Comparison of Renal Allograft Outcomes in Combined Liver-Kidney Transplantation Versus Subsequent Kidney Transplantation in Liver Transplant Recipients: Analysis of UNOS Database

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Background. There may be an allograft-enhancing effect by the liver on the renal allograft in the setting of simultaneous combined liver-kidney transplantation (CLKT) from the same donor. This study was performed to investigate whether an existing liver allograft could protect a kidney allograft from immunologic injury due to histoincompatibility in liver transplant recipients who received sequential kidney transplantation (KALT).
Methods. Using the United Network for Organ Sharing database covering January 1996 to December 2003, outcomes of 352 KALT were compared to 1,136 CLKT. Incidence of acute and chronic rejection and rejection-free renal graft survival was compared between two groups.
Results. Renal half-life of KALT allografts was shorter than CLKT group (6.6±0.9 vs. 11.7±1.3 years, $P<0.001$). Incidence of chronic rejection in KALT group was higher than CLKT group (4.6 vs. 1.2%, $P<0.001$). One and three-year rejection-free renal graft survival of KALT and CLKT groups were different (77% and 67% KALT vs. 85% and 78% CLKT, respectively; $P<0.001$). Among human leukocyte antigen mismatched and sensitized patients, rejection-free renal graft survival of KALT group was inferior to the CLKT group (75% at 1 year and 61% 3 years vs. 86% at 1 year and 79% 3 years, $P<0.001$).
Conclusion. Liver allograft provided renal graft immunoprotection if both organs are transplanted simultaneously (immunogenetic identity), but not for kidneys transplanted subsequently.

Keywords: Rejection, Graft survival.

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Renal dysfunction is commonly seen in patients undergoing orthotopic liver transplantation (OLT) and up to 8% of recipients receive hemodialysis prior to liver transplantation (*1*). Combined liver-kidney transplantation (CLKT) is performed in OLT patients with irreversible renal dysfunction (*2*). Calcineurin inhibitor-based immunosuppression may result in a 30% decline of glomerular filtration rate during the first six months following OLT (*3*). Ten years after OLT, up to 18% of recipients develop end-stage renal failure (*3*), many of whom will be considered for renal transplantation (*4*).

We and others have previously shown a lower incidence of renal allograft loss from chronic rejection in patients who received a simultaneous CLKT from the same donor compared to those patients who received a kidney alone transplant (*5–9*). This observation suggests that there may be an immunoprotective effect on the transplanted kidney by the liver allograft.

There are several postulated mechanisms to account for the observed immunoprotection. Existing alloantibodies and cytotoxic T lymphocytes in the systemic circulation may be neutralized by soluble class I (human leukocyte antigen [HLA]-A and -B) antigens that are produced by the liver allograft (*10*, *11*). More recently, soluble HLA-G antigen, which has inhibitory properties towards major immune effectors involved in graft rejection (specifically natural killer and cytotoxic T cells), has also been proposed to be involved (*12*). Another mechanism may be clearance of preformed antibodies by Kupffer cells in the hepatic allograft (*13*, *14*). Patients with a positive crossmatch prior to liver transplantation have been shown to have a negative crossmatch following implantation of the new liver. Additionally, hematopoietic chimerism may play a role in the immunoprotection, as demonstrated by the presence of donor leukocytes within the liver graft and the generation of new hepatocytes, cholangiocytes, duct cells, and endothelial cells from recipient extrahepatic stem cells (*15–17*).

It is not known whether this immunoprotection is donor specific. Therefore, it is unclear whether this apparent immunoprotection would be present when a kidney from a different donor is transplanted at a later time following liver transplantation. A comparison of outcomes of the renal allograft in kidney transplantation after liver transplantation (KALT) versus CLKT group may provide additional insight into the mechanism of immunoprotection in the setting of liver and kidney transplantation.

The aim of this study is to compare the clinical outcomes of the renal allograft in the setting of simultaneous CLKT from a single donor with that of a KALT from different donors, utilizing the UNOS Scientific Renal Transplant Registry Database from 1996 to 2003.

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PATIENTS AND METHODS

Between January 1996 and December 2003, 352 kidney transplantations performed in liver transplant recipients (KALT) were identified from the Organ Procurement and Transplant Network (OPTN)/United Network for Organ Sharing (UNOS) data as of July 4, 2004. During this same period, 1,136 CLKT were also reported to UNOS. The outcomes of these two groups were compared.

Statistical Analysis

Patient and graft survival rates were estimated using the Kaplan-Meier product limit method. The log-rank test was used for comparison of the survival curves. Nonparametric Kruskal-Wallis equality of populations rank test was used to compare continuous variables. Chi-square test was used to compare categorical variables. *P* values less than 0.05 were considered as statistically significant. All reported *P* values were two-tailed. The *P* values listed for causes of patient deaths and graft loss represent a measure of association between the overall causes of the two groups. For graft survival, all patient deaths were considered as graft failure regardless graft functioning status at the time of patient death. For death-censored graft survival (Fig. 1), all patient deaths treated as lost to follow-up. Rejection-free graft survival (Figs. 2 and 3) was computed according to the following equation: $P(T>t)=S(t)$ where P is the probability of a patient whose graft is functioning through time (T) without any rejection (t) and S is the survival function. Briefly, nonimmunological failure and death were treated as lost to follow-up. Therefore, all patients were followed to one of the following criteria: 1) the first biopsy confirmed rejection episode during the initial hospital stay; 2) the first clinical rejection at consecutive UNOS database follow-up records if no rejection episode during the initial hospital stay; 3) graft failure if no acute or chronic rejection was previously reported; 4) patient death if no acute or chronic rejection or graft failure was reported prior to patient death; or 5) last follow-up report if criteria one through four did not occur. Discharge date or follow-up date was treated as the date of the occurrence of the first rejection when the first rejection episode was reported in UNOS transplant registry form or the corresponding follow-up form, respectively. Since graft survival curves on a logarithmic scale are straight after one year, we assumed constant yearly graft loss rate beyond one year after transplantation. The natural logarithm of two divided by the constant yearly graft loss rate yielded the estimated half-life of a functioning graft at one year posttransplantation.

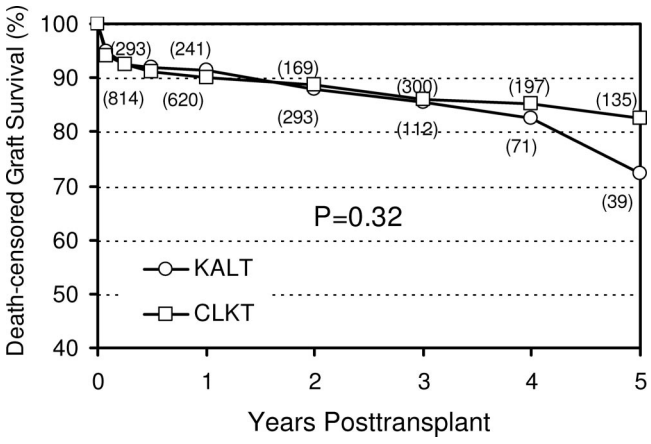

FIGURE 1. Death-censored graft survival of KALT and CLKT patients. Numbers in parentheses indicates patients number at risk at each follow-up time.

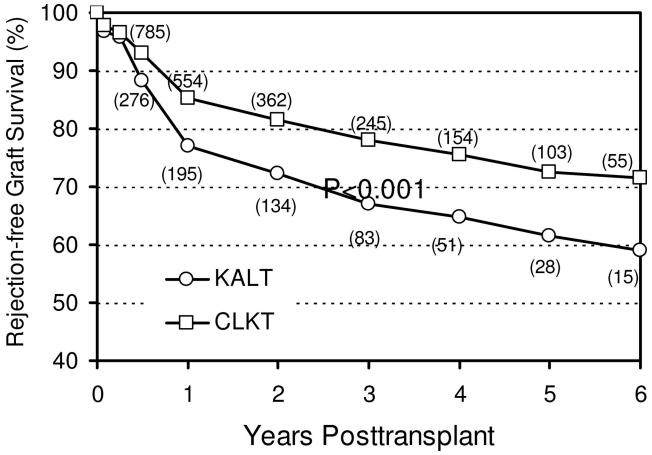

FIGURE 2. Rejection-free graft survival of KALT and CLKT patients. Numbers in parentheses indicates patients number at risk at each follow-up time.

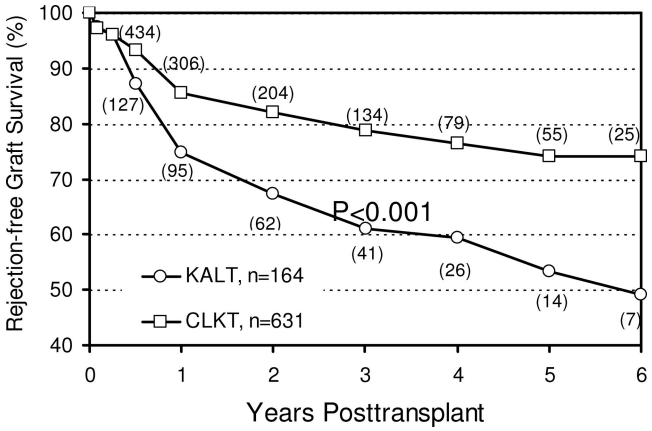

FIGURE 3. Rejection-free graft survival of sensitized (peak PRA>0%) KALT and CLKT patients who received HLA mismatched grafts. Numbers in parentheses indicates patients number at risk at each follow-up time.

RESULTS

The demographic and clinical characteristics of the two groups are shown in Table 1. A higher percentage of CLKT recipients were African American compared to KALT recipients (13% vs. 7%, $P=0.002$). Recipients in the KALT group were older (53.9 vs. 47.5 years, $P<0.001$) and were more likely to be on dialysis (77% vs. 52%, $P<0.001$) at the time of transplantation. A greater proportion of CKLT recipients were hospitalized at the time of transplantation compared to KALT recipients (41% vs. 3%, $P<0.001$). Among the hospitalized CLKT patients, 49% were in the intensive care unit, whereas none of the patients in the KALT group required intensive care treatment at the time of transplantation ($P<0.001$).

TABLE 1. Recipient characteristics

	KALT	CLKT	*P* value
Age	53.9±11.3 (352)	47.5±14.5 (1136)	<0.001
Height (cm)	171.2±11.8 (304)	167.4±19.3 (881)	0.02
Weight (kg)	74.7±17.4 (273)	74.3±22.5 (898)	0.91
Peak panel reactive antibody			<0.001
0	42.5% (149)	44.5% (505)	
1–10	28.5% (100)	12.9% (147)	
11–100	27.1% (95)	18.3% (208)	
Unknown/missing	2.0% (7)	24.3% (276)	
Female	32% (112)	36% (412)	0.13
African Americans	7% (23)	13% (143)	0.002
No dialysis at transplant	23% (79)	48% (548)	<0.001
Medical condition at transplant			<0.001
ICU	0% (0)	20% (231)	
Hospitalized but not ICU	3% (12)	21% (235)	
Not hospitalized	97% (340)	59% (670)	
On life support at transplant	0% (0)	8% (95)	<0.001
Waiting time (days)	437±402 (352)	141±249 (809)	<0.001

Data are mean±SD or percent (n).
PRA, panel reactive antibody; ICU, intensive care unit.

TABLE 2. Donor and graft characteristics

	KALT (n)	CLKT (n)	*P* value
Age (mean years±SD)	37.3±16.2 (352)	33.1±16.1 (1136)	<0.001
Height (cm)	177.0±22.2 (352)	166.5±22.7 (1135)	0.56
Weight (kg)	74.7±21.3 (352)	70.9±20.5 (1136)	0.003
Serum creatinine (mg/dl)	1.0±0.9 (349)	1.0±0.9 (1128)	0.07
Female	42% (147)	42% (481)	0.85
African Americans	8% (28)	12% (140)	0.02
Cause of death			0.80
Anoxia	9% (30)	10% (113)	
CVA/stroke	39% (139)	36% (410)	
Head trauma	48% (169)	49% (560)	
CNS tumor	2% (6)	2% (23)	
Others	2% (8)	2% (28)	
Cold ischemia time (hr)	20.7±8.3 (266)	12.3±6.0 (712)	<0.001
Warm ischemia time (min)	26.5±21.3 (200)	30.1±17.7 (521)	0.01
No. of HLA-A, B, DR antigen mismatch	3.2±1.8	4.8±1.1	<0.001

CVA, cerebrovascular accident; CNS, central nervous system.

The clinical characteristics of the donors for CLKT and KALT were similar with regards to gender, renal function, and causes of death. However, donors for CLKT recipients were younger (33.1 vs. 37.3 years, $P<0.001$; Table 2). Renal allograft cold ischemia time was longer (20.7 vs. 12.3 hr, $P<0.001$) and warm ischemia time was shorter (26.5 vs. 30.1 hr, $P=0.01$) in the KALT group compared to the CLKT group.

Although patient and renal graft survival rates were not significantly different between the two groups, patient survival approached statistical significance ($P=0.06$), which was likely caused by the high morbidity of CKLT at the time of transplantation (Fig. 4). Other than cardiovascular complications, which occurred more often in the KALT group compared to the CLKT group (4% vs. 2%, $P<0.04$), the causes of patient death were similar among the two groups (with infection being the most common etiology). The causes of renal allograft loss among the two groups were also similar with the exception of chronic rejection which occurred more frequently in the KALT group (4.6%) compared to the CLKT group (1.2%; $P<0.001$). There was no statistically significant association between the overall causes of death in both groups.

No patient in the KALT group and only three in the CLKT group developed hyperacute rejection. The incidence of acute rejection as a cause of graft loss was similar between

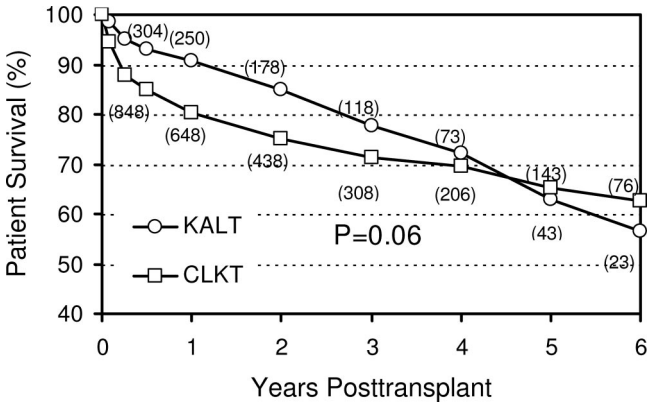

FIGURE 4. Patient survival of KALT and CLKT patients. Numbers in parentheses indicates patients number at risk at each follow-up time.

the two groups (KALT 1.4% vs. CLKT 1.1%). The incidence of acute rejection requiring treatment during the initial hospital stay for transplantation was comparable; KALT recipients (6.3%) vs. CLKT recipients (7.0%; $P=0.65$). However, the six-month and one-year cumulative acute rejection rates among KALT recipients were significantly higher (KALT 15.4% vs. CLKT 10.3% at six-months, $P=0.009$; KALT 18.0% vs. CLKT 11.8% at 1-year, $P=0.003$). The incidence of chronic rejection in the KALT group was significantly higher than that in the CLKT group (4.6% vs. 1.2%, $P<0.001$). Acute and chronic graft loss resulted in significantly shortened half-life among KALT renal allografts compared to CLKT group (6.7 ± 0.9 yrs vs. 11.7 ± 1.3 yrs, $P<0.001$).

Death-censored renal graft survival was similar between the two groups (92%, 86% at one year and three years for KALT vs. 91%, 86% at one year and three years for CLKT, $P=0.38$; Fig. 5). To further discern immune differences between KALT compared to CLKT, the effect of rejection on renal graft survival was analyzed. Rejection-free graft survival was significantly lower for the KALT group compared to CLKT (77% at one year and 67% at three years vs. 85% at one year and 78% at three years; $P<0.001$; Fig. 1). Rejection-free graft survival in kidney allografts with two risk factors (HLA mismatch and panel reactive antibody) was superior among CLKT group compared to KALT group (86% and 79% at one year and three years vs. 75% and 61% at one year and three years, respectively; $P<0.001$; Fig. 2). Within the KALT group, renal allografts with two risk factors yielded a significantly lower rejection-free survival rate compared with those allografts with lower risk (74.8% at one year, 61.0% at three years [n=164] vs. 79.0% at one year and 72.8% at three years [n=187], log-rank $P=0.05$).

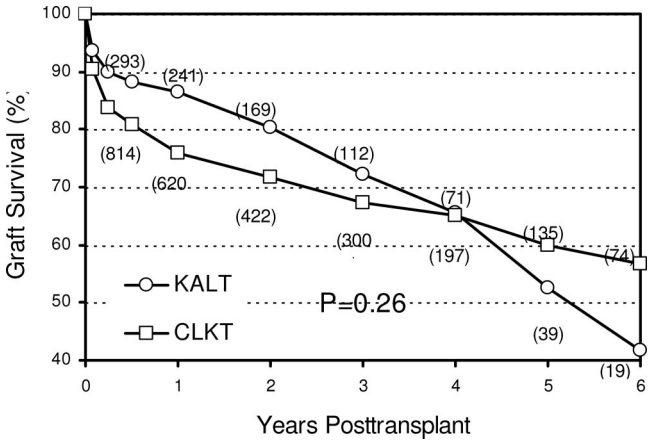

FIGURE 5. Graft survival of KALT and CLKT patients. Numbers in parentheses indicates patients number at risk at each follow-up time.

DISCUSSION

Approximately 10–20% of patients undergoing OLT have renal insufficiency (*18*), such that 2% will require simultaneous combined liver kidney transplant (*4*). The use of calcineurin inhibitors in liver transplantation has led to improved survival, but both cyclosporine and tacrolimus are nephrotoxic, contributing to the development of end-stage renal disease (ESRD) in approximately 18% of OLT patients after 13 years (*3*). Once renal failure ensues in OLT patients, survival is shortened compared to patients without renal failure. Among OLT patients with ESRD, survival is higher in those who receive a subsequent kidney transplantation compared to OLT patients who are managed on hemodialysis.

This study was conducted to elucidate the mechanism of immuno-protection by the hepatic allograft on the kidney allograft in the setting of CLKT from the same donor. This was done by comparing the outcomes of the kidney allograft in CLKT patients with those in OLT patients who underwent a subsequent renal transplantation from a different deceased donor. Although overall patient survival was similar among the two groups, first year survival in the CLKT group was considerably lower, as a result of the severity of medical condition at the time of transplantation (*5*). Death during the first year was mainly due to infection rather than an immunologic cause (*5*). When deaths during the first year were censored, the half-life of the renal grafts was significantly longer in the CLKT group compared to KALT patients. This appears to be an immunological phenomenon as evidenced by superior rejection-free graft survival. In addition, lower frequency of rejection-free graft loss was found among high-risk HLA mismatched and sensitized recipients in the CLKT versus KALT. In rejection-free graft survival acute and chronic rejection were salient features of better results with CLKT. This difference is underscored by the higher proportion of African Americans in the CLKT group, which is a demographic characteristic associated with decreased graft survival (*19*, *20*).

In our analysis, we used death-censored graft survival to eliminate most of the comorbidities such as diabetes, hypertension, donor age, and duration of dialysis prior to renal transplant, which are potential confounding factors with respect to outcomes. As such, we found no differences in death-censored graft survival between KALT vs. CLKT.

The findings of this study may provide additional insight into the immunological mechanism of the protection of the liver allograft on the kidney allograft in the setting of CLKT. Donor-specific antibodies, which are of recipient origin and directed toward the donor mismatched antigens, have been implicated in 30–75% of acute renal rejection (*21*–

23) and over 50% of chronic refection (*24–26*). In CLKT, all donor mismatched antigens are identical for both kidney and liver allografts as the organs are from the same donor. On the other hand, in the KALT recipient, it is highly improbable that donor HLA antigens from the renal and hepatic allografts are matched: the probability of zero mismatch is one in 4,000 (*27*). Therefore, in a CLKT, an immune response by the recipient would be directed toward common antigens shared by the liver and kidney allografts, whereas in the setting of KALT, the immune response would be directed to antigens not shared by the kidney and the liver allografts.

The lower incidence of chronic rejection and longer half life of renal allografts in the CLKT group compared to the KALT group in this study are consistent with the earlier findings in the rat model reported by Gugenheim et al. (*14*, *28*). Gugenheim reported a reduction in the level of lymphocytotoxic antibodies in sensitized rats that underwent extracorporeal liver hemoperfusion. As in the KALT paradigm, there was a significant reduction in lymphocytotoxic antibodies as compared to control rats in which a third-party liver hemoperfusion was performed. Based on immunofluorescence examination of the hemoperfused liver and blockade of Kupffer cells, Gugenheim and colleagues further hypothesized that non-parenchymal liver cells play a critical role in the absorption of lymphocytotoxic antibodies (*28*). An alternate explanation for the apparent immunoprotection of the liver is the neutralization of donor-specific lymphocytotoxic antibodies and cytotoxic T lymphocytes by soluble class I (HLA-A and -B) antigens that are produced by the liver allograft (*10*, *11*). Creput et al. analyzed the expression of HLA-G in kidney and liver biopsies of 40 combined transplant recipients and demonstrated that there was a correlation between the expression of HLA-G in biliary epithelial cells (BEC) and the absence of renal graft owing rejection. More recently, Creput et al. reported the detection of HLA-G in the liver allograft and serum to be associated with a lower frequency of acute rejection of hepatic and renal allograft in CLKT (*12*).

We acknowledge the limitations of this study which are intrinsic to the retrospective analysis of the UNOS database. This includes the inability to verify the accuracy of the data and to control for multiple clinical variables such as immunosuppression regimens, as we have previously noted (*5*). There were also significant differences in patient characteristics such as older recipients, older donors and greater number of recipients on hemodialysis in the KALT group compared to the CLKT group which may have biased patient survival rates. On the other hand, the large number of patients and the database variables allowed us to utilize rejection-free analysis, which should not have been influenced by these confounding factors. Practically, the size of this study cannot be replicated, even in a multicenter study.

In summary, overall patient and graft survival were similar in KALT and CLKT groups. However, among patients rejection-free graft survival and high risk HLA mismatched and sensitized recipients, graft survival was higher in the CLKT group with a concomitant overall significant increase in graft half-life. Furthermore, cumulative incidence of rejection was higher at six months and one year in the KALT group. These findings suggest that the immunoprotection conferred by the liver on the kidney allograft maybe HLA (*immunogenetic*) specific.

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