SLKT) with a reported incidence up to 40%. Given the scarcity of renal allografts, it is crucial to minimize the development of KDGF among SLKT recipients to improve patient and graft outcomes. We sought to assess the role of preoperative recipient and donor/graft factors on developing KDGF among recipients of SLKT.

Methods: A retrospective review of 194 patients who received SLKT in the period from January 2004 to March 2017 in a single center was performed to assess the effect of preoperative factors on the development of KDGF.

Results: Kidney delayed graft function was observed in 95 patients (49%). Multivariate analysis revealed that donor history of hypertension, cold static preservation of kidney grafts [versus using hypothermic pulsatile machine perfusion (HPMP)], donor final creatinine, physiologic MELD,

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CONFLICT OF INTEREST

None.

and duration of delay of kidney transplantation after liver transplantation were significant independent predictors for KDGF. KDGF is associated with worse graft function and patient and graft survival.

Conclusions: Kidney delayed graft function has detrimental effects on graft function and graft survival. Understanding the risks and combining careful perioperative patient management, proper recipient selection and donor matching, and graft preservation using HPMP would decrease KDGF among SLKT recipients.

Keywords

delayed graft function (DGF); dysfunction; kidney (allograft) function; organ perfusion; preservation

1 | INTRODUCTION

Approximately 20% of patients with end-stage liver disease (ESLD) develop renal dysfunction (RD) while awaiting liver transplantation (LT).^{1–3} The continued increase in LT waitlist and the increasing recipients' medical acuities have led to consequent increase in the number of simultaneous liver and kidney transplantations (SLKT).⁴ SLKT promises less kidney allograft rejection than staged kidney transplantation after liver transplantation (KALT) based on the findings that liver allografts provide immunoprotection for renal allografts from the same donor.^{5–8} Despite reports of inferior patient and graft survival outcomes when compared to kidney transplantation alone (KTA),^{9,10} SLKT continues to be a viable option based on evidence of better kidney function and patient and graft survival when compared to liver transplantation alone among recipients with RD.^{7,11}

Kidney delayed graft function (KDGF) remains a major challenge with a wide range of incidence from 23% to 67%.^{12–21} The detrimental effects of KDGF include prolonged hospital stay, re-initiation of post-transplant dialysis, increased incidence of acute graft rejection, higher incidence of graft loss, and recipient mortality especially among elderly patients.^{22–26} An exceptionally high incidence of KDGF has been reported among SLKT recipients with high medical acuity at the time of transplantation.²⁷ Accordingly, recent reports recommended deferral of SLKT in highest acuity recipients to avoid renal allograft futility.^{27,28}

The use of hypothermic pulsatile machine perfusion (HPMP) has helped dramatically reduce the development of KDGF following cadaveric renal transplantation.^{15,16,21,29,30} However, reports assessing the impact of HPMP on developing KDGF among SLKT recipients are lacking. Therefore, we sought to evaluate the impact of HPMP, among other preoperative recipient and donor factors, on the development of KDGF in SLKT recipients with the aim of identifying preoperative risk factors associated with developing KDGF prior to proceeding with kidney transplant surgery.

2 | MATERIALS AND METHODS

2.1 | Study design

A retrospective review of a prospectively maintained transplant database was performed for all patients who received SLKT at University of California, Los Angeles, in the period from January 1, 2004, to March 31, 2017, with a minimum follow-up of 1 year. From August 1, 2015, to November 30, 2016, HPMP was utilized for all kidney allografts allocated to adult patients undergoing SLKT. Recipients were divided into 2 groups based on the presence of delayed kidney graft function (kDGF) or immediate kidney graft function (kIGF). The study was approved by the UCLA Institutional Review Board.

2.2 | Study end-points and definitions

The primary end-point was development of kDGF, defined as dialysis requirement within the first 7 days after transplantation. Secondary end-points included renal allograft function at 3 and 12 months after transplant using serum creatinine and glomerular filtration rate (GFR) estimated by the Modification of Diet in Renal Disease (MDRD) formula,³¹ actuarial (death-censored) kidney graft survival, and patient survival. Kidney allografts were considered lost in cases of graft nephrectomy or irreversible loss of graft function requiring re-initiation of permanent dialysis or kidney retransplantation. Other end-points included duration of postoperative stay in intensive care unit (ICU), overall hospital stay, incidence of acute kidney graft rejection, and renal allograft futility (defined as death or continued dialysis requirement 3 months after transplantation). Patient acuity was reflected by physiologic MELD score at the time of transplantation.³²

2.3 | Transplant protocol

Patients with ESLD and concomitant renal dysfunction in the form of chronic kidney disease for more than 3 months (glomerular filtration rate (GFR) <40 mL/min, diabetes mellitus, proteinuria ≥ 2 g/d, renal biopsy showing >30% glomerulosclerosis or interstitial fibrosis, or metabolic disease) or acute kidney injury requiring dialysis at least twice a week for a minimum of 4 weeks were evaluated for SLKT.²⁸ Recipients received intraoperative induction by hydrocortisone. Induction with basiliximab in a two-dose regimen of 20 mg intravenously (IV) on days 0 and 4 was performed to delay the initiation of calcineurin inhibitors followed by postoperative maintenance using triple immunosuppression therapy (corticosteroids, antimetabolite, and calcineurin inhibitor).³²

Intraoperatively, liver transplantation is initially performed by the liver transplant team followed by kidney transplantation performed by the kidney transplant team in the same operative setting. In case of patient instability, kidney transplantation is deferred until the patient's general condition improves and allows for proceeding with kidney transplantation.

2.4 | Kidney allograft preservation

Kidney allografts were preserved using either cold static preservation (CSP) or HPMP. All kidney allografts procured for SLKT were initially flushed with and stored in University of Wisconsin solution at the time of procurement. They were then either kept in ice (CSP) or placed on HPMP until transplantation. For HPMP, kidney grafts were placed on LifePort®

Kidney Transporter machine (Organ Recovery Systems) upon arrival at the recipient hospital and were kept until the time of transplantation. Kidney Preservation Solution-1 (KPS-1)³³ was used and maintained at temperature less than 5°C. No medications were used in the solution. Pumping parameters such as pressure, flow rate, and resistance were recorded at initiation and termination of pumping. None of the grafts were discarded based on the pumping parameters.

2.5 | Data collection

Preoperative recipient variables included demographics, indications for liver and kidney transplantation, surgical and medical history, preoperative laboratory values, physiologic MELD, allocation MELD at time of listing (if different from physiologic MELD), need for and duration of pretransplant hospitalization, need for life support measures (mechanical ventilation, vasopressors) within 24 hours of surgery, and type and duration of preoperative RRT. Donor variables included demographics, cause of death, organ procurement organization (OPO) location, medical comorbidities, laboratory values, kidney donor risk index (KDRI),³⁴ liver donor risk index,³⁵ kidney graft preservation method (CSP or HPMP), and graft type [donation after brain death (DBD), donation after cardiac death (DCD), and extended criteria donor (ECD) defined as donor age >60 years, or age between 50 and 59 years with 2 of the following criteria: history of hypertension, death from cerebrovascular accident, or final serum creatinine level > 1.5 mg/dL]. Operative variables included organ warm ischemia time (WIT) and cold ischemia time (CIT), use of intraoperative hemodialysis or veno-venous bypass, blood transfusions, laboratory parameters, and need for abdominal packing.³⁶ The duration of delay between kidney and liver transplantation reflected on the length of kidney CIT and was estimated by difference between kidney and liver CIT.

Postoperative outcomes included overall patient and actuarial renal allograft survival, duration of postoperative ICU stay, overall hospital stay, dialysis requirement, and its duration. Patients were followed up for a minimum of 1 year. Graft function was estimated using serum creatinine and GFR at 3 and 12 months of post-transplant follow-up. Patients who were on RRT at the time of follow-up were assigned a creatinine level of 4.0 mg/dL.²⁷

2.6 | Statistical analysis

Descriptive statistics are reported for the entire study cohort. Categorical variables are summarized as numbers and percentages; continuous variables are summarized as medians and interquartile ranges (IQR). The groups were compared using Pearson's chi-square/Fisher's exact test for categorical variables and Mann-Whitney *U* test for continuous variables. Overall patient survival and death-censored kidney graft survival were estimated using the Kaplan-Meier method. The difference between survival curves was compared using log-rank test. Generalized Wilcoxon test was used in case the curves crossed. Multivariable logistic regression analysis was performed to identify the recipient and donor factors that would contribute to the development of kDGF. All variables with $P < 0.15$ in univariate analysis, or those thought to be important on clinical grounds, were entered in a stepwise backward elimination multivariate logistic regression analysis to identify preoperative recipient, donor, and graft risk factors highly associated with kDGF prior to proceeding with kidney transplantation. The strength and clinical utility of the variables

were assessed using the area under the receiver operating curve (AUROC). Area larger than 0.70 was considered to create a good and clinically sound model valid for clinical use.³⁷ All analyses were performed using IBM® SPSS® Statistics version 24 (IBM Corporation).

3 | RESULTS

During the study period, 219 patients received SLKT. Twenty-five patients were excluded for the following reasons: recipient age <18 years (n = 20), intraoperative or postoperative death within 24 hours post-transplant (n = 2), SLKT combined with multivisceral (bowel/pancreas) transplantation (n = 1), and missing data regarding dialysis requirement within the first seven days postoperatively (n = 2). The remaining 194 adult recipients of SLKT represented our study cohort and were included in the analysis (Figure 1).

The median follow-up was 33 months (IQR: 13–76 months).

The median age of SLKT recipients was 57.4 years (IQR = 49.2–63.4), the majority of whom were male (n = 125, 64.4%), and the median body mass index (BMI) was 26 kg/m² (IQR = 22–30). The most common indication for LT was viral hepatitis (n = 59, 30.4%), followed by liver graft failure requiring retransplantation (n = 39, 20.1%), alcoholic cirrhosis (n = 35, 18%), and nonalcoholic steatohepatitis/cryptogenic cirrhosis (n = 35, 18%). Hepatorenal syndrome (54.1%, n = 105), diabetic nephropathy (16.5%, n = 32), and calcineurin-inhibitor induced nephropathy (10.3%, n = 20) were the most common indications for kidney transplantation.

The median physiologic MELD score at the time of SLKT was 36 (IQR = 29–40), and the median allocation MELD score at listing was 32 (IQR = 23–38). A total of 144 (74.2%) patients required preoperative hospitalization. Ninety-six out of 144 patients (66.7%) were in the transplant ICU within 24 hours of SLKT. A total of 184 (94.8%) patients were on preoperative dialysis for a median duration of 53 days (IQR = 26–197). Mechanical ventilation at the time of transplantation was required in 49 patients (25.3%) and vasopressor support in 51 patients (26.3%). Regarding recipient morbidity, 98 patients had history of diabetes (50.5%), and 114 patients had history of hypertension (58.8%).

The median donor age was 34 years (IQR = 23–48); most were male (n = 121, 62.4%), and more than half were Caucasian (n = 106, 54.6%). The most common cause of donor death was head trauma (n = 83, 42.8%), followed by cerebrovascular accident (n = 71, 36.6%) and anoxia (n = 34, 17.5%). Most of the kidney grafts utilized were of left laterality (n = 134, 69.1%) and derived from local OPO (n = 138, 71.1%). Nine kidney grafts were derived from donors with history of diabetes (4.6%) and 37 kidney grafts from donors with history of hypertension (19.1%). Seven grafts were from DCD donors (3.6%), and 19 grafts were from ECD donors (9.8%). The median donor final creatinine was 1mg/dL (IQR = 0.8–1.3), and the median kidney donor risk index (KDRI) was 0.94 (IQR = 0.79–1.25). HPMP was used for preservation of 24 kidney grafts (12.4%), whereas 170 grafts (87.6%) were kept in CSP until the time of transplantation. The median time lapse to initiation of HPMP was 5.1 hours (IQR = 4.8–5.3), whereas the median duration of pumping was 9.9 hours (IQR = 6.5–19.6). The median initial pressure of pumping was 28 mm Hg (IQR = 27–29), and the median final

pumping pressure was 29 mm Hg (IQR = 24–30). The median initial flow rate was 39 mL/min (IQR = 16–54), and the median final flow rate was 169 mL/min (IQR = 123–183). The median initial resistance was 0.58 mm Hg/mL/min (IQR = 0.47–1.25), and the median final resistance was 0.15 mm Hg/mL/min (IQR = 0.09–0.21).

The median time of delay of kidney transplantation after liver transplantation was 367 minutes (IQR = 290–488). The median kidney CIT was 800 minutes (IQR = 682–1008), and 61 patients (31.4%) were placed on intraoperative dialysis. Ninety-five patients (49%) required dialysis within the first 7 days postoperatively and accordingly recognized to have developed KDGF. Among recipients with KDGF, 74/95 patients (77.9%) became dialysis independent, with the majority (72/74, 97.3%) achieving dialysis independence within 90 days post-transplant (Figure 2). Renal allograft futility was observed in 33 patients (17%). During a median follow-up of approximately 33 months, overall patient survival at 1, 3, 5, and 10 years was 83.9%, 75.5%, 73.4%, and 60.4%, respectively; actuarial kidney graft survival (censored for recipient death) at 1, 3, 5, and 10 years was 89.7%, 82.5%, 81.6%, and 70.4%, respectively. The leading cause for recipient mortality after SLKT was sepsis with multisystem organ failure (MSOF, $n = 26$, 48.1%), followed by cardiopulmonary failure ($n = 13$, 24.1%) (Table 1).

3.1 | Comparison between recipients with KDGF and KIGF

Compared to patients with KIGF, KDGF patients were more likely to be hospitalized before transplantation (83.2% vs 65.74%, $P = 0.005$) with significantly longer preoperative ICU stay (3 vs 0 days, $P = 0.044$), as well as longer overall hospital stay (24 vs 13 days, $P = 0.004$) (Table 2). Patients with KDGF were more critically ill and had higher physiologic MELD at time of transplantation (37 vs 34, $P = 0.003$) and required more vasopressor support (35.8% vs 17.2%, $P = 0.003$), mechanical ventilation (32.6% vs 18.2%, $P = 0.021$), and RRT (98.9% vs 90.9%, $P = 0.011$) prior to transplantation when compared to KIGF patients. The length of preoperative dialysis was comparable between the groups (53 vs 53 days, $P = 0.454$). There were more DCD (5.3% vs 2%, $P = 0.226$) and ECD grafts (12.8% vs 7.1%, $P = 0.192$) among KDGF patients. Subanalysis of the seven DCD grafts revealed that the incidence of KDGF was lower among DCD grafts placed on HPMP (1/3, 33.3%) compared to those kept in CSP (4/4, 100%) which approached statistical significance ($P = 0.053$). Patients with KDGF were more likely to receive kidney grafts from donors with history of hypertension (26.9% vs 12.2%, $P = 0.011$), as well as kidney grafts from donors with higher final creatinine (1.1 vs 0.9 mg/dL, $P < 0.001$) and KDRI (0.95 vs 0.93, $P = 0.036$). In terms of graft preservation, KIGF patients had more grafts preserved using HPMP (rather than being kept in CSP) compared to those with KDGF (16.2% vs 8.4%, $P = 0.102$). The duration of delay of kidney transplantation after liver transplantation was significantly longer among KDGF patients compared to those with KIGF (394 vs 354 minutes, $P = 0.012$); this was reflected by kidney cold ischemia times that were significantly longer among KDGF patients compared to KIGF patients (880 vs 767 minutes, $P = 0.006$). Recipient and donor characteristics such as age, sex, and BMI, and recipient time on waiting list were similar between the groups.

Postoperatively, patients with kDGF had longer overall postoperative hospital stay (44 vs 23 days, $P < 0.001$) and longer postoperative ICU stay (18 vs 9 days, $P < 0.001$). Renal functions at three and twelve months post-transplant were significantly worse among kDGF patients in comparison with those with kIGF as evidenced by significantly higher serum creatinine and lower MDRD-GFR (Figure 3). Renal allograft futility was also significantly higher among kDGF patients compared to those with kIGF (30.5% vs 4%, $P < 0.0001$). Biopsy-proven acute kidney allograft rejection was higher among kDGF patients; however, it was not statistically significant (8.5% vs 5.1%, $P = 0.347$).

Death-censored kidney graft survival rates (actuarial kidney graft survival) among kDGF patients were 82.1%, 70.1%, 68.2%, and 57.8% compared to 96.9%, 95.1%, 95.1%, and 86.1% among kIGF patients at 1, 3, 5, and 10 years, respectively. Death-censored kidney graft survival rates were significantly worse among kDGF patients compared to kIGF patients ($P < 0.0001$; Figure 4A).

Overall patient survival for kDGF patients was 74.7%, 68.8%, 66.5%, and 64.1% compared to 92.9%, 83.1%, 81.3%, and 55% for kIGF patients at 1, 3, 5, and 10 years, respectively. The difference in overall patient survival was worse among recipients with kDGF compared to those with kIGF (log-rank $P = 0.12$) especially during the first few years post-transplant (generalized Wilcoxon $P = 0.003$; Figure 4B).

3.2 | Multivariate analysis of preoperative predictors of kDGF

Multivariate analysis was performed to evaluate preoperative risk factors that would contribute to kDGF prior to transplantation of kidney graft. That analysis revealed five significant preoperative factors detailed in Table 3. Donor history of hypertension (OR 3.62, $P = 0.004$), cold static preservation (OR 3.34, $P = 0.029$), every unit increase in donor final creatinine (OR 2.11, $P = 0.015$), every unit increase in physiologic MELD at time of transplantation (OR 1.08, $P = 0.004$), and every minute delay in kidney transplantation after liver transplantation (OR 1.001, $P = 0.012$) were associated with increased risk of developing kDGF. The fitness of the model was statistically significant over the constant-only model, $X^2 (8, N = 194) = 47.54$, $P < 0.001$. The calculated area under ROC curve was 0.77 (95% CI 0.703–0.84, $P < 0.001$).

3.3 | Comparing SLKT recipients who had their kidney allografts placed on HPMP versus those kept on CSP

Subanalysis of HPMP versus CSP of kidney allografts was done for the sake of clear data presentation and showed no significant difference between the groups in terms of kidney allograft function at 3 months and 1 year postoperatively (Table 4). Length of postoperative hospital stay and ICU stay was significantly longer among those with HPMP, but kidney-graft-biopsy-proven acute tubular necrosis was significantly lower among the HPMP group. The development kDGF was lower among the HPMP group (33.3% vs 51.2%, $P = 0.102$) as was the incidence of acute kidney allograft rejection (0% vs 7.7%, $P = 0.158$), but neither comparison reached statistical significance. Grafts that developed kDGF after placement on HPMP and those that developed kDGF on CSP had comparable outcomes in terms of overall graft function and graft recovery (Table 5).

4 | DISCUSSION

This study represents one of the largest single-center series analyzing preoperative predictors of KDGF among SLKT recipients in the post-MELD era. Despite the presence of more than 10 definitions for KDGF in the literature,³⁸ we used the most commonly used and widely accepted one, which is dialysis requirement in the first week after transplantation. Many have criticized such definition for the confusion it holds regarding the subjectivity of the decision for dialysis, and whether it reflects a real transplant function derangement or just clinician practice, especially in the setting of SLKT. However, it appears easier to use this definition to be able to communicate the results and compare it with many other reports in the literature.

The incidence of KDGF among SLKT recipients was obviously higher than the rates reported for KTA, which can likely be attributed to the physiologic differences between the two patient populations.^{16–22,39,40} SLKT recipients are more critically ill and demonstrate higher acuity based on the higher MELD at time of transplantation.⁴¹ Additionally, approximately half of SLKT patients required preoperative ICU admission in comparison with KTA population who generally get admitted from home on the day of transplant. Furthermore, the longer kidney CIT reflected by the delay in kidney transplantation among SLKT recipients contributed to the increase in the risk of KDGF.⁴²

Among the preoperative factors assessed, donor history of hypertension, cold static preservation of kidney grafts until transplantation (versus HPMP), higher donor final creatinine, higher physiologic MELD, and longer duration of delay of kidney transplantation after liver transplantation were found to be significant independent predictors for developing KDGF. Many of these factors agree with previously published reports assessing risk factors for KDGF.^{13,17,21,22,42–45} With regard to donors with history of hypertension, we found that they belonged to an older group of donors with median age of 49 years (IQR = 40–56), versus donors without a history of hypertension (median age: 29 years, IQR = 21–43). We used the duration of delay between kidney and liver transplantation as a surrogate for kidney CIT in the multivariate analysis since it is easier to determine prior to implantation of the kidney as our intention is to evaluate preoperative risk factors that would contribute to the development of KDGF. This finding is not in agreement with the study performed by the group of Indiana University, which reported that delaying kidney implantation offers better kidney allograft outcomes. However, it is important to note that the patient populations were quite different in multiple ways: (a) The mean MELD in the Indiana cohort was 26 versus 32 at UCLA; (b) all the Indiana kidneys were placed on pump regardless of whether they were implanted immediately after the liver or 48 hours after, but at UCLA, only a small fraction were placed on pump; (c) the Indiana group as a policy delayed the kidney transplant 2–3 days after liver transplantation, regardless of how sick or well the recipient was. This all meant that at UCLA, it was the sicker patients who had a delay in kidney transplantation. This makes a direct comparison of the two studies difficult.³⁰

The use of DCD grafts was not statistically significant on univariate analysis. However, it did show association with developing KDGF among other risk factors in multivariate analysis. On the other hand, ECD grafts did not show any association with the development

of KDGF. Several previous reports have highlighted the strong association between the use of DCD grafts and the development of KDGF.^{12,39} Thus, some may argue that avoiding the use of DCD grafts may help reduce the incidence of KDGF. Data from previous studies suggested that HPMP use significantly reduces the incidence of KDGF among DCD kidneys.^{46,47} However, others failed to support this finding.⁴⁸ In this study, further subanalysis of DCD grafts revealed the lower incidence of KDGF among DCD grafts placed on HPMP compared to those kept in CSP (33.3% vs 100%, $P = 0.053$). But the relatively small numbers of DCD grafts in this study render it insufficient to confirm such assumption or go with or against the use of DCD grafts. The current indications for the use of DCD grafts per se in SLKT recipients are driven by other donor factors and by recipient acuity; they are mostly dominated by the severity of ESLD of the recipient.

Simultaneous liver and kidney transplantation recipients on pretransplant dialysis were also associated with higher odds of developing KDGF, which approached statistical significance on multivariate analysis. However, the duration of preoperative dialysis was not associated with risk of developing KDGF. This deviates from reports that identified the duration of preoperative dialysis as a risk factor associated with higher incidence of developing KDGF.^{12,22,43}

In our series, HPMP reduced the incidence of KDGF from 51.2% to 33.3%. However, this difference was not statistically significant on univariate analysis. This is probably due to the higher acuity of the recipients who had ESLD and higher MELD, in addition to the small number of kidney grafts placed on HPMP versus those kept in CSP (24 vs 170), possibly leading to inadequate power. Furthermore, kidney grafts placed on HPMP in this study had to be kept in ice for a median of 5.1 hours prior to initiation of pumping, which may have blunted the full beneficial effect of HPMP on graft function. The initial CSP prior to pumping is explained by the fact that our OPO is among the minority that do not routinely place kidneys on HPMP immediately after procurement in the donor hospital. Accordingly, for a kidney to be pumped, it had to be packed with ice and transported to our center with inevitable delay in initiation of pumping. On the other hand, many other OPOs are currently employing selective, if not preferential, pumping of kidney grafts using HPMP at the site of procurement, which allows for the full benefit of the pump on graft function. Despite that, multivariate analysis revealed that the use of HPMP lowered the odds of developing KDGF by approximately 3-fold among the other risk factors. It is obvious that a larger-scale comparison is necessary to determine the significance of this observation.

There was no impact for retransplantation, donor age, sex, history of diabetes mellitus, or donor cause of death on developing KDGF, which differs from results of previously published reports.^{12,13,22,44} Furthermore, we did not find significant impact for recipient chronic medical condition, such as diabetes mellitus or hypertension, on developing KDGF, which makes it more likely to assume that immediate pretransplant SLKT recipients' general condition or acuity rather than the chronic medical condition most strongly influences immediate post-transplant allograft function.

In terms of post-transplant outcomes, postoperative ICU and overall hospital stay were significantly longer among KDGF patients, similar to data from previously published studies.

^{17,42,49} It is not surprising that patients with kDGF had significantly worse kidney graft function at three and twelve months after transplant, which agrees with studies results performed on KTA patients.^{12,17,49} There was no observed difference in the incidence of biopsy-proven acute graft rejection, potentially attributed to the immunoprotective effect of the liver allograft procured from the same donor, which is not the case among KTA recipients who experience higher rates of acute graft rejection.^{17,22,49,50}

The decline in short-term graft function among recipients with kDGF appeared to translate in the long-term graft and patient survival. Overall patient survival and death-censored allograft survival among the whole cohort of recipients of SLKT were comparable to those reported in the literature.^{51,52} The difference in death-censored kidney allograft survival for patients with kDGF compared to those with iGFR is striking with a 5-year actuarial graft survival of 67.9% among kDGF patients compared to 95% among iGFR patients. Graft survival among SLKT recipients with kDGF may not be comparable to that among KTA patients with kDGF because of the differences in patient physiology and operative exposure.^{12,44,49,53} Studies comparing outcomes of SLKT to KTA reported inferior kidney graft survival rates among SLKT recipients.^{52,54}

Overall patient survival rates were worse among kDGF patients in the first few years post-transplant; however, the difference tended to decline and became less pronounced later. This is consistent with the findings reported by the group from Indiana University and the group from the University of Miami where kDGF was a strong independent predictor of patient mortality following SLKT.^{30,52}

Such findings support the idea that the severity of illness of SLKT recipients at the time of transplantation is the main factor predisposing for increased incidence of kDGF, worse short-term kidney allograft function, and inferior long-term kidney allograft survival. Some may argue that these results may give the impression that SLKT should not be performed among patients with high medical acuity. However, by advocating for sequential kidney transplantation after LT in high-medical acuity recipients with ESLD and RD, we may inadvertently increase the risk of LT recipient mortality, as well as liver graft failure.^{11,51}

A better goal would be development of strategies that help to improve early graft function such as the recently proposed standardized use of HPMP with possible delay in kidney transplantation until adequate recovery from the complex LT surgery. The recently implemented United Network for Organ Sharing policy for SLKT allocation offers a “safety net” for high-medical acuity patients who continue to have RD following LT.⁵⁵ This policy aims at establishing a more equitable allocation of renal allografts given the growing utilization of SLKT with resultant diversion of kidney grafts from patients awaiting KTA. Such a policy may provide better chances for ESLD patients with concurrent RD who are too sick to go through this complex SLKT in that if they received LT initially and continued to show persistent RD post-LT (ie, chronic dialysis dependence or GFR $\leq$ 20 mL/min), they will be prioritized to receive kidney transplant once listed in the period from 60 to 365 days following LT.⁵⁵ The use of HPMP with delay in performing CRT after LT was recently proposed and published by the Indiana group who concluded that delaying CRT for more than 48 hours post-LT is not associated with kDGF and provides improved graft function, as

well as better patient and graft survival.³⁰ While, as noted above, the fundamental difference in patient populations between the two studies may explain why we found delay to be associated with worse results instead, their results support the notion that use of HPMP in and of itself did not significantly reduce or prevent the development of kDGF. Rather, allowing patient recovery and better hemodynamic stability by delaying the kidney transplant surgery after LT helps to improve outcomes. This technique cannot yet be standardized in most centers, and no other data yet exist to validate the impact of this approach on short and long-term survival.

The primary limitation of this study is that it is a single-center retrospective cohort study. One can possibly argue an “era effect” since the study was performed over a 13-year period; however, we did not appreciate marked differences in pattern or trend of incidence of kDGF among SLKT recipients on a yearly basis during the study period. Despite that, being a single-center study carries the benefit of having the same primary surgical team performing both liver and kidney transplants without substantial differences in transplant protocols during the entire study period. We did not validate our results with an external cohort. However, we have compared them to results published from previous studies. We could not study the impact of preformed donor-specific antibody (DSA), as well as the number of HLA mismatch, since most of these data were missing, especially for SLKT performed in the earlier era. Therefore, their effect was excluded from the analysis in addition to the fact that our center’s protocols do not depend on the results of such cross-matching in the decision-making process. Interestingly, Hanish et al in their study found the incidence of acute cellular rejection and antibody-mediated rejection to be less common among SLKT recipients compared to those receiving KTA regardless of the levels of preoperative panel reactive antibodies or DSA, and that a high level of DSA should not preclude SLKT.⁴¹ However, their effect on developing kDGF was not clearly assessed. Regarding the inclusion of retransplanted patients in our study cohort, it was difficult to exclude them since they represent a significant proportion of our patient population, and despite that, they did not seem to pose increased risk of developing kDGF.

In conclusion, the incidence of kDGF among recipients of SLKT remains high based on the definition of dialysis requirement within the first 7 days after transplant. It is obviously higher than the reported rates of kDGF among recipients of KTA, which may raise the need for reconsideration of refinement of the definition of kDGF among SLKT patient population, who are physiologically different in terms of sickness compared to those receiving KTA. The study offers an acceptable model of preoperative predictors of kDGF among SLKT recipients with high MELD. Donor history of hypertension and cold static preservation of kidney graft were the strongest predictors of kDGF, followed by donor final creatinine, physiologic MELD, and longer period of delay between liver and kidney transplantation. It identifies the impact of matching proper donors for such sick group of patients in an attempt to mitigate kDGF. It also demonstrates that patient severity of illness plays a key role in developing kDGF, which requires better understanding of the risk factors to provide proper perioperative patient care and implement careful patient selection criteria to achieve optimal outcomes. Furthermore, kDGF did not only affect short-term kidney graft function, but also had detrimental effects on long-term graft function and graft survival. The use of HPMP did not appear to be the only factor protecting against kDGF. Other factors

proved to play important roles. The advocacy toward the use of HPMP to improve early graft function among DCD grafts cannot yet be confirmed in this study owing to the small numbers of DCD grafts included. Further prospective studies with larger numbers of patients undergoing SLKT are indeed required to validate and confirm such conclusions.

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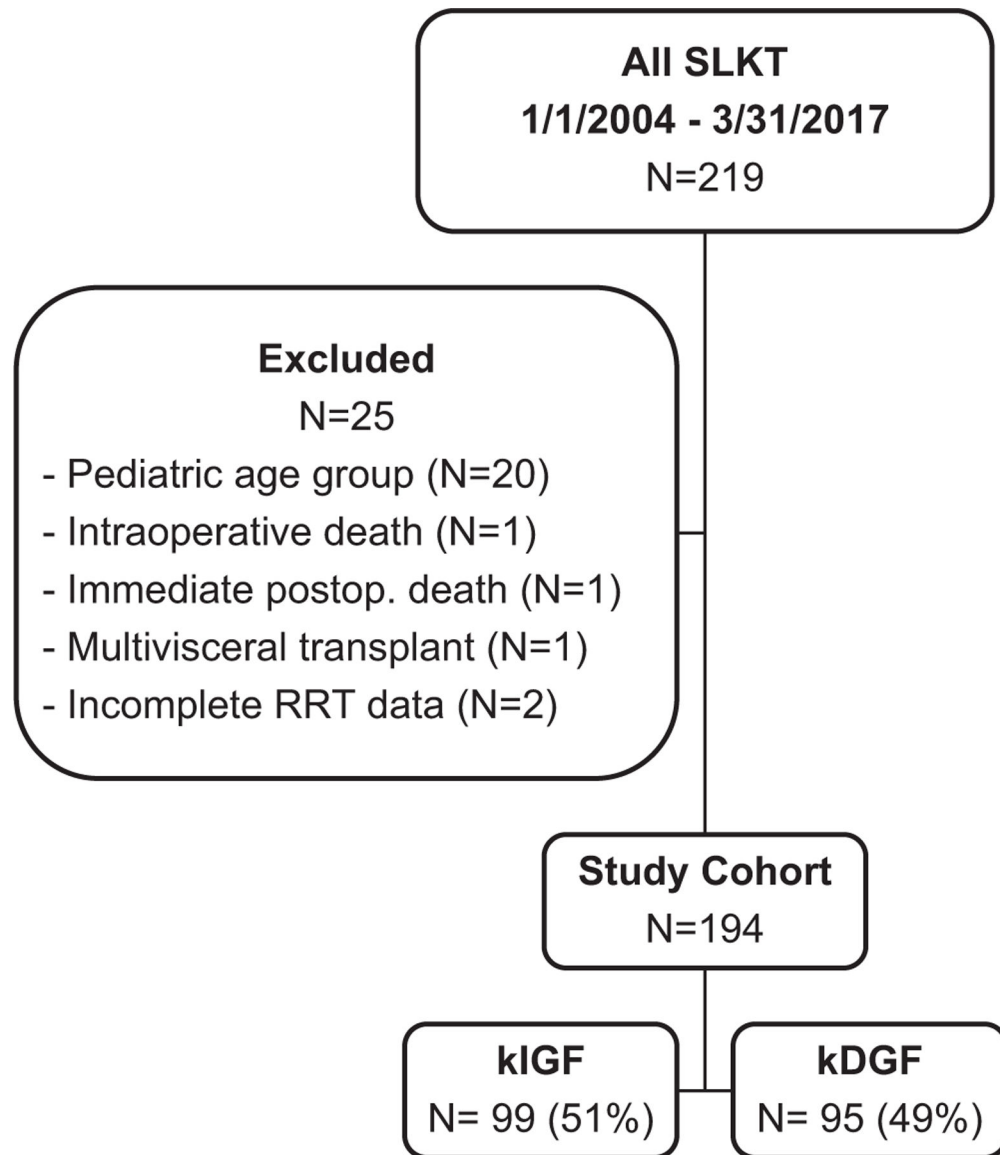


FIGURE 1.

Flowchart showing study design and the population of patients included in the analysis over a 13-y period. kDGF: kidney delayed graft function; kIGF: kidney immediate graft function

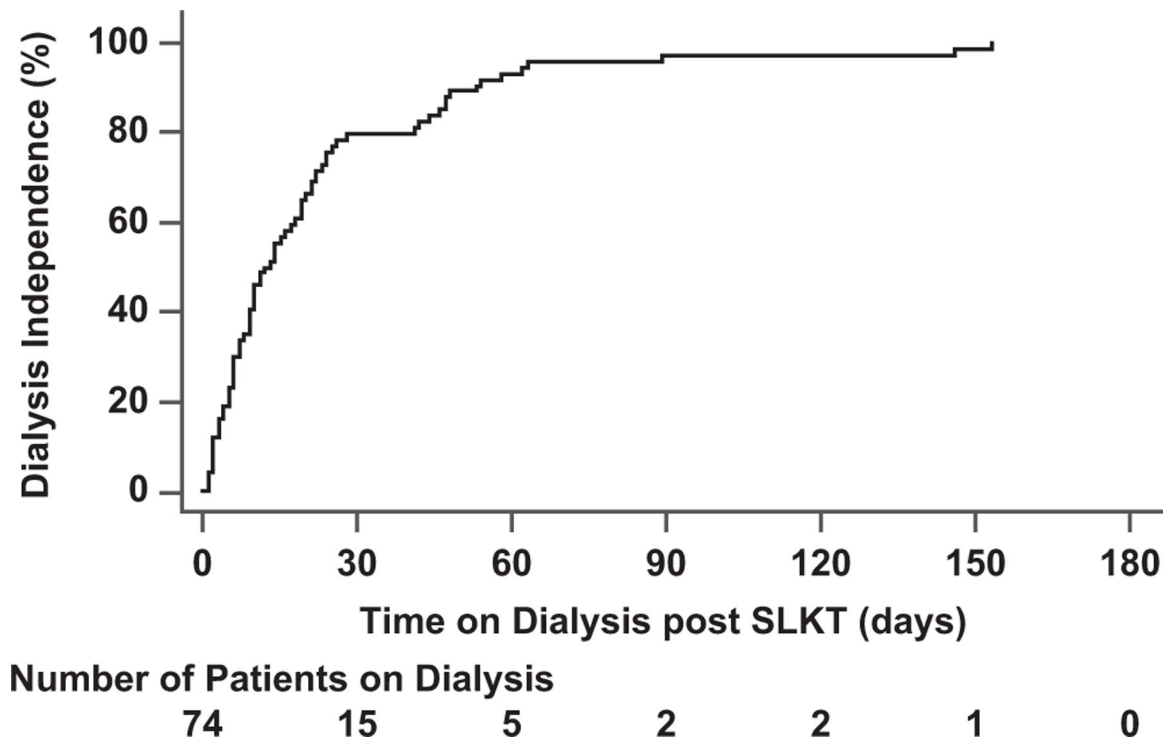
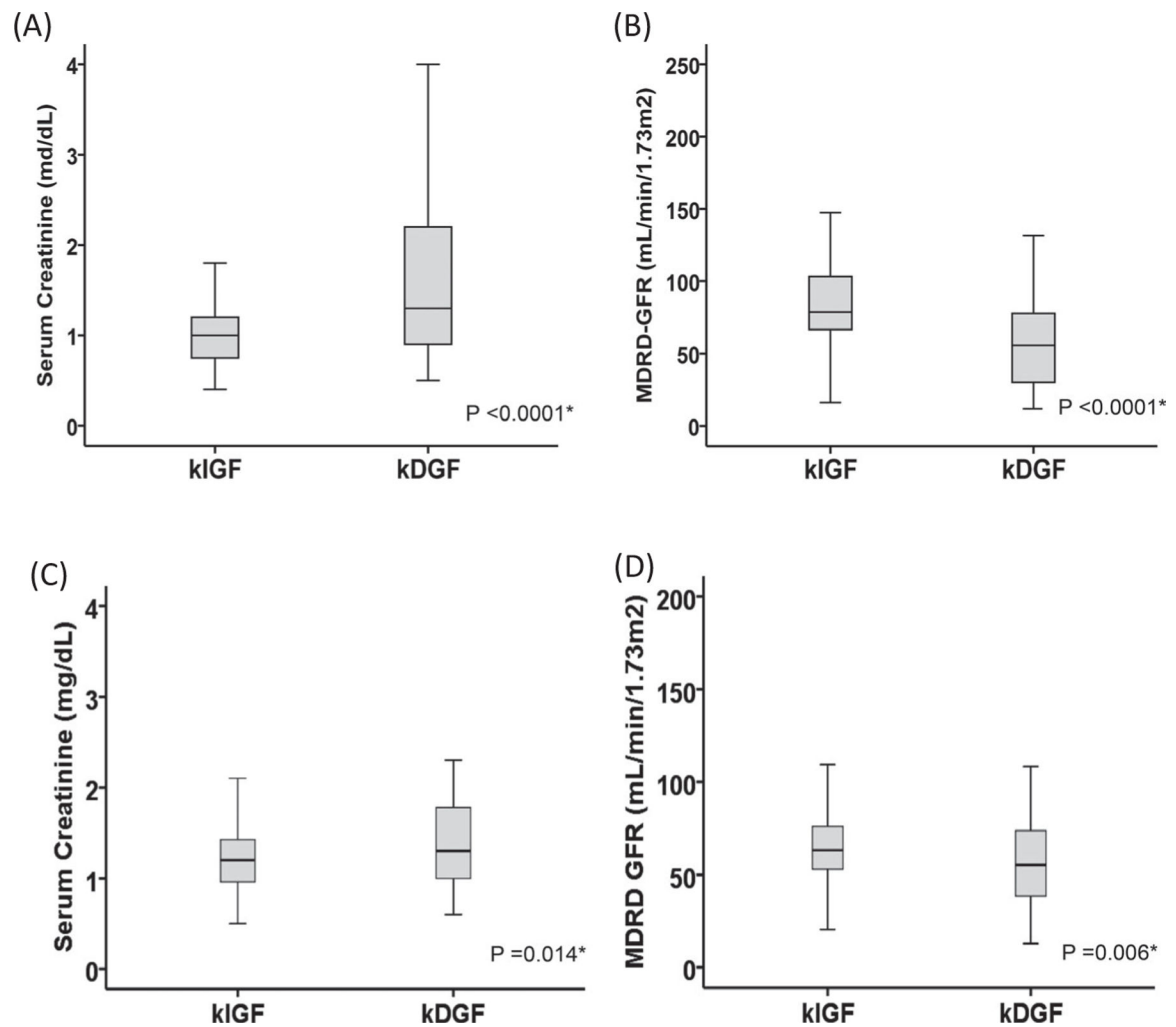


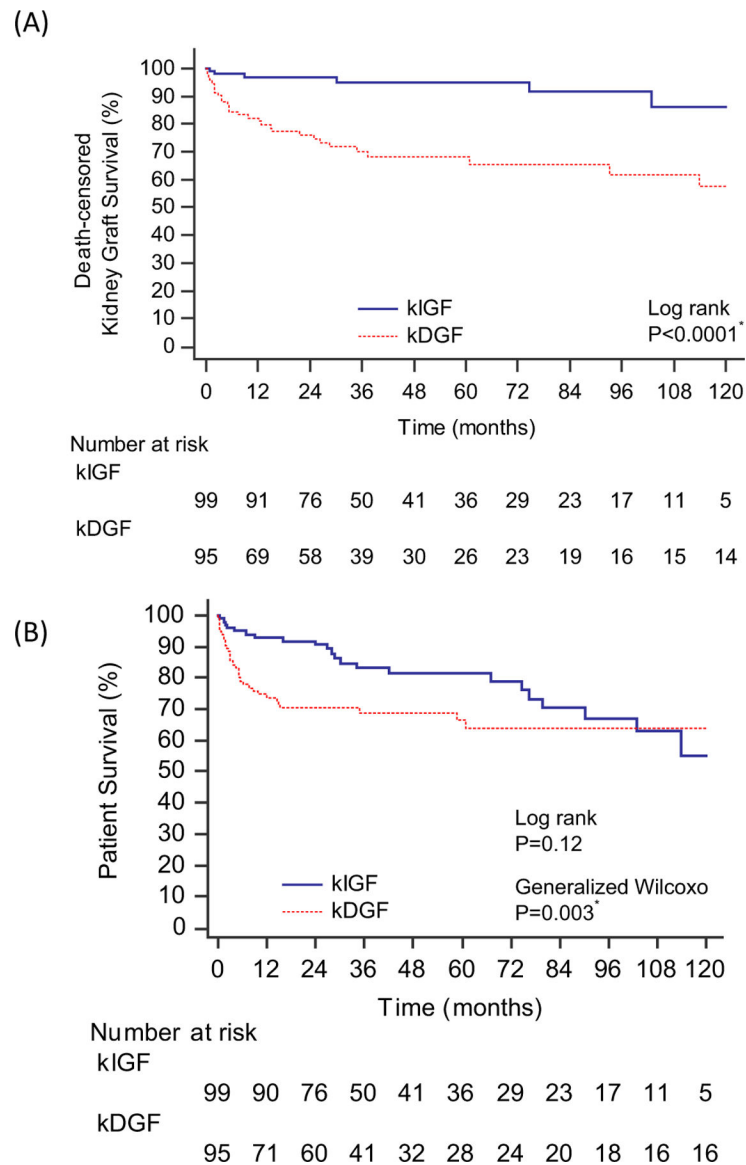
FIGURE 2.

Time to dialysis independence among 74 SLKT recipients with kDGF who recovered their graft function. Greater than 95% of patients regained their renal allograft function within 90 d post-SLKT

**FIGURE 3.**

Graft function at 3 and 12 mo after transplant. A, Serum creatinine at 3 months, B, MDRD-GFR at 3 months, C, serum creatinine at 12 months, and D, MDRD-GFR at 12 months.

Recipients with kDGF had significantly worse graft function at 3 and 12 mo postoperatively compared to those with kIGF. kDGF: kidney delayed graft function; kIGF: kidney immediate graft function

**FIGURE 4.**

A, Death-censored kidney graft survival in kIGF and kDGF recipients showing significantly higher rate of graft loss among kDGF patients. B, Patient survival among SLKT recipients with kIGF and kDGF showing inferior survival rates among kDGF patients, more significantly during the first few years post-SLKT

TABLE 1

Cause of mortality among SLKT patients

Cause of mortality	N = 54
MSOF/graft failure due to sepsis	26 (48.1%)
Cardiopulmonary failure	13 (24.1%)
Intracranial hemorrhage	4 (7.4%)
Kidney graft failure/MSOF without sepsis	5 (9.3%)
Metastatic renal cell carcinoma	1 (1.8%)
Other/unknown	5 (9.3%)

MSOF, multisystem organ failure.

TABLE 2
Comparison of preoperative factors, intraoperative factors, and postoperative outcomes among patients with KDGF and kIGF

Variables	kDGF (n = 95)	kIGF (n = 99)	P
Recipient demographics and preoperative factors			
Recipient age (y)	57.8 (47.1–63.4)	57.3 (51.1–63.4)	0.696
Recipient sex, male	60 (63.2%)	65 (65.7%)	0.716
Recipient BMI (Kg/m ²)	26.4 (22.7–30.6)	25.3 (21.9–28)	0.190
Time on waitlist (days)	34 (14–272)	41 (14–300)	0.845
Allocation MELD at listing	32 (23–38)	32 (21–38)	0.488
Physiologic MELD at time of SLKT	37 (31–41)	34 (28–38)	0.003 *
Recipient history of hypertension	52 (54.7)	62 (62.6%)	0.264
Recipient history of diabetes mellitus	49 (51.6%)	49 (49.5%)	0.772
Duration of preoperative RRT (days)	53 (33–145)	53 (18–240)	0.454
Liver retransplantation	22 (23.2%)	17 (17.2%)	0.298
Kidney retransplantation	1 (1.1%)	4 (4%)	0.189
Hospitalization	79 (83.2%)	65 (65.7%)	0.005 *
Preoperative overall hospital stay (days)	24 (9–49)	13 (1–34)	0.004 *
Preoperative ICU stay (days)	3 (0–19)	0 (0–15)	0.044 *
Vasopressor requirement	34 (35.8%)	17 (17.2%)	0.003 *
Mechanical ventilation	31 (32.6%)	18 (18.2%)	0.021 *
Dialysis	94 (98.9%)	90 (90.9%)	0.011 *
Chronic pretransplant dialysis (>2 mo)	42 (44.2%)	43 (43.4%)	0.913
Donor/kidney allograft factors			
Donor age (y)	35 (24–48)	33 (21–45)	0.391
Donor sex, male	56 (58.9%)	65 (65.7%)	0.335
Donor BMI (Kg/m ²)	24.9 (22.1–29.4)	25.2 (22.1–28.3)	0.575
Donor cause of death			
Trauma	40 (42.1%)	43 (43.4%)	0.758
Cerebrovascular accident	36 (37.9%)	35 (35.4%)	
Anoxia	15 (15.8%)	19 (19.2%)	

Variables	kDGF (n = 95)	kIGF (n = 99)	P
Other cause	4 (4.2%)	2 (2%)	
Placement of kidney graft on HPMP	8 (8.4%)	16 (16.2%)	0.102
DCD donor type	5 (5.3%)	2 (2%)	0.226
ECD donor type	12 (12.8%)	7 (7.1%)	0.192
Kidney donor risk index	0.95 (0.81–1.36)	0.93 (0.77–1.1)	0.036*
Donor history of diabetes mellitus	4 (4.3%)	5 (5.1%)	0.781
Donor history of hypertension	25 (26.9%)	12 (12.2%)	0.011*
Donor final creatinine	1.1 (0.9–1.4)	0.9 (0.7–1.15)	<0.001*
Kidney CIT (min)	880 (702–1264)	767 (648–901)	0.006*
Liver CIT (min)	426 (329–539)	405 (300–495)	0.187
Duration of delay of kidney after liver transplantation (min)	394 (303–885)	354 (280–447)	0.012*
Intraoperative factors			
Liver WIT (min)	42 (35–52)	39 (35–48)	0.114
Placement on intraoperative dialysis	37 (38.9%)	24 (24.2%)	0.027*
Transfused packed RBCs	29 (18–43)	18 (12–27)	<0.001*
Damage control (abdominal packing)	26 (27.4%)	11 (11.1%)	0.004*
Postoperative outcomes			
Length of postoperative ICU stay (days)	18 (8–35)	9 (6–16)	<0.0001*
Total length of postoperative hospital stay (days)	44 (24–68)	23 (14–51)	<0.001*
Serum creatinine at 3 mo postoperatively (mg/dL)	1.3 (0.9–2.2)	1 (0.74–1.2)	<0.0001*
MDRD-GFR at 3 mo postoperatively (mL/min/1.73 m ²)	55.6 (29–78.5)	78.7 (66.5–103.3)	<0.0001*
Serum creatinine at 1 y postoperatively (mg/dL)	1.3 (1–1.8)	1.2 (0.94–1.43)	0.014*
MDRD-GFR at 1 y postoperatively (mL/min/1.73 m ²)	55.2 (36.2–75.2)	63.1 (52.8–76.1)	0.006*
Renal allograft fertility	29 (30.5%)	4 (4%)	<0.0001*
Acute kidney allograft rejection	8 (8.5%)	5 (5.1%)	0.347

Continuous data are reported as median (interquartile range).

Categorical data are reported as n (%).

* Statistical significance at $P < 0.05$.

TABLE 3

Multivariate analysis of preoperative risk factors contributing to KDGF

Preoperative factors	OR	95% CI for OR	P-value
Preoperative dialysis	8.66	0.73–102.8	0.087
DCD type of kidney graft	5.74	0.89–36.85	0.065
Donor history of hypertension	3.62	1.51–8.71	0.004 *
Cold static preservation of graft (vs HPMP)	3.34	1.13–9.87	0.029 *
Donor final creatinine level (mg/dL)	2.11	1.16–3.86	0.015 *
Physiologic MELD at time of SLKT	1.08	1.02–1.14	0.004 *
Duration of delay of kidney after liver transplant	1.001	1.00–1.002	0.012 *
Recipient age	0.97	0.94–1.01	0.099

* Statistical significance at $P < 0.05$

TABLE 4

Comparison of kidney allografts placed on HPMP versus those kept on CSP

Variables	HPMP (n = 24)	CSP (n = 170)	P
Delay of kidney after liver transplantation (min)	374 (349–1259)	364 (280–471)	0.034 *
Total length of postoperative hospital stay (days)	39 (31–73)	32 (17–58)	0.026 *
Length of postoperative ICU stay (days)	16 (10–30)	11 (7–26)	0.043 *
Serum creatinine at 3 mo (mg/dL)	1.07 (0.9–1.45)	1.1 (0.8–1.4)	0.713
MDRD-GFR 3 at months (mL/min/1.73 m ²)	65.7 (45.2–92.6)	72.3 (51.9–92.5)	0.419
Serum creatinine at 1 y (mg/dL)	1.3 (0.92–1.4)	1.3 (1–1.5)	0.781
MDRD-GFR at 1 y (mL/min/1.73 m ²)	60.6 (43.7–77.2)	60 (46.3–75.6)	0.888
Kidney delayed graft function	8 (33.3%)	87 (51.2%)	0.102
Overall renal recovery	22 (91.7%)	149 (87.6)	0.745
Renal allograft utility (RAF)	2 (8.3%)	31 (18.6%)	0.215
Biopsy-proven acute tubular necrosis	3 (12.5%)	56 (32.9%)	0.042 *
Biopsy-proven acute kidney allograft rejection	0	13 (7.7%)	0.158

* Statistical significance at $P < 0.05$.

TABLE 5

Comparison of KDGF grafts placed on HPMP and CSP

Variables	HPMP with KDGF (n = 8)	CSP with KDGF (n = 87)	P
Delayed renal recovery from KDGF	6 (75%)	66 (75.9%)	1.00
Duration of dialysis till recovery of renal functions	31 (8–50)	10 (6–23)	0.22
Serum creatinine at 3 mo (mg/dL)	1 (0.88–1.75)	1.2 (0.9–1.5)	0.72
MDRD-GFR 3 at months (mL/min/1.73 m ²)	65.1 (38–91.2)	62.5 (48–81.9)	0.85
Serum creatinine at 1 y (mg/dL)	1.16 (0.89–1.86)	1.3 (1–1.5)	0.99
MDRD-GFR at 1 y (mL/min/1.73 m ²)	61.9 (28.6–78.5)	58.3 (47.3–79.3)	0.75

Continuous data are reported as median (interquartile range).

Categorical data are reported as n (%).