Characteristics of Liver Transplantation in Argentina: A Multicenter Study

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ABSTRACT

Introduction. There is a lack of information regarding outcomes after liver transplant in Latin America.

Objectives. This study sought to describe outcomes after liver transplant in adult patients from Argentina.

Methods. We performed an ambispective cohort study of adult patients transplanted between June 2010 and October 2012 in 6 centers from Argentina. Only patients who survived after the first 48 hours postransplantation were included. Pretransplantation and posttransplantation data were collected.

Results. A total of 200 patients were included in the study. Median age at time of transplant was 50 (interquartile range [IQR] 26 to 54) years. In total, 173 (86%) patients had cirrhosis, and the most frequent etiology in these patients was hepatitis C (32%). A total of 35 (17%) patients were transplanted with hepatocellular carcinoma. In patients with cirrhosis, the median Model for End-Stage Liver Disease (MELD) score at time of liver transplant was 25 (IQR 19 to 30). Median time on the waiting list for elective patients was 101 (IQR 27 to 295) days, and 3 (IQR 2 to 4) days for urgent patients. Almost 40% of the patients were readmitted during the first 6 months after liver transplant. Acute rejection occurred in 27% of the patients. Biliary and vascular complications were reported in 39 (19%) and 19 (9%) patients, respectively. Renal failure, diabetes, and dyslipidemia were present in 40 (26%), 87 (57%), and 77 (50%) at 2 years, respectively.

Conclusions. We believe the information contained in this article might be of value for reviewing current practices and developing local policies.

LIVER transplant (LT) is a well-established therapeutic practice in Argentina for patients with end-stage liver disease. In Argentina, the first LT was performed in 1988, and during past decades the annual number of LTs has increased steadily, placing Argentina at the top of Latin American LT rates [1]. This was possible due to the advances in surgical techniques, peritransplant intensive care, and immunosuppressive regimens, which resulted in significant improvements in short-term survival.

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Although there is continual worldwide improvement in patient survival, LT patients may experience serious complications that not only contribute to significant morbidity and mortality, but also represent an extremely high cost to the health care system. A clear example of these are post-LT infections, which are estimated to occur in more than 50% of the LT recipients, being one of the most frequent complications during the early postoperative period [2,3] and remaining the most common indication of hospital readmission [3]. New-onset diabetes mellitus (NODM) after LT is another well-known complication; it occurs in 2.5% to 25% [4] of LT recipients and in 40% to 60% of hepatitis C virus–infected LT recipients [5]. Chronic renal failure after LT, mainly related to calcineurin inhibitors (CNI) toxicity [6–8], continues to be a major complication, with an incidence that ranges from 20% to 80%. In Argentina, studies in patients on the waiting list and post-LT survival have been published [9–11], although very limited data exist for the post-LT period. Understanding post-LT complications might be useful to develop strategies to predict and prevent them, improving the quality of care and potentially reducing overall costs. The aim of this study was to describe the characteristics and outcomes of patients after LT in Argentina.

PATIENTS AND METHODS

We performed an ambispective multicenter cohort study of patients who underwent LT from June 2010 to October 2012 in the 6 LT centers from Argentina that performed the largest numbers of LT when the study took place.

Argentina has a single national waiting list. The *Instituto Nacional Central Único Coordinador de Ablación e Implante* (INCUCAI) is the national institute for organ allocation, and organ procurement is exclusively run by the state, with no private procurement agencies. Since Argentina adopted the Model for End-Stage Liver Disease (MELD) system in 2005 as allocation policy, all patients were grouped into 2 categories: emergency or elective. Emergency status is considered for patients with acute liver failure and for patients with primary graft failure or those with hepatic artery thrombosis during the first postoperative week. Elective patients are stratified according to the MELD score. A specific regulation includes 3 situations for MELD upgrading, which includes familial amyloidotic polyneuropathy (16 points), hepatopulmonary syndrome (20 points), and stage II hepatocellular carcinoma (HCC) (22 points); these regulations contemplate 1 additional point in MELD scores every 3 months on the waiting list. By 2010 there were more than 20 authorized LT centers in Argentina, which has a population of 40,117,096 [12]. The centers involved in the study were the Hospital Italiano de Buenos Aires, Hospital Universitario Fundación Favaloro, Sanatorio Allende de Cordoba, Hospital Universitario Austral, Hospital Alemán and Hospital General de Agudos Dr. Cosme Argerich.

Patients included in this study were older than 18 years and were transplanted using a cadaveric donor. Exclusion criteria included prior LT, combined transplant, and death during the first 48 hours after LT. Patients were followed up from the day of LT until death, retransplantation, or the end of the 2-year follow-up period.

Each center provided detailed information for the patients included in the study. Data collection was performed using an electronic form. The information collected included: demographics (age/sex); date of enrollment on the waiting list; primary diagnosis of liver disease at listing; Child-Pugh and MELD scores at inclusion on the waitlist and at the day of transplantation; history of diabetes before LT; donor characteristics; immunosuppression received; laboratory determinations at months 1, 3, 6, 12 and 24 after LT; medical and surgical complications; all-cause hospital readmissions; and graft and patient survival. All data records were checked for missing values and inconsistencies; queries were sent to all participating institutions, and corrections were made at the data-coordinating center, namely Hospital Italiano in Buenos Aires.

The estimated glomerular filtration rate (GFR) was calculated at each time point with the Modified Diet in Renal Disease (MDRD) GFR [13]. The definition of pre-LT diabetes included a history of diabetes or use of insulin or oral hypoglycemic medications. The definition of new-onset diabetes after transplantation (NODAT) was based on International Consensus Guidelines on NODAT 2003, which recommended that the diagnosis of NODAT should be based on the American Diabetes Association (ADA) criteria for type 2 diabetes [14,15]. Dyslipidemia was defined using the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III criteria [16]. Renal failure was defined as the presence of a GFR of <50 mL/min/1.73 m^2 using the MDRD equation. Liver allograft rejection was diagnosed by biopsy according to Banff criteria [17]. Patient management and immunosuppression regimens were determined in each center. The study was conducted according to the principles of the Declaration of Helsinki and the Guidelines for Good Clinical Practices ICH E6. The study protocol was approved by the ethics committees of the participating hospitals.

STATISTICAL ANALYSIS

Discrete variables are presented as absolute and relative frequencies (percentages). Continuous variables are shown as median and interquartile ranges (IQR: 25th percentile and 75th percentile). To estimate the cumulative incidence of death, we calculated the time from LT to the date of death. The cumulative incidence of death at 1 and 2 years is reported with its corresponding 95% confidence interval (95% CI). The STATA software (StataCorp, version 14.2) was used for data analysis.

RESULTS

Liver Transplant Centers

A total of 200 patients were enrolled in the study. The total number of transplanted patients per center was as follows: Hospital Italiano from Buenos Aires: 64 (32%), Hospital Universitario Fundación Favaloro: 36 (18%), Sanatorio Allende: 33 (17%), Hospital Univeritario Austral: 32 (16%), Hospital Alemán 25 (12%), and Hospital Dr. Cosme Argerich 10 (5%).

Indications for Liver Transplant

Primary diagnoses at time of listing are shown in Table 1. Overall, 173 (86%) patients had cirrhosis, of which hepatitis C and alcohol-related liver disease were the 2 most frequent etiologies. Acute liver failure and other indications for LT were registered in 10 (5%) and 17 (9%) patients,

Table 1. Characteristics of Patients on the Liver Transplant Waiting List

Characteristics	Results n = 200
Age at transplant (y), median and IQR	50 (26–64)
Sex (male), no. (%)	116 (58%)
HIV positve, no. (%)	10 (5%)
Primary diagnosis at listing, no. (%)	
Cirrhosis	173 (86%)
Hepatitis C	56 (32%)
Alcoholic liver disease	41 (24%)
Cryptogenic cirrhosis	27 (16%)
Autoimmune hepatitis	22 (13%)
Primary biliary cirrhosis	11 (6%)
Primary sclerosing cholangitis	6 (3%)
Nonalcoholic steatohepatitis	5 (3%)
Secondary biliary cirrhosis	3 (2%)
Hepatitis B	2 (1%)
Acute liver failure	10 (5%)
Autoimmune hepatitis	3 (30%)
Toxic hepatitis	2 (20%)
Hepatitis B	2 (20%)
Indeterminate	1 (10%)
Hepatitis A	1 (10%)
Other	1 (10%)
Other	17 (9%)
Hepatocellular carcinoma, no. (%)	35 (17%)
ABO blood group, no. (%)	
O	88 (44%)
A	86 (43%)
B	23 (11%)
AB	3 (2%)
Diabetes, no. (%)	36 (18%)
MELD score at listing, median and IQR*	17 (14–23)
MELD score at transplant, median and IQR	25 (19–30)
Body weight, median and IQR	75 (64–84)
Child-Pugh score, median and IQR	10 (9–12)
Total bilirubin(mg/dL), median and IQR	5.5 (2.3–12.4)
Prothrombin time (seg), median and IQR	40 (26–75)
International normalized ratio prothrombin time, median and IQR	1.9 (1.4–2.7)
Creatinine (mg/dL), median and IQR	1 (0.7–1.5)
Glomerular filtration rate at transplant, median and IQR	88 (62–133)

Abbreviations: IQR, interquartile range; MELD, Model for End-Stage Liver Disease.
*Excludes urgent category and MELD exception.

respectively. Thirty-five (17%) of the patients were transplanted with HCC, 19 (54%) of whom had a diagnosis of hepatitis C–related cirrhosis. Of the 200 LTs performed in this period, 190 were elective and 10 were emergency candidates.

Pretransplant Patient Characteristics and Time on Waiting List

Baseline characteristics of the study population are shown in Table 1. Most of the patients were middle-aged men, with a median age of 50 (IQR 26 to 64) years. Sixty-seven (33%) patients were between the ages of 60 and 70 years, and only 7 (4%) patients were more than 70 years old at the time of LT.

Table 2. Median (and Interquartile Range) Time on Waiting List According to the ABO Group for Elective Patients (Patients Listed as Urgent Are Excluded), N = 190

Blood Type	Number of Patients	Days on the Waiting List
All	190	101 (27–295)
O	82	109 (31–386)
A	82	87 (20–266)
B	23	111 (13–207)
AB	3	47 (29–801)

The median waiting time for the 190 elective patients was 101 (IQR 27 to 295) days. The median waiting time for the 10 emergency patients was 3 (IQR 2 to 4) days. Tables 2 and 3 show the median time on the waiting list according to the ABO group for patients with and without MELD exception for HCC, respectively.

Donor Characteristics

The median age of donors was 40 (IQR 27 to 53) years. Seventy (35%) donors were older than 50 years. The oldest donor was 84 years old. The most common causes of death were cerebrovascular disorders and head trauma, in 98 (49%) and 86 (43%) cases, respectively. In regard to donor history of infections, Chagas-positive, anti-hepatitis B core, and hepatitis C virus–positive donors were reported in 11 (5%), 9 (4%), and 2 (1%) patients, respectively.

Immunosuppression

All patients received steroid-based induction regimens. Sixty-eight (34%) patients received induction therapy with an interleukin-2 receptor antagonist. The initial maintenance regimen during the first 72 hours after LT included steroids in all patients, calcineurin inhibitors in 100 (50%) patients, and mycophenolate in 36 (18%) patients. Of the 100 patients who received calcineurin inhibitors, 76 (76%) received tacrolimus, and 24 (24%) received cyclosporine. None of the patients received mammalian target of rapamycin (mTOR) inhibitors during the first 72 hours after LT.

Of the 153 patients who completed the 2-year follow up, 62 (40%) were receiving steroids, 133 (87%) calcineurin inhibitors (79% tacrolimus, 21% cyclosporine), and 86 (56%) mycophenolate. A total of 23 (15%) patients were receiving mTOR inhibitors, of whom 16 (70%) received

Table 3. Median (and Interquartile Range) Time on the Waiting List for Patients With Hepatocellular Carcinoma and Supplementary Points Subdivided According to ABO Group, N = 35

Blood Type	Number of Patients	Days on the Waiting List
All	35	117 (35–195)
O	14	164 (35–201)
A	17	76 (36–118)
B	4	162 (61–2230)

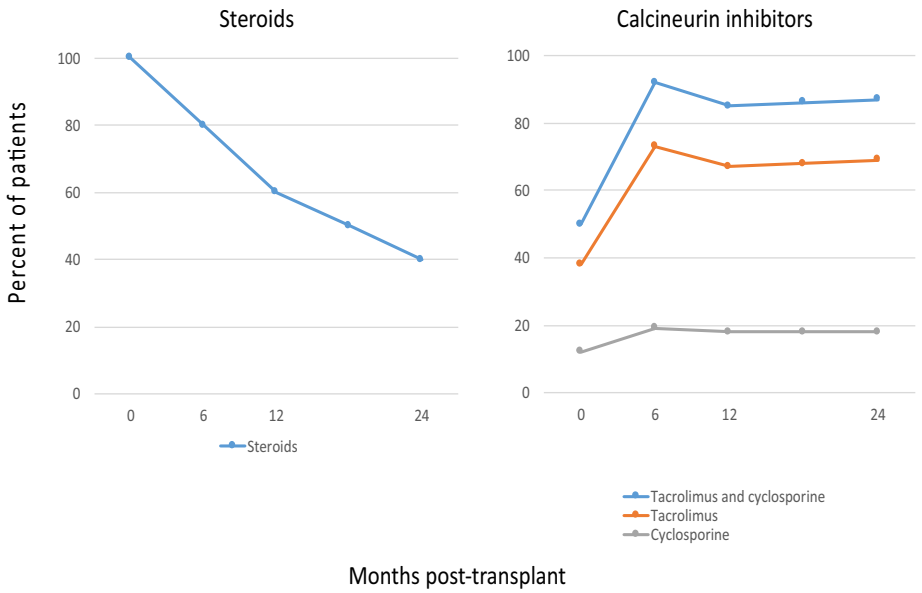

Fig 1. Proportion of patients receiving steroids and calcineurine inhibitors since transplant during the study period. 0 = Liver transplant day, n = 200; at 6 months, n = 184; at 12 months, n = 179; at 24 months, n = 153.

sirolimus and 7 (30%) received everolimus (Figs 1 and 2). The main reasons for prescription of mTOR inhibitors (either with or without CNI inhibitors) were renal failure in 13 (57%) patients, preoperative HCC in 4 (17%) patients (CNI), neurotoxicity in 3 (14%) patients, HCC recurrence in 2 (9%) patients, and refractory acute rejection in 1 (3%) patient.

Patient Outcomes and Posttransplant Complications

Of the 200 patients, 153 were alive after 2 years, 12 were retransplanted, 28 died, and 7 were lost to follow up. The overall survival rates of patients who survive past the first 48 hours after LT were 91% (95% CI 86% to 94%) and 85% (95%CI 79 to 89%) at 1 and 2 years, respectively. The causes of death are shown in Table 4. Of the 12 (6%) patients who underwent retransplantation, the median time between the primary transplantation and retransplantation was 110 (IQR 11 to 361) days. The main indication of retransplantation was hepatic artery thrombosis in 4 (34%) patients, followed by chronic rejection in 3 (25%) patients, biliary complications in 3 (25%) patients, primary nonfunction in 1 (8%) patient, and hepatitis C virus recurrence in 1 (8%) patient.

Other Complications

During the first 6 months of LT, 54 (27%) patients experienced 62 episodes of acute rejection. The severity of the acute rejection episodes was as follows: 15 (24%) mild, 22

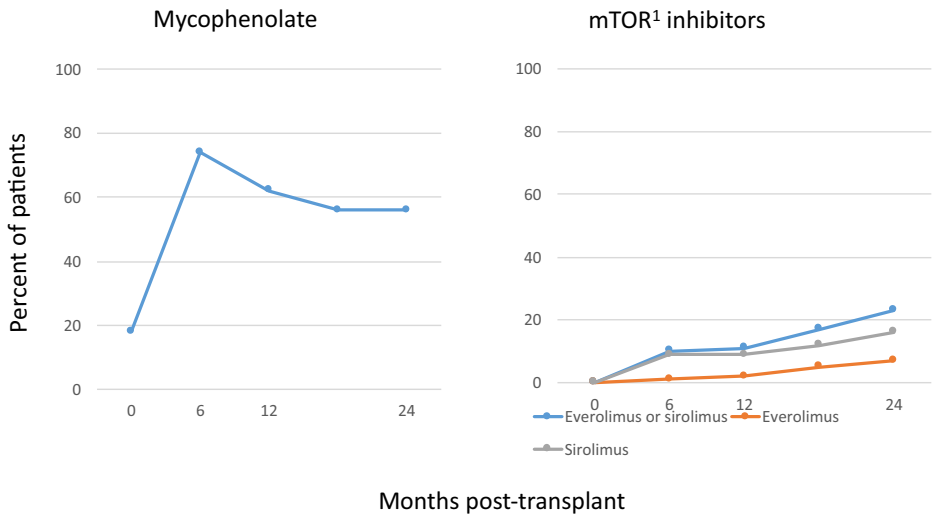

Fig 2. Proportion of patients receiving mycophenolate and mammalian target of rapamycin (mTOR) inhibitors since transplant during the study period. 0 = Liver transplant day, n = 200; at 6 months, n = 184; at 12 months, n = 179; at 24 months, n = 153.

Table 4. Causes of Death After Liver Transplant

Cause of Death	Patients N = 28
Gastrointestinal bleeding	1 (4%)
Primary nonfunction	2 (7%)
Infection	14 (50%)
Bacterial infection	12 (43%)
Fungal infection	1 (4%)
Other	1 (4%)
Recurrence of hepatocellular carcinoma	1 (4%)
Recurrence of hepatitis C virus	2 (7%)
De novo tumor*	2 (7%)
Chronic rejection	1 (4%)
Others causes	5 (17%)
Cardiovascular	2 (7%)
Cerebrovascular	3 (11%)

*One lung and one colorectal cancer.

Table 5. Posttransplant Vascular and Biliary Complications

Complication	Total N = 200
Vascular complication*	19 (9%)
Thromboses of the hepatic artery	12 (63%)
Early	6 (50%)
Late	6 (50%)
Thromboses of the portal vein	7 (37%)
Early	3 (40%)
Late	4 (60%)
Biliary complication	39 (19%)
Biliary anastomotic stricture	26 (67%)
Ischemic-type biliary lesion	7 (18%)
Bile leak	6 (15%)

*Vascular complications were classified as early (occurring during the first 30 days after liver transplant) or late (occurring more than 30 days after liver transplant).

(35%) moderate, 16 (26%) severe; no data were available for 9 (15%) of the episodes. A total of 194 infections in 130 (65%) patients were documented during the study period. There were 117 (60%) bacterial infections, of which 49 (42%) occurred during the first month. Viral infections were registered in 55 (28%) patients; cytomegalovirus (CMV) infections were reported in 36 (65%) of them. Fungal infections were documented in 15 (8%) patients; 14 (93%) of them reported as Candida species and 1 case as cryptococcal disseminated infection. Chagas transmission was documented in 3 (27%) of the 11 patients who received organs from *Trypanosoma cruzi*–infected donors. All were treated with benznidazole.

Of the 153 patients who were alive 2 years after LT, 87 (57%) were diabetic (55 [63%] of them with diagnosis of NODM). Seventy-seven (50%) patients were dyslipidemic. The median creatinine at 2 years of LT was 1.18 mg/dL (IQR 0.9 to 1.4), and median GFR was 61.5 (IQR 48 to 80) mL/min. Forty (26%) patients had a GFR lower than 50 mL/min; only 3 of them were under everolimus, and 7 under sirolimus. Of the 35 patients transplanted with HCC, 7 (20%) developed HCC recurrence within 2 years of LT. Vascular and biliary complications and readmission are shown in Table 5 and Fig 3, respectively.

DISCUSSION

Seventeen percent of LTs are currently being performed in Latin America, and the top LT rates were found in Argentina, with 10.4 LT per million people per year [1]. Despite the comparable outcomes to those in Europe and North America [9], there is still a lack of data from our region.

As expected, cirrhosis continues to represent the main indication of LT, with a large predominance of hepatitis C–related cirrhosis within this group of patients. It is noteworthy that autoimmune cirrhosis continues to be a leading cause of LT in Argentina [18,19]. We found that autoimmune hepatitis (AIH) was the main etiology in urgent LT, in contrast to the situation in Europe and North America, where AIH is considered a relatively rare disease and represents an infrequent indication for LT, accounting for only 4% to 5% of LT procedures [20,21].

In the pre-MELD era, patients with blood group O had longer waiting times for LT than patients with other blood groups [22,23]. Although our study was not powered to analyze this issue, a clinically significant shorter waiting time for LT was observed for patients with blood type A than for patients with other blood types.

We found that 35% of our donors were past the age of 50 years; this is also similar to reports from the United States [24]. Contradictory results have been obtained from different studies, according to which the donor age is an independent risk factor on the LT outcomes [25–28]. In our region, the use of older donors is crucial because of donor shortage.

In our study, we found that almost 40% of the patients were readmitted during the first 6 months of LT; infectious complications were frequent, affecting 65% of the patients, and were caused predominantly by bacterial origin. This is similar to what has been previously reported [29,30].

In our region, extended screening for endemic infections is mandatory. It is known that the transmission rate from *Trypanosoma cruzi* seropositive donors to seronegative LT recipients is approximately 20% [31]. In our study, we found that 5% of the donors were positive for *Trypanosoma cruzi*, and had similar transmission rates to seronegative recipients.

Some regional public health problems, such as Chagas disease, tuberculosis, and some regional parasitoses, deserve special consideration during the pretransplantation assessment to implement adequate treatment or posttransplant prophylaxis. Biliary tract complications occurred in 19% of the patients, which is consistent with worldwide reports [32–34]. Anastomotic biliary strictures followed by ischemic lesions were the most frequent complications. Vascular complications occurred in 9% of the patients and mostly consisted of hepatic artery thrombosis, which was observed

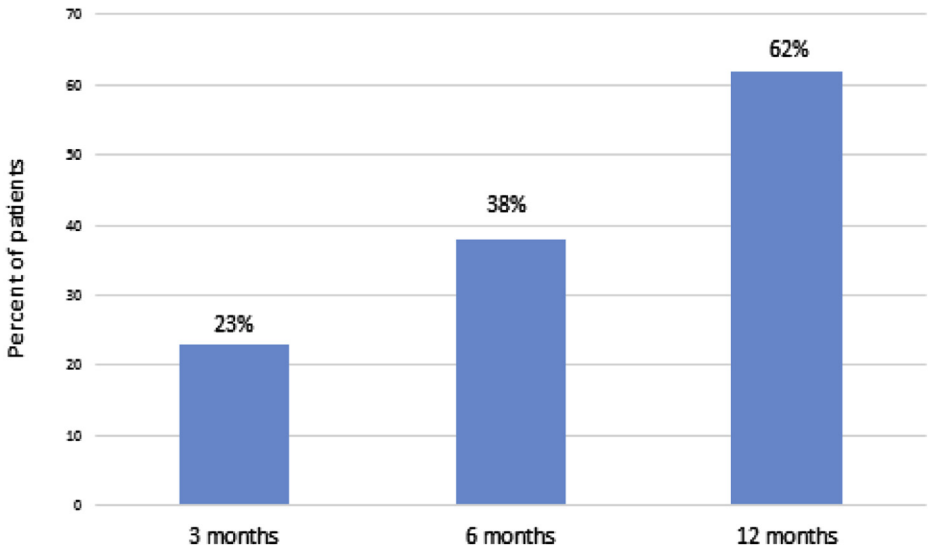

Fig 3. Cumulative incidence of readmission to the hospital at 3 months (n = 43/186), 6 months (n = 71/184), and 12 months (n = 96/179) after liver transplant.

in 6% of the patients and is consistent with prior reports [35]. Acute cellular rejection episodes were observed in 27% of the patients, which is lower than previously reported [36], and could be explained by the fact that protocol biopsies were not performed in all centers.

Regarding long-term complications, it was striking to find that 57% of the patients had diabetes and most of them had NODM at 2 years after LT. Immunosuppressive drugs, and moreover steroids, have a known diabetogenic effect and are a major contributor to the development of NODM. It is important to manage NODM with therapeutic and preventive steps such as individual use of the immunosuppressive regimen with corticosteroid tapering or discontinuation, as early as possible. We found that 2 years after LT, 40% of recipients were still receiving steroids, a situation that must be reversed because of the knowledge gained from already-published data showing a negative impact of NODM on patient and graft survival after LT [14,37].

It is known that mortality is higher in LT recipients with posttransplant renal failure than in patients with preserved renal function [6,38,39]. Two years after LT, 1 in every 4 patients in our study had a GFR lower than 50 mL/min. This situation underestimates the real burden of post-LT renal failure because patients who died or were retransplanted before that time were not taken into account. Although current guidelines suggest that CNI reduction or CNI-free protocols might overcome this issue [40,41] in our study, 2 years after LT, only 10 (25%) patients with GFR lower than 50 mL/min were previously switched to mTOR inhibitors, or used a combination of low-dose CNI and mTOR inhibitors.

Finally, we found LT survival rates of 91% and 85% at 1 and 2 years, respectively. It should be noted that patients who died during the first 2 days of LT were excluded from this analysis. This is a limitation of our study, which was mainly designed to study post-LT long-term outcomes. In conclusion, we believe that the information contained in this article might be of value to review current practices and develop local policies.

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