

# The experience of the Fundacion Valle Del Lili in Cali, Colombia with Combined Liver and Kidney Transplantation

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## Abstract

**Introduction:** Combined liver and kidney transplantation (CLK) has been shown to be a good alternative for patients with concomitant diagnosis of chronic kidney disease (CKD) and end-stage liver disease. Some studies have also shown immunological benefits from combined transplantation with decreased rates of kidney graft rejection.

**Objective:** The objective of this study was to describe the indications and clinical outcomes of CLK transplant recipients in a highly complex hospital.

**Materials and Methods:** CLK transplant patients were selected from the institutional transplant registry (Trenal) from 2000 to 2011. Demographic and clinical characteristics were described and survival of patients and grafts were estimated with the Kaplan-Meier method.

**Results:** Over a period of 11 years, 16 CLK transplants were performed. This was 1.51% of kidney transplants and 3.48% of liver transplants done in the institution during this period. Most recipients were male (10/16). The median age was 56.5 years. The median MELD was 17 (IQR: 12.5 to 20.5, range: 8 to 24). The most frequent diagnosis was liver cirrhosis due to NASH (4/16). All patients had been diagnosed with CKD: four cases were secondary to diabetes mellitus. The most common indications for transplants were difficult to manage ascites, recurrent encephalopathy and malnutrition. The average liver cold ischemia time was 7.3 hours, and the average kidney cold ischemia time 9.6 hours. The five-year liver graft survival rate was 87.5%, and the five-year kidney graft survival rate was 67.3%. Four patients died: two as the result of sepsis and two as the result of malignancy.

**Conclusion:** CLK transplantation results at the Fundación Valle del Lili have been satisfactory and comparable to those reported by other transplant centers.

## Keywords

Combined liver-kidney transplant, survival, graft rejection.

## INTRODUCTION

The first combined liver and kidney transplantation (CLK - Combined Liver-Kidney) was reported by Margreiter in 1984. (1) CLK transplantation has shown itself to be a good therapeutic alternative for patients with terminal liver disease and chronic kidney disease. (2) According to the OPTN (Organ Procurement and Transplantation

Network), 5,816 CLK transplants were conducted in the United States between 1988 and June 2014. The recommendations of the American consensus on transplant CLK show the survival benefits for patients with pre-transplant serum creatinine > 2.0 mg / dL and who were on dialysis who underwent CLK compared to similar patients who received only liver transplants. (3). Various studies have found that liver transplantation protects the renal graft

and decreases the rate of acute renal graft rejection. (4, 5) CLK transplantation also improves patient quality of life by allowing people with chronic kidney disease (CKD) to live independently of dialysis. In addition, it has benefits in terms of the costs involved. (6) The Fundación Valle del Lili is a clinic that has had extensive experience in solid organ transplantation since 1995. In 2000, the foundation performed its first CLK transplant. Since then, CLKs have been performed on 16 patients. The purpose of this study was to describe our experience in the management of patients with combined liver and kidney transplant.

## PATIENTS AND METHODS

Data were obtained from the kidney and liver transplantation registry of TRENAL (Translational kidney research – from physiology to clinical application). Since 2010, this registry has existed. It includes information from renal transplants performed since 1995 at the Fundación Valle del Lili. All CLK transplant patients between 2000 and 2011 have been included. Demographic and clinical information related to the reason the transplantation was performed, early surgical and medical complications (in the first three months post-transplant) and late complications (occurring three months or more after transplant) were systematically collected. Admission to the waiting list was determined by pretransplant clinical evaluation, and each case was discussed on the board of the institution. At the time of transplant, the recipient was selected on the basis

of blood group compatibility. No cytotoxicity tests of the donor were done prior to transplantation.

Immunosuppression was administered according to the immunological and clinical conditions of each patient. Fifteen patients received a calcineurin inhibitor, thirteen received mycophenolate, two received azathioprine, and sixteen were given steroids. Induction of tolerance by monoclonal antibody therapy was used in three cases. Post-transplant follow-up was based on regular monthly check-ups of patients. Demographic and clinical characteristics of patients were described. Averages and interquartile ranges (IQR) or averages and  $\pm$  standard deviation (SD) were used for quantitative variables. Proportions were used for qualitative variables. Patient survival time and renal and liver graft survival times were calculated with the Kaplan Meyer method using STATA 12.

## RESULTS

Between 2000 and 2011, 1059 kidney transplants and 459 liver transplants were done at this institution. In the same period, 16 CLK transplants CLK were performed (1.51% of all kidney transplants and 3.48% of all liver transplants). Ten patients were men, and six were women. The median age at transplantation was 56.5 years (IQR 50.7 to 64.5, range 3 to 69). This includes two pediatric patients aged three and seven years old. Patients' liver and kidney disease etiologies are described in Table 1. One patient had a pre-transplant liver biopsy which showed primary biliary cir-

**Table 1.** Characteristics of CLK transplant recipients at the Fundación Valle del Lili in Cali, Colombia

Patient	Age (years)	Sex	Kidney Pathology	Liver pathology
1	65	M	Glomerulonephritis	HCV Cirrhosis + Hepatocellular carcinoma
2	68	M	DM nephropathy	Cirrhosis due to NASH
3	35	M	IgA nephropathy	Cirrhosis due to NASH + Hemochromatosis
4	55	M	Unknown	Hepatocellular carcinoma + Cryptogenic cirrhosis
5	50	M	Unknown	Cirrhosis due to alcohol
6	69	F	DM nephropathy	HCV Cirrhosis
7	60	M	Unknown	Autoimmune cirrhosis
8	66	F	Unknown	Cryptogenic cirrhosis
9	54	F	DM nephropathy	Cirrhosis due to NASH
10	57	F	DM nephropathy	HCV Cirrhosis
11	3	F	Polycystic kidney disease (PKD)	Congenital Hepatic Fibrosis
12	58	M	Drug-induced nephrotoxicity	Cirrhosis due to NASH
13	7	M	Primary hyperoxaluria	Primary hyperoxaluria
14	52	M	Unknown	Primary biliary cirrhosis
15	55	M	Glomerulonephritis	Cirrhosis due to alcohol
16	63	F	Unknown	Chronic cholangitis

hosis. Three patients had pretransplant kidney biopsies two of which showed proliferative glomerulonephritis and one of which showed terminal kidney failure.

Patient's medical histories showed that six patients had Type 2 diabetes mellitus, four had dyslipidemia, three had arterial hypertension, and three had histories of malignancy. The median MELD (Model for End-stage Liver Disease) score was 17 (IQR 12.5 to 20.5, range 8-240,029) One of two pediatric patients had a PELD (Pediatric End-Stage Liver Disease) score of 1 and had been diagnosed with congenital hepatic fibrosis. The PELD score was not calculated for the other pediatric patient because the diagnosis indicated primary hyperoxaluria transplantation. The mean cold ischemia time for livers was 7.3 hours with SD  $\pm$  2.3 (range 4-12). For kidneys it was 9.6 hours with SD  $\pm$  2.2 (range 6-12). The average time on the waiting list was 157 days, with SD  $\pm$  112 (range 1-422). Two patients were transplanted at zero urgency. The median follow up time was 35 months (IQR 18-48, range from 0.07 to 156). Three patients received monoclonal antibody therapy to induce tolerance: one received daclizumab and two received basiliximab.

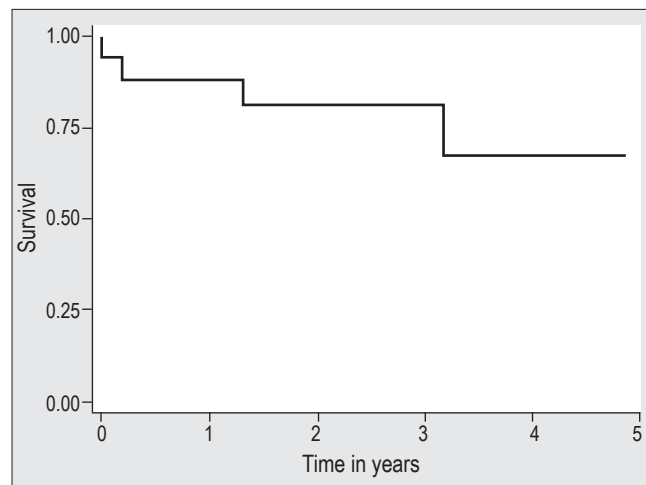
Table 2 shows surgical and medical complications. At least one complication was documented in each of 11 patients (68%). Three patients had early biliary complications, five patients had late biliary complications, two suffered from bleeding, and one developed a cytomegalovirus infection. Three patients were diagnosed with mild acute liver graft rejection. Two of these occurred between 3 and 9 months after transplant, and one occurred 10 years after transplantation. These diagnoses were made on the bases of clinical signs associated with abnormal liver profiles and confirmed by biopsies in two patients and in one by the patient's response to empirical treatment. The 7-year-old patient was diagnosed with acute renal graft rejection by biopsy three months after transplantation. All events of acute rejection were treated with steroids, and all patients responded to treatment. The one year survival rate for patients, liver grafts and kidney grafts was 87.5% while the three five year survival rates were all 67.3% (Figure 1). Two patients died as the result of sepsis: one in the immediate postoperative period and the other in the third month after transplantation. Two patients died of cancer after the first year after transplantation. One had B-cell lymphoma and the other suffered recurrence of hepatocellular carcinoma. Of the 12 patients whose grafts continue to function, none has required retransplantation.

## DISCUSSION

The combined liver and kidney transplant program at the Fundación Valle del Lili has a low incidence of acute rejection of renal allografts which is similar to those reported by

**Table 2.** Early and late surgical and medical complications in CLK transplant recipients at the Fundación Valle del Lili in Cali, Colombia

Post-transplant complications	n
<b>Early Surgical Complications</b>	
Biliary fistula	2
Bleeding	2
Hepatic artery thrombosis	1
Ureteral obstruction	1
Ischemia with necrosis of the left colon	1
Cyclosporine nephrotoxicity	1
<b>Delayed Surgical Complications</b>	
Biliary duct stenoses	5
Eventration	1
<b>Delayed Medical Complications</b>	
De novo DM	3
Arterial hypertension	3
Cyclosporine nephrotoxicity	1
Recurrence of hepatocellular carcinoma	1
Malignancy (B cell lymphoma)	1
Deep vein thrombosis	1
Veno-occlusive liver disease	1
Cytomegalovirus	1



**Figure 1.** Patient survival time and graft survival time in liver and kidney transplant recipients at the Fundación Valle del Lili in Cali, Colombia

other transplant groups (Table 2). (2,7,8) In the literature, the rate of occurrence of major complications in combined kidney and liver transplants is no higher than that of complications of liver transplants alone. (9-13) In our study population, five year patient, kidney graft and liver graft survival rates were all 67.3%. These data are similar to those reported in other series as well as in the database of United

Network for Organ Sharing (UNOS) which reports a five year survival rate of 58%. (7,11,14-17) The five year survival rates for hepatic and renal grafts censored for death was 100%. Of the 16 combined liver and kidney transplants performed at our institution, only one pediatric patient (6.7%) had acute renal graft rejection in the third month after transplantation. Two patients (12.5%) had mild acute liver graft rejection in the first year. According to our statistics (unpublished data), in the same periods of time after transplantation incidences of acute rejection were higher for patients who received only a kidney transplant (20%) as well as for those who received only a liver transplant (21%).

Creput et al. reported that the incidence of acute rejection, for both kidney and liver grafts in patients with simultaneous liver and kidney transplant was lower than for patients with liver or kidney transplants alone. (17) Fong and colleagues have also reported a comparison of the incidence of acute kidney graft rejection in patients who had only kidney transplants with those who underwent CLK transplants showed a lower incidence in the CLK transplant patients. (14) A review of other related reports found that the incidence of acute renal graft rejection annually in patients receiving either liver or kidney transplantation is about 18%, while in patients with combined liver and kidney transplants the rate was 11.8%. (2) This is explained by publications describing the protective role of hepatic graft for kidney graft functioning not only in the initial phase after transplantation but also in long term maintenance. This occurs through reduction of levels of reaction to donor specific antibodies. (3) This may be a result of mediation by activation of the enzyme indoleamine 2,3-dioxygenase (IDO). (18)

## CONCLUSIONS

The MELD score which incorporates renal function was created to improve efficiency, reduce mortality of patients on the waiting list and make entry onto the transplant list more objective. Its use has increased the number of combined liver and kidney transplants. Since this occurred, there has been a decrease of CKD among liver transplant recipients, shorter stays in the ICU and lower health care costs as a result of the immune protection of kidney graft by the liver in patients who undergo combined transplantation. (2) What is clear is that the use of calcineurin inhibitors, drug interactions and the risk of infection after liver transplantation cause kidney disease to progress. It also appears that the results of simultaneous combined liver and kidney transplantation are better than the results of a sequential transplantation of liver first followed by kidney. (2, 9)

Indications for simultaneous liver-kidney transplant are clear when the patient is on dialysis with irreversible

kidney disease and for patients with glomerular filtration rates (GFR) less than 40 mL/min (Although some authors define the limit at 30 mL/min.) (16, 19) Independent of GFR, irreversible chronic renal failure is an indication for combined liver kidney transplantation given the nephrotoxic effects on native kidneys of calcineurin inhibitors which are used after liver transplantation. (9, 12, 15) Determination of the possibility of recovering functioning of native kidneys after liver transplantation has been of particular interest. In order to improve decision making about allocation of organs available for transplantation, studies have been conducted that include performance of radioisotope renography using either MAG3 or DTPA before and after transplantation and the use of biomarkers in serum creatinine. (20,21). Our study did not document changes in the functioning of native kidneys that may have occurred after transplantation, but this is a topic for future studies. Combined liver and kidney transplantation at our center compares well with those reported by medical centers in other countries which have more experience. The clinical outcomes have proven that this is a good therapeutic option for patients who have concurrent terminal liver disease and chronic kidney disease.

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