Long-Term Outcome of Combined Liver-Kidney (Simultaneous or Sequential) Transplantation in Spain, 1991-2007

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Abstract

Background: ***Combined liver-kidney transplantation seems to be the best option for patients suffering from simultaneous chronic liver and kidney failure. However, there is lack of long-term follow-up studies of such patients.*** **Methods:** ***A retrospective epidemiological study was conducted in 16 nephrology and hepatology centers in Spain. Patients receiving a combined liver and kidney allograft (simultaneous or sequential) from 1991-2007 were included.*** **Results:** ***Among 190 transplanted patients, 150 (78.9%) had simultaneous liver-kidney transplantation, 36 (19.0%) sequential liver-kidney transplantation, and four (2.1%) sequential kidney-liver transplantation. Patients were mainly men (78.1%), mean ± standard deviation age was 51.3 ± 9.5 years for simultaneous liver-kidney transplantation, 47.3 ± 6.1 years for sequential kidney-liver transplantation, and 54.4 ± 11.4 years for sequential liver-kidney transplantation. The most frequent cause of kidney failure was primary glomerulonephritis, whereas alcoholic cirrhosis was the main cause of liver disease. Patient survival at 10 years was 57.1% for simultaneous liver-kidney transplantation, 67.3% for sequential kidney-liver transplantation, and 81.1% for sequential liver-kidney transplantation. Kidney graft survival at 10 years was 68.8% for simultaneous liver-kidney transplantation, 73.3% for sequential liver-kidney transplantation, and 100% for sequential kidney-liver transplantation. Liver graft survival was 81.4% for simultaneous liver-kidney transplantation, 66.7% for sequential kidney-liver transplantation, and 100% for sequential liver-kidney transplantation. Acute renal graft rejection was observed in 2.7% for simultaneous liver-kidney transplants and 8.3% for sequential liver-kidney transplants, while acute liver graft rejection was observed in 12.7% simultaneous liver-kidney transplant patients.*** **Conclusions:** ***Retrospective data from patients receiving combined liver-kidney transplantation show similar graft and patient survival to that obtained in patients only receiving a liver transplant, suggesting that both simultaneous and sequential liver-kidney transplantation can be considered a valid option for patients waiting for a liver transplant and suffering from chronic kidney disease.*** **(Trends in Transplant. 2013;7:11-22)**

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Key words

Combined transplantation. Kidney. Liver. Simultaneous. Survival.

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Introduction

Improved surgical techniques and postoperative management in single transplantation (liver or kidney) has led to an improvement of graft and patient survival. However, some of these patients may require a subsequent liver or kidney transplant, mainly because of the nephrotoxic effect of calcineurin inhibitors, or the acceleration of preexisting liver or kidney disease[1-3].

Since the first combined liver-kidney transplantation (CLKT) performed by Margreiter, et al.[4] in 1984, either simultaneous or sequential liver-kidney (LKT) or kidney-liver transplantation (KLT) has become more usual in patients suffering from concurrent irreversible failure of both organs[5,6]. Ideal candidates for CLKT are those with end-stage liver disease in association with irreversible renal disease. Therefore, acquired viral hepatitis in dialysis patients and hereditary disorders such as polycystic liver-kidney disease currently represent the most frequent indications for such a procedure[7,8]. Two different single-center retrospective studies performed in Spain focusing on LKT transplantation[9,10] showed that the main causes of liver and kidney failures were cirrhosis (especially induced by hepatitis C virus and alcohol), and chronic glomerulonephritis, respectively.

Similarly to other transplant settings, CLKT has increa sed risk of infections and malignancies, although renal graft rejection has interestingly been shown to be significantly lower in simultaneous liver/kidney transplantation (SLKT) as compared to LKT, or even to renal transplantation alone[11,12]. Some studies on combined transplantation suggest that the transplanted liver may confer a protective effect on the simultaneous engraftment of the kidney[11,13], although there have also been reports suggesting that liver does not always protect the kidney from acute rejection[14]. Even though the mortality causes are similar in both transplant settings, it is important to highlight infectious diseases as the most relevant, especially because they are a very important factor of postoperative morbidity and mortality[15].

However, there is some reluctance among the transplant community because some patients undergoing a SLKT might have reversible renal failure and, thus, could benefit from just a single liver transplant[16]. Therefore, basic and clinical investigations are necessary to define an optimal algorithm. Moreover, sometimes the degree of liver or renal failure is not equivalent at the time of combined transplantation, and it would be useful to have algorithms and clinical guidelines.

Spain is one of the leading countries in organ donation[17,18]. During 2007, 1,550 true solid donors were registered in Spain, yielding a rate of 34.3 per million population (pmp). A total of 2,211 (48.9 pmp) kidney transplants and 1,112 (24.6 pmp) liver transplants were performed[17,18].

Despite the fact that CLKT has been considered a therapeutic option for those patients suffering from concomitant liver and kidney disease, few long-term CLKT studies have been reported so far in Spain and most of them have a smaller number of patients[9,10]. Furthermore, there is little information about the current data related to the number of CLKT transplants performed, the type, and conditioning causes.

It was proposed that a retrospective multicenter and long-term follow-up study review be made of procedures already performed that addresses the reality of the different options of CLKT, either SLKT, or LKT, or KLT transplantation in Spain. The main goals of this study were to describe the number of patients that received a CLKT in the past 16 years, characterize the patient's demographic profile,

identify the main immunosuppressive regimens used, and describe patient and graft survival and causes of death.

Subjects and methods

The PERLA study is a multicenter, retrospective study conducted between July 2007 and March 2008 in 16 nephrology and hepatology centers in Spain. Retrospective data was collected at different time points: at discharge, first six months (Evaluation 1), > 6-12 months (Evaluation 2), > 1-3 years (Evaluation 3), > 3-5 years (Evaluation 4), > 5-7 years (Evaluation 5), > 7-10 years (Evaluation 6), and > 10-15 years (Evaluation 7). In sequential transplantation, retrospective data from the second transplanted organ was obtained.

The population studied was all patients with CLKT (simultaneous or sequential) performed from 1991 to 2007 in the participating centers. Cases were eligible if they were 18 years or older and if they had had a CLKT (simultaneous or sequential) in the past 16 years. Recipients of non-liver-kidney solid organ transplants were excluded from the study.

A systematic, consecutive sampling was carried out by nephrologists and hepatologists in the participating outpatient clinics, which yielded the inclusion of 190 patients fulfilling all inclusion and exclusion criteria. All patients signed the informed consent for their participation in the study and an ethics committee approved the study.

The study information was obtained by the extraction of medical records. Main relevant information included patient demographics, virologic serology, blood-test data, hepatorenal failure, immunosuppressive treatment, acute rejection episodes, and patient and graft survival. Data were collected at baseline, at discharge, and during follow-up.

Kidney and/or liver rejection were suspected by graft malfunction and confirmed by biopsy (according to Banff criteria)[19].

Statistical analysis

Patient and graft survival data were calculated from the time of simultaneous transplantation, or in cases of sequential grafting, from the time of second organ transplantation, until the data of the patient's death or graft failure, respectively. Survival rates of patients, kidneys, and livers were determined by Kaplan-Meier analysis. Continuous variables were reported as a mean standard deviation (SD) and compared using the Student *t* test. The χ^2 test was used to compare categorical variables. For statistical comparison of survival distributions, the Wilcoxon test was used, and for mean comparison the Kruskal-Wallis or Mann-Whitney were performed. Values of $p < 0.05$ were considered to be significant. All data were analyzed using the software package SAS 9.1.3 (Cary, North Carolina, USA).

Results

Study population

The study population comprised 190 transplanted (simultaneous or sequential) patients for the last 16 years (from 1991 to 2007). A total of 150 patients (78.9%) had SLKT, with a median follow-up period of 3.1 years (range 0.03-15.07 years).

Forty patients (21.1%) received a sequential transplantation (four [2.1%] KLT and 36 [19.0%] LKT). Median follow-up time for KLT patients was 7.1 years (range 0.37-10.04 years). The LKT patients showed a median follow-up period of 3.1 years (range 0.12-11.01 years).

Main baseline clinical and demographic characteristics of all evaluated patients are described in table 1.

Surgical techniques

Liver transplantation was performed using standard techniques. Most patients were transplanted with a piggy-back liver transplant (81.7% SLKT, 75% KLT, and 57.1% LKT).

Kidney was implanted in the left iliac fossa in 49.7% SLKT, 33.3% KLT, and 21.1% LKT, respectively. Kidney was implanted in the right iliac fossa in 37.9% SLKT, 66.7% KLT, and 78.8% LKT.

The mean cold ischemic time in SLKT was significantly lower than in LKT ($p < 0.0001$) (Table 1).

Immunosuppressive regimen

As shown in table 1, induction therapy was basically done using monoclonal antibodies rather than polyclonal antibodies, and both were given in less than 50% of the transplanted patients. All patients received therapy with a calcineurin inhibitor (CNI) drug (either cyclosporine or tacrolimus). The most frequent immunosuppressive combination in SLKT patients was CNI plus mycophenolate mofetil/enteric-coated mycophenolate acid (MMF/EC-MPS) plus steroids and CNI + MMF/EC-MPS in LKT patients.

Renal and liver allograft function

Renal (creatinine clearance and proteinuria levels) and liver function (aspartate aminotransferase, alanine aminotransferase, and bilirubin levels) procedures are shown in figure 1.

No relevant changes in other main biological parameters were observed along the follow-up period (Table 2).

Kidney and liver acute rejection

Four out of 150 (2.7%) SLKT patients and three out of 36 (8.3%) LKT patients experienced acute kidney graft rejection. Graft rejection was biopsy proven in two SLKT and in one LKT patients.

All acute kidney graft rejection happened in an early period (< 3 months posttransplantation), except for one LKT patient that had a second acute rejection episode four months after the first one.

Nineteen out of 150 (12.7%) SLKT patients experienced an acute liver graft rejection episode, being biopsy proven in only 16 cases (three grade I, five grade II, and eight grade III). There were no acute liver rejections within KLT patients.

Eleven (57.9%) patients had an early acute liver rejection (< 3 months posttransplantation) and in eight (42.1%) patients this was later than three months (1.1 [0.1-56.2] months).

In SLKT patients, acute liver rejection was associated with higher MMF pretransplant dosage: nine patients with a mean of 1,888.9 (333.3) mg/dl vs. 72 patients with a mean of 1,597.2 (464.5) mg/dl; $p = 0.036$. Moreover, use of cyclosporine at discharge was associated significantly with a higher incidence of acute rejection than in patients treated with tacrolimus (20.4 vs. 5.5%; $p = 0.010$).

No significant associations with acute liver or kidney rejections were found with other treatment or patient characteristics.

Posttransplant complications and concomitant treatments

Posttransplant complications are depicted in figure 2. The main complications were infectious diseases and hypertension. Respiratory, urinary, digestive, and cutaneous infectious diseases were mainly due to bacteria (100, 86.7, 75.0, and 40%, respectively). Virus caused digestive infections (25%), and

Table 1. Donor and recipient characteristics, causes of liver and kidney failure, and immunosuppressive treatments

Donor and recipient characteristics	SLKT (n = 150)	KLT (n = 4)	LKT (n = 36)	P[1]
Recipient (mean ± SD)				
– Age (years)	51.3 ± 9.5	47.3 ± 6.1	54.4 ± 11.4	0.1562
– Male (%)	74.1	75.0	85.3	0.3313
– BMI (kg/m^2)	24.3 ± 4.3	25.9 ± 3.5	24.6 ± 2.9	0.6989
– SBP (mmHg)	130.6 ± 23.7	120.0[2]	153.9 ± 19.4	< 0.0001
– DBP (mmHg)	73.7 ± 12.3	60.0[2]	81.2 ± 10.1	0.0031
– Serum creatinine level (mg/dl)	5.0 ± 2.6	1.8 ± 0.5	6.9 ± 1.9	< 0.0001
– Dialysis (%)	64.9	–	88.6	0.0105
– Dialysis time (months)	4.0 ± 5.3	–	1.2 ± 1.5	< 0.0001
– MELD score	22.5 ± 5.1	7.0[2]	–	–
– CTP score	8.4 ± 1.8	8.3 ± 2.5	–	–
Donor (mean ± SD)				
– Age (years)	38.4 ± 15.5	39.4 ± 9.4	47.3 ± 16.4	0.0072
– Male (%)	63.4	100.0	75.0	0.8537
– Cold ischemic time (h)[3]	8.2 ± 4.5	3.9 ± 0.7	18.9 ± 8.0	< 0.0001
– Time from first to second transplant (years)	–	9.3 ± 9.1	6.1 ± 3.6	–
Main serologic status[4] (n)	Donor/recipient	Donor/recipient	Donor/recipient	
– HIV+	1 / 3	0 / 0	0 /0	–
– CMV+	87 / 102	3 / 4	15 / 19	–
– HBV+	- / 19	- / 2	- / 1	–
– HCV+	- / 56	- / 3	- / 11	–
– HVB+/HCV+	- / 9	- / 1	- / 0	–
Causes of end-stage organ failure (%)	**SLKT (n = 150)**	**KLT (n = 4)**	**LKT (n = 36)**	**P[1]**
Renal disease				
– Primary glomerulonephritis	34.7	75.0	19.4	0.0780
– Previous transplant failure	10.7	25.0	0.0	0.0404
– Polycystic kidney disease	10.7	0.0	5.6	0.3515
– Calcineurin inhibitor toxicity	0.7	0.0	16.7	< 0.0001
– Diabetes	3.3	0.0	8.3	0.1843
– Idiopathic	5.3	0.0	5.6	0.9563
– Others	19.3	0.0	36.1	–
Liver disease				
– Cirrhosis	81.3	100.0	88.9	0.2806
• Alcohol	43.0	0.0	60.6	0.0549
• Hepatitis C	33.9	50.0	27.3	0.4751
• Hepatitis B	7.4	25.0	0.0	0.0939
• Alcohol + Hepatitis C	5.8	0.0	6.1	0.9203
• Hepatitis B + Hepatitis C	5.8	25.0	0.0	0.1319
• Alcohol + Hepatitis B + Hepatitis C	0.8	0.0	0.0	0.6234
• Others	3.3	0.0	6.1	0.5292
– Primary hyperoxaluria	2.0	0.0	0.0	0.3922
– Cystic liver-kidney disease	8.7	0.0	2.8	0.2292
– Tumor	4.7	25.0	5.6	0.8230
– Others	9.3	0.0	13.9	0.0117
Immunosuppressive treatments (%)	**SLKT (n = 135)***	**KLT (n = 4)**	**LKT (n = 27)***	**P[1]**
Induction	40.7	25.0	29.6	0.6468
– Basiliximab	20.7	0.0	3.7	0.0306
– Daclizumab	8.9	0.0	25.9	0.0156
– ATG	8.9	25.0	0.0	0.1011
– OKT3	2.2	0.0	0.0	0.4259
IS combined treatments	(n = 108)†	(n = 3)†	(n = 31)†	
– CNI + MMF/EC-MPS + steroids	45.4	33.3	29.0	0.1039
– CNI + steroids	36.1	33.3	22.6	0.1581
– CNI + MMF/EC-MPS	16.7	0.0	41.9	0.0030
– CNI + mTOR + steroids	1.8	33.3	6.5	0.1770

1Statistical differences between SLKT and LKT groups were evaluated; 2Only one patient; 3Range of 1.5-35.0 h, 3.3-4.8 h and 7.0-45.0 h for SLKT, KLT and LKT, respectively; serology profile referred to the second organ transplant.

*Induction data were missing in 15 patients (10.0%) in SLKT and in 11 patients (28.2%) in LKT groups.

†IS combined treatment data were missing in 42 patients (28.0%) in SLKT, one patient (25.0%) in KLT and nine patients (25.0%) in LKT groups.

SLKT: simultaneous liver-kidney transplantation: LKT: sequential liver-kidney transplantation; KLT: sequential kidney-liver transplantation SD: standard deviation; DBP: diastolic blood pressure; SBP: systolic blood pressure; MELD: Model for End-Stage Liver Disease; CTP: Child-Turcotte-Pugh; ATG: antithymocyte globulin; OKT3: muromonab-CD3; mTOR: mammalian target of rapamycin inhibitor; MMF/EC-MPS: mycophenolate mofetil/enteric-coated mycophenolate acid; IS: immunosuppressive.

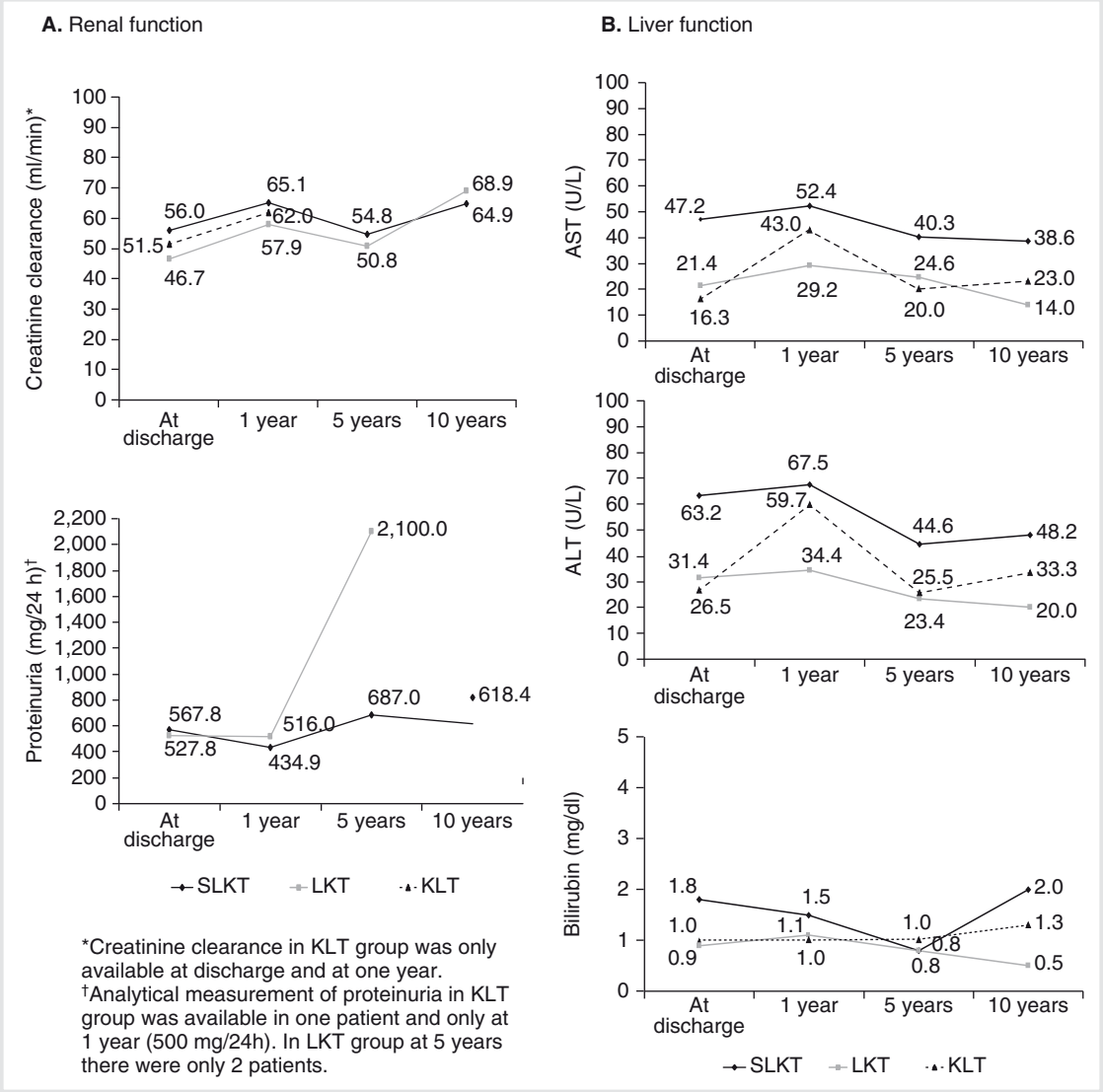

Figure 1. *Renal function **(A)** and liver function **(B)***
SLKT: simultaneous liver-kidney transplantation: LKT: sequential liver-kidney transplantation; KLT: sequential kidney-liver transplantation; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

cutaneous infections (60%). Finally, fungi were responsible for 13.3% of urinary infections and one (100%) cerebral infection.

The most frequent concomitant treatments at patient discharge were antihypertensives (21.3% SLKT, 75.0% KLT, and 55.6% LKT), anti-ulcer treatments (56.0% SLKT, 100.0% KLT, and 58.3% LKT), erythropoietin (10.0% SLKT, 25.0% KLT, and 19.4% LKT), and anti-cytomegalovirus prophylactic treatments (10.0% SLKT, 0.0% KLT, 16.7% LKT).

Graft and patient survival

About 70% of kidney transplanted patients (68.8% SLKT and 73.3% LKT) and 100% of KLT remained with a functioning kidney graft at 10 years (follow-up median of 3.1 years

Table 2. Analytical data during the study follow-up

	At discharge		1 year		5 years		10 years	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
SLKT								
– Glucose (mg/dl)	125	103.2 (41.3)	106	112.0 (39.9)	52	108.6 (31.4)	27	112.7 (35.1)
– Hemoglobin (g/dl)	113	10.2 (1.6)	97	13.3 (1.7)	45	13.0 (1.8)	26	12.8 (2.2)
– Total cholesterol (mg/dl)	87	178.2 (48.7)	85	177.9 (41.5)	41	173.9 (34.7)	26	182.1 (34.3)
– Albumin (g/l)	98	33.8 (5.8)	87	41.2 (5.7)	43	42.4 (5.4)	24	40.1 (6.1)
LKT								
– Glucose (mg/dl)	30	128.0 (56.9)	25	120.0 (37.5)	10	101.3 (22.1)	1	98.0
– Hemoglobin (g/dl)	29	10.5 (1.0)	21	14.4 (2.0)	8	13.5 (2.0)	0	–
– Total cholesterol (mg/dl)	30	167.6 (45.3)	24	187.0 (53.4)	9	170.6 (33.9)	1	225.0
– Albumin (g/l)	28	34.6 (6.1)	20	42.6 (4.0)	9	41.3 (3.7)	1	45.0
KLT								
– Glucose (mg/dl)	4	90.3 (7.0)	3	102.0 (10.0)	2	100.5 (17.7)	1	99.0
– Hemoglobin (g/dl)	4	8.9 (0.9)	2	12.8 (4.0)	2	13.0 (0.0)	0	–
– Total cholesterol (mg/dl)	4	187.8 (19.5)	3	186.7 (32.9)	2	198.0 (0.0)	1	159.0
– Albumin (g/l)	3	31.7 (1.5)	2	40.5 (2.1)	1	39.0	0	–

SLKT: simultaneous liver-kidney transplantation: LKT: sequential liver-kidney transplantation; KLT: sequential kidney-liver transplantation SD: standard deviation.

for SLKT, 7.1 years for LKT, and 3.1 years for KLT). Twenty-three out of 135 (17.0%) SLKT and five out of 28 (17.9%) LKT patients lost their kidney graft. No patients in the KLT group lost their kidney graft. The main reasons were: death with functioning graft (52.2% graft losses in SLKT patients), primary graft failure (8.7% in SLKT patients), acute rejection (8.7% in SLKT patients), chronic allograft nephropathy (17.4% in SLKT and 40.0% in LKT patients), relapse of baseline disease (8.7% in SLKT patients), and unknown (60.0% in LKT patients, 4.3% in SLKT patient).

Kaplan-Meier estimates of kidney graft survival in SLKT and LKT patients were 11.8 years (95% CI: 10.6-13.0), and 8.7 years (95% CI: 7.0-10.5), respectively. Mean survival could not be calculated in the KLT group since no patients lost their kidney graft (Fig. 3 A).

Among liver transplanted patients, 81.4% of SLKT, 66.7% of KLT, and 100% of LKT remained with a functioning liver graft at the end of the follow-up period.

Twenty-two out of 135 SLKT (16.3%) and one out of three KLT (33.3%) patients had liver graft loss.

The main reasons were: death (30.4% graft losses in SLKT and 50% in KLT), chronic rejection (13.0% in SLKT), relapse of baseline illness (13.0% in SLKT), and arterial thrombosis (8.5% in SLKT).

Kaplan-Meier estimates of liver graft survival in patients with SLKT were 12 years (95% CI: 10.8-13.3), and in KLT patients this was 6.8 years (95% CI: 1.7-12.0) (Fig. 3 B). Mean survival could not be calculated in the LKT group since no patients lost their liver graft.

Mean patient survival was nine years for SLKT (95% CI: 7.10-10.0), 7.5 years for KLT (95% CI: 1.8-13.2), and 9.5 years for LKT (95% CI: 7.9-11.1), respectively (Fig. 3 C). Patient survival at 10 years among SLKT, LKT, and KLT was 57.1, 67.3, and 81.1%, respectively.

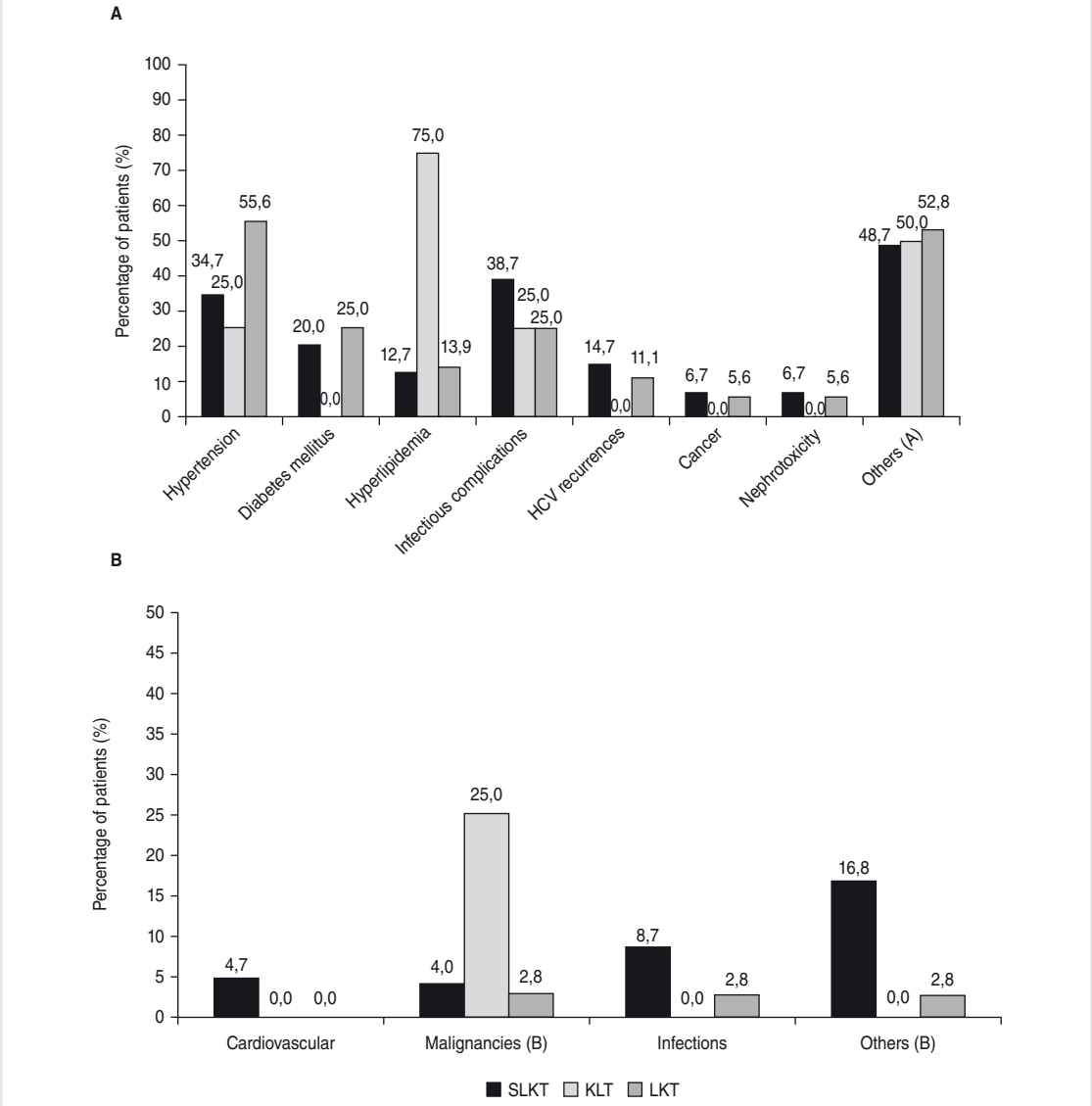

Figure 2. *Main posttransplant complications **(A)** and causes of death **(B)**.*
SLKT: simultaneous liver-kidney transplantation: LKT: sequential liver-kidney transplantation; KLT: sequential kidney-liver transplantation.

Discussion

The incidence of chronic renal insufficiency associated with chronic liver failure defined by National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) and American Association for the Study of Liver Diseases (AASLD) guidelines, respectively, has increased in recent years. Approximately 10-20% of patients undergoing liver transplantation have renal insufficiency[20] and about 2% of patients undergoing liver transplantation will require SLKT. Furthermore, the advent of CNI in non-renal transplant organs has been shown to induce nephrotoxicity, contributing to the development of end-stage renal disease in approximately 18% of liver transplant patients after 13 years[21].

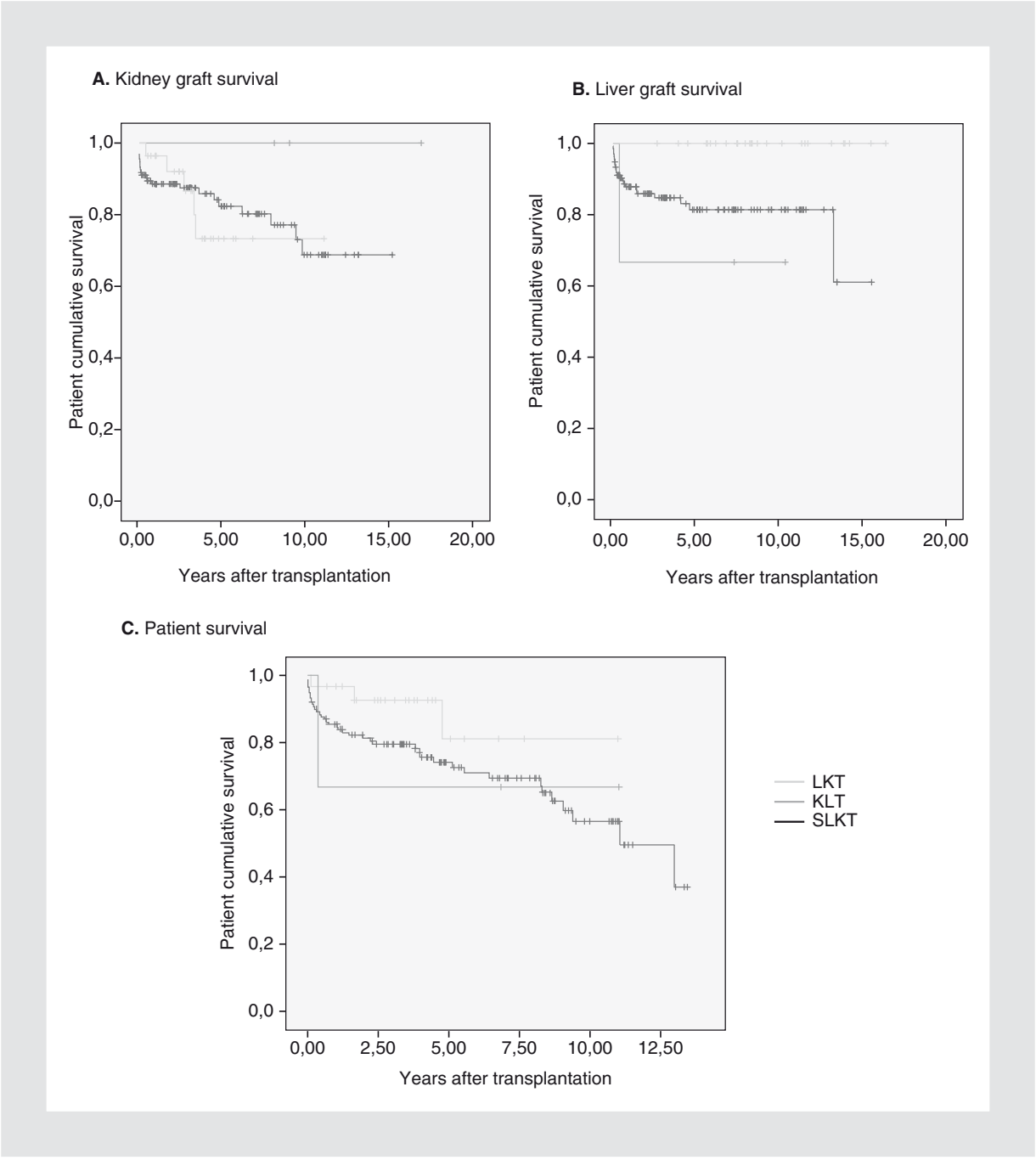

Figure 3. *Comparison of kidney graft survival, liver graft survival and patient survival, between simultaneous liver-kidney transplantation, sequential liver-kidney transplantation and sequential kidney-liver transplantation groups* ***(A, B and C)****.*
SLKT: simultaneous liver-kidney transplantation: LKT: sequential liver-kidney transplantation; KLT: sequential kidney-liver transplantation.

Few studies evaluating the outcome of CLKT have been conducted. Here, we report a 16-year follow-up retrospective multicenter study which included 190 patients with combined liver-kidney (either simultaneous or sequential) transplantation, with SLKT being the most important proportion of them (78.9%). In fact, long-term follow-up studies reported low percentages of SLKT, such as 2.8% in Chile[25], 3.4% in China[22], 6.7% in the EU[11], and 2% in Spain[9], as compared to all liver transplants performed during the same period of time.

Nevertheless, the United Network for Organ Sharing (UNOS) database reported 76.3% of SLKT and 23.7% of LKT among all CLKT during the same period of time[25]. As our study includes a relevant number of SLKT, it has allowed us to assess both patient and graft survival rates among this group of transplanted patients in Spain.

Patients with SLKT compared to LKT showed a significantly younger donor age and a shorter cold ischemia time. Moreover, the pretransplant condition of SLKT recipients was significantly better as their renal function was better preserved, although they showed a longer time on dialysis than the others, thus suggesting a much slower deterioration of renal function among SLKT recipients.

On the other hand, comparisons of demographic and preoperative donor data between SLKT and KLT are not feasible because of the small number of patients evaluated with KLT.

Etiology of liver failure was especially due to cirrhosis, which was mainly caused by alcohol and/or hepatitis C. Regarding the etiology of kidney failure, primary glomerulonephritis was the predominant cause observed. These results are in concordance with those previously published by two single-center Spanish studies[9,10].

The patient survival rates among SLKT, LKT, and KLT at 10 years in our study are acceptable (57.1% SLKT, 67.3% KLT, and 81.1% LKT). Very similar data, especially in the SLKT group, were reported in the Spanish Liver Transplant Registry (from 1984 to 2009) in patient survival when only evaluating liver transplantation at such follow-up[23]. Comparable patient survival rates were observed between SLKT and KLT. Nonetheless, in a Chinese study, better results were seen in SLKT as compared to liver transplant patients (70.1 and 58.0% at two years, and 62.2 and 50.4% at five years, respectively)[22], whereas other studies reported similar survival rates between SLKT and LT (67 vs. 69%, respectively)[24]. In this regard, a single-center Spanish study reported a mean patient survival among SLKT of 65 months, similar to that obtained in liver transplant recipients during the same period[9].

Regarding kidney graft survival, our study also shows acceptable half-life survival, being higher in the SLKT than in the LKT cohort (11.8 vs. 8.7 years, respectively). Similarly, the UNOS database[25] described a better renal allograft outcome in SLKT as compared to LKT (11.7 vs. 6.6 years, respectively). Interestingly, and similarly to previous reports[10,26], a very low incidence of acute renal graft rejection was observed in our study (only 2.7% in SLKT and 8.3% in LKT), and significantly lower rates than those reported among single renal transplanted patients with current immunosuppressive regimens[27]. Therefore, these data suggest the potential immunological protection that the liver may have towards other allografts, especially when both organs are simultaneously transplanted[25].

Regarding acute liver rejection, the incidence in our cohort was also rather low (12.7%) as compared to that reported among liver transplanted patients[28]. No acute rejection was detected in KLT, probably due to the small sample size of this group.

Our results suggest that the graft survival rate among SLKT patients is satisfactory and similar to the results obtained in patients receiving a liver transplant, with a low acute rejection rate. Thus, it seems to be feasible that overcoming the immunological barrier could avoid acute allograft rejection episodes.

The main limitation of this study is that the observational and retrospective design may have induced some unmeasured bias, as some posttransplant complications may have not been totally registered in the patients'

files. Moreover, due to the multicenter and long-term follow-up study, patients were subjected to non-homogeneous and differing management and treatment protocols. Furthermore, patient survival of SLKT versus LKT recipients is biased because the LKT group was highly selected as they had to survive at least long enough to receive a kidney after their liver transplant. Another limitation is the very low sample size of KLT cohort.

Some relevant strengths of our study are the relatively large sample size of SLKT and LKT patients as compared to previously published reports, and also the longer-term follow-up of these patients. In addition, this study represents a broad spectrum of the main Spanish transplant centers, thus showing a good representation for the evaluated cohorts. The agreement with some results from previous studies supports the external validity of our findings.

Since the introduction of the Model for End-Stage Liver Disease (MELD) system in 2002 in the USA[29,30], the number of SLKT has dramatically increased to over 300%[31]. The MELD score was implemented to help allocate livers to those recipients in greatest need, and to improve the number of patients on the liver transplant waiting list. Relatively heavy weighting of the serum creatinine in the MELD correlates with a high MELD score[32].

Patients with hepatorenal syndrome who require renal support should generally be treated by liver transplantation alone, since the majority will achieve a recovery of renal function post-liver transplantation. However, sometimes it is difficult to determine the renal failure origin and a renal biopsy is not always feasible. The controversy is in the subgroup of patients who require prolonged renal support, and it is this group that should be considered for CLKT, which significantly decreases their survival[33]. In these cases, the relative lack of donors should also be taken into consideration.

One the other hand, evaluating patients with advanced chronic liver disease and pretransplantation acute kidney injury is challenging and an appropriate selection of candidates for SLKT continues to be very difficult.

Despite two consensus conferences, consensus guidelines are not yet in place to clearly delineate indications for SLKT[32].

Controversies in SLKT are based upon questions about the interactions of liver and kidney disease that, to date, still remain unanswered[16]. In our experience, combined renal and hepatic transplantation shows good patient and allograft survival results at medium and long-term follow-up, similar to single hepatic transplantation. Therefore, combined organ transplantation is a valid therapeutic alternative with good long-term results. We suggest that combined liver-kidney (either simultaneous or sequential) transplantation should be considered as a good option for those patients suffering from both liver and kidney end-stage diseases.

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