Original

Case series of liver transplantation in "Dr. Rafael Ángel Calderón Guardia Hospital"

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Conflicts of interest: the authors declare that they have no conflicts of interest concerning this publication. Dr. Espinoza was the initiator and coordinator of this research when she worked for the Immunology Unit of the Hospital "Dr. Rafael Ángel Calderón Guardia", and was also the director of Dr. Catarinella's graduation thesis. She currently works as Medical Manager at Roche Central America and Caribbean, for the areas of Nephrology and Transplantation, Foundation Medicine and Publications.
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Abstract

Aim: To analyze the outcomes, most frequent complications, and characteristics of the patients enrolled in the Liver Transplant Program from the Hospital "Dr. Rafael Ángel Calderón Guardia".

Methods: This is a retrospective investigation that involves the revision of clinical records from the patients that received a liver transplant between the years 2009 and 2018 in the Hospital "Dr. Rafael Ángel Calderón Guardia". The following variables were considered: age, gender, nationality, city of residence, manifestations of the liver disease, reason for the liver transplant, clinical outcomes after transplant, comorbidities, medication received, important laboratory results, and biopsies. The data analysis was performed with STATA, using a statistical significance threshold of a p < 0.05.

Results: The sample was composed of a total of 45 liver transplant surgeries and 44 patients who received a liver transplant between the years 2009 and 2018. The patients mostly came from the city of San José. The average age at the time of the surgery was 51 years. The most common liver disease that led to transplant was alcoholic cirrhosis, followed by NASH and cryptogenic cirrhosis. The most common complications of the liver disease documented before transplant were esophageal varicose veins, gastrointestinal bleeding, and hepatic-renal syndrome. 10 of the patients included in the study died, which corresponds to 22.7% of the sample.

Conclusion: the mortality observed in the liver transplant cases analyzed was 22.7%, most of the cases were taken to transplantation due to liver disease related to alcoholic cirrhosis, steatohepatitis, and cryptogenic cirrhosis.

Keywords: transplant, liver transplant, solid organ transplant, immunosuppression, liver.

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Orthotopic liver transplantation (OLT) is the only curative treatment for patients with acute or chronic end-stage liver disease of any etiology, some biliary tract diseases, such as primary sclerosing cholangitis, and primary/secondary liver tumors in selected patients. It should be considered as a therapeutic option in any patient with end-stage liver disease in whom surgery can extend life expectancy or improve quality of life. [1]

In 1967 Dr. Thomas Starzl performed the world's first successful liver transplant in Denver, Colorado. In Europe, it was performed by Sir Roy Calne in Cambridge in 1968. In Latin America, it was performed in 1968 in Sao Paulo, Brazil, and the second in 1969 in Santiago, Chile. [1] And in Costa Rica it was performed in 1993 by Dr. Fernando Ferraro Dobles at the Hospital "Dr. Rafael A Calderon Guardia" (HCG).

In 2009, the transplant session began, where all possible recipients for transplants are presented. In 2015 the liver clinic was founded, where all cases of oncological liver pathology are analyzed. Both sessions are made up of a multidisciplinary team and are still active today.

This study includes all patients who underwent liver transplantation at the HCG from 2009 to 2018. The objective was to analyze the results and evolution of the program, as well as the most frequent complications and the characteristics of the liver diseases that led to liver transplantation.

Methods

This is a retrospective investigation involving the review of the clinical records of patients who received a liver transplant between the years 2009 and 2018 in the HCG

The data were extracted and tabulated anonymously, to maintain confidentiality, using a coding system, and safeguarded by the researchers. The following categorical or discontinuous variables were considered: age, sex, nationality, place of origin, manifestations of liver disease, the reason for transplantation, post-transplantation clinical course, comorbidities, medications used, complications, relevant results of laboratory tests, and biopsies. The continuous variables taken into account were routine metabolic parameters and results of immunological tests determined in the clinical laboratory of the HCG.

To guarantee the integrity and veracity of the data, a physical data collection sheet was used for each file, and then the information was transcribed into a *Microsoft Excel* spreadsheet. The clinical records of each patient stored in the archive and the clinical laboratory database were used as sources of information. This research had the authorization of the Institutional Scientific Ethical Committee, the protocol number assigned by the evaluating committee is HSJD-07-CEC-2018.

The data were presented in numbers and expressed as frequency percentages, compared using the chi-square test. A logistic regression analysis was also performed to identify whether there was a greater risk of presenting complications according to the pathologies presented before transplantation or in the immediate, mid-term, or follow-up postoperative period. Statistical calculations were carried out with STATA statistical packages, using a *p-value of* less than 0.05 as the threshold for statistical significance.

Results

The sample consisted of a total of 45 liver transplant surgeries and 44 patients seen at HCG, who required liver transplantation between April 2009 and August 2018, mainly from the province of San Jose. The average age at the time of transplantation was 51.1 ± 11.2 years, 46.8 ± 13.2 for females, and 53.9 ± 9.3 for males ($p<0.05$; Table 1).

The hepatopathy that most frequently led to transplantation was ethyl alcoholic cirrhosis, which was documented in 14 patients, followed by non-alcoholic steatohepatitis in 7 patients and cryptogenic cirrhosis in 5 patients. In addition, 4 patients were transplanted for Wilson's disease, 3 for hemochromatosis, 2 for alpha 1 antitrypsin deficiency, 2 for cirrhosis due to hepatitis B virus, and then individually there were cases of autoimmune hepatitis, cirrhosis due to hepatitis C virus, Budd-Chiari syndrome, primary biliary cirrhosis, drug-induced liver failure, and primary sclerosing cholangitis.

Table 1. Complications of liver disease before transplantation							
	Period 1		**Period 2**			**Global**	
	04/2009-04/ 2014		05/2014-08/2018			04/2009-08/2018	
	(n=14)		(n=25)			(n=39)	
	N	%	N	%	p**	N	%
Hepatorenal syndrome	1	7.1	5	20.0	0.286	6	15.4
Hepatocarcinoma	2	14.3	3	12.0	0.838	5	12.8
Esophageal varicose veins	4	28.5	9	36.0	0.637	13	33.3
Digestive bleeding	4	28.5	5	20.0	0.542	9	23.1
Refractory ascites	1	7.1	4	16.0	0.427	5	12.8
Bacterial peritonitis	0	0.0	2	8.0	0.277	2	5.1
Portal venous thrombosis	0	0.0	3	12.0	0.177	3	7.7
Acute liver failure	0	0.0	1	4.0	0.448	1	2.6
Hepatic hydrothorax	0	0.0	1	4.0	0.448	1	2.6
Coagulopathy	0	0.0	0	0.0		0	0.0
**according to chi-square test							

Regarding nutritional status, pre-transplant BMI was available for 25 patients in total, for whom the average was 27.14 kg/m^2. It was observed that most of the women were in the obese group, while most of the men were in the overweight group. Only seven patients had normal BMI before transplantation.

It was documented that the main complications of liver disease that the patients had had before transplantation were: esophageal varicose veins, upper gastrointestinal bleeding, and hepatorenal syndrome (Table 1). The severity of liver disease at the time of transplantation was analyzed using the MELD, MELD-Na, and Child-Pugh scales. Regarding the Child-Pugh classification: 7 patients had a Child-Pugh A classification before transplantation, 16 patients had a B classification and 12 patients had a C classification, for 9 patients the data were not available. Regarding the MELD: 3 patients had a classification lower than 10 points, 20 patients between 10 and 18 points and 10 patients between 19 and 24 points, and 10 patients higher than 24 points, the calculation was not available for one patient. As for the MELD-Na: one patient had a score lower than 10, 18 patients had a score between 10 and 18, 12 patients between 19 and 24, and 13 patients higher than 24.

Regarding the comorbidities accompanying hepatopathy, we were able to collect infection from 41 patients. Hypertriglyceridemia and arterial hypertension were documented in 11 patients each, representing 28%. Overweight was present in 9 patients, representing 23%. In 32% of the cases, no comorbidity was reported in the clinical record. Another comorbidity was documented in 10 patients (26%). This percentage is composed of patients who individually presented ulcerative colitis, hypothyroidism, thrombophilia, Ménière's syndrome, osteoporosis, psoriasis, benign prostatic hyperplasia, intestinal polyps, polycystic kidney disease, diabetes mellitus, heart disease, and smoking.

Seventy-two percent of patients were overweight before transplantation, with no statistically significant difference between men and women. These data were obtained from the body mass index documented in the files.

100% of the transplants were performed with the cadaveric donor. The waiting time for transplantation was highly variable, with an average of 130 to 160 days. No statistically significant relationship was found between waiting for time and MELD, MELD-Na, and Child-Pugh severity stratification percentages.

Of the 44 patients included in the study, 10 died in total, 22.7%. Of these, two were transplanted for Wilson's disease and one for each of the following pathologies: hemochromatosis, cryptogenic cirrhosis, alcoholic cirrhosis, non-alcoholic hepatic steatosis, cirrhosis due to hepatitis B virus, α-1 antitrypsin deficiency, and Budd-Chiari syndrome.

When mortality was compared with the severity of liver disease, according to the MELD, MELD-Na, and Child-Pugh scales, no statistically significant difference was found. We also found no relationship between mortality and the cause of liver disease or with the age of the patients at the time of transplantation.

However, a statistically significant difference was found when dividing the population into two groups: patients transplanted during the period from April 2009 to April 2014 and those transplanted during the period from May 2014 to August 2018. Overall mortality among both groups decreased from 36.8% to 11.5%, and mortality during the first 30 days after surgery decreased from 23.3% to 7.6%. The average age of the patients for each of the subgroups had no statistically significant difference, nor did the frequency of any of the complications of liver disease, nor MELD.

Complications that arose after transplantation were classified into medical and surgical and then into those that arose in the immediate or mediate postoperative period (before hospital discharge) and those that were documented during outpatient follow-up. In addition, as with mortality, an analysis was made in subgroups according to the date of transplantation. (Table 2 and Table 3)

Table 2. Complications during the immediate and intermediate postoperative period						
	Period 1		Period 2		Global	
	04/2009-04/ 2014		05/2014-08/2018		04/2009-08/2018	
	(n=14)		(n=25)		(n=39)	
	n	%	n	%	n	%
Surgical complications						
Budd Chiari acute	0	0	1	4	1	2.6
Post or intraoperative bleeding	0	0.0	2	8.0	2	5.1
Biliary anastomosis leak	1	7.1	0	0.0	1	2.6
Partial bowel occlusion	1	7.1	0	0.0	1	2.6
Hepatic artery thrombosis	0	0.0	1	4.0	1	2.6
Medical Complications						
Acute kidney injury	3	21.4	13	52.0	16	41.0
Encephalopathy	0	0.0	1	4.0	1	2.6
Coagulopathy	1	7.1	1	4.0	2	5.1
Cardiac arrhythmias	1	7 .1	0	0.0	1	2.6
Bronchopneumonia	0	0.0	2	8.0	2	5.1
Bacteremia	1	7.1	2	8.0	3	7.7
Reversible posterior leukoencephalopathy	1	7.1	0	0.0	1	2.6

Table 3. Complications during outpatient follow-up						
	Period 1		**Period 2**		**Global**	
	04/2009-04/ 2014		05/2014-08/2018		04/2009-08/2018	
	(n=14)		(n=25)		(n=39)	
	n	%	n	%	n	%
Surgical complications						
Surgical Wound Infection	0	0.0	1	4.0	1	2.6
Biltema	0	0.0	1	4.0	1	2.6
Incisional hernia	3	21.4	1	4.0	4	10.2
Biliary stricture	4	28.6	3	12.0	7	18.0
Hepatic artery thrombosis	1	07.1	2	8.0	3	7.7
Portal thrombosis	0	0.0	1	4.0	1	2.6
Medical Complications						
Acute on chronic liver failure	1	7.1	0	0.0	1	2.6
Chronic Kidney Disease	1	7.1	1	4.0	2	5.1
Carbohydrate intolerance	4	28.6	0	0.0	4	10.2
Diabetes	0	0.0	1	4.0	1	2.6
Hypertriglyceridemia	0	0.0	1	4.0	1	2.6
Acute rejection	5	35,7	12	48.0	18	45.2
Chronic rejection	1	7.1	0	0.0	1	2.6
Urinary tract infection	3	21.4	1	4.0	4	10.2
Bronchopneumonia	2	14.3	1	4.0	3	7.7
Aspergillosis	2	14.3	0	0.0	2	5.1
Myelotoxicity	3	21.4	2	8.0	5	12.8
Chronic diarrheal disease	1	7.1	0	0.0	1	2.6
Dilated heart disease	0	0.0	1	4.0	1	2.6
C. difficile diarrheal disease	0	0.0	2	8.0	2	5.1
Nonalcoholic steatohepatitis	1	7.1	1	4.0	2	5.1
Perianal Condylomatosis	0	0.0	1	4.0	1	2.6

Infectious complications in the immediate and mediate postoperative period were mainly due to Gram-negative bacteria. *Escherichia coli* was isolated in two cases, *Klebsiella pneumonia* in two cases, *Granullicatella adiaens* in one case, and *Acromobacter* in one case. In addition, methicillin-resistant *Staphylococcus aureus* was isolated in one patient.

The mean final BMI for 22 patients from whom data were obtained was 28.2 ± 5.25 kg/m2, compared to a pre-transplant mean of 27.14 ± 4.2 kg/m2. This difference was not statistically significant.

Discussion

The difference found between men and women is consistent with data published in other similar studies. In the United States, for example, there are fewer women than men on the waiting list for liver transplantation (38% vs. 62%) and women are twice as likely as men to receive a graft from both cadaveric and living donors. [2]

Internationally, transplant recipients have an average age between 50 and 64 years of age, with women more often at the extremes of this range.

[3]The average age at the time of transplantation in the present study was 51 years, which is consistent with these statistics; however, we did not find a sex distribution by age similar to those reported worldwide. This is probably due to the considerably smaller sample size in this study.

Leonard *et al*. documented that between 1990 and 2003 the percentage of obese patients at the time of liver transplantation increased from 15% to 25%. [4] Later Kim *et al* reported that by 2011 34.4 % of patients on the waiting list for liver transplantation were obese. [5] In the present study, 72% of the patients for whom data were available were overweight before transplantation, with no statistically significant difference between men and women. It is important to clarify that this measurement has limitations since patient weight may be overestimated in patients with ascites.

Paradoxically, there is insufficient evidence regarding the impact of overweight or obesity on morbidity and mortality after surgery. [6] In a study that included 43,478 patients with hepatitis C virus cirrhosis on the waiting list for liver transplantation, obesity was associated with a lower likelihood of receiving a graft; however, there was no difference in survival when compared with the normal weight group. [7]

In this study, the vast majority of patients were transplanted because of chronic pathologies such as cirrhosis compared to acute liver failure. This is consistent with European data, where 50% of liver transplants are due to cirrhosis. [8]

It is noteworthy, however, that even though in the United States the most prevalent disease in liver transplant recipients is cirrhosis due to hepatitis C virus, [9] in the present study there is only one patient with this diagnosis. Given that this is an infectious disease, the geographical and epidemiological factors may influence this finding, as well as the sample size.

Overall mortality decreased by 25.3 percentage points between the first and second periods analyzed, and mortality during the first 30 days after surgery decreased by 15.7 percentage points. Since there is no statistically significant difference between the characteristics of the patients in both groups, this improvement in survival could be attributed to the experience acquired by the medical team that manages these patients and the acquisition of new equipment and technology in the hospital.

The incidence of acute kidney injury in the immediate and mediate postoperative period exceeds that reported in other series, which is 8% at one-year post-transplant. [10] The factors that increase the risk of developing renal injury at any time after transplantation are several: the clinical condition before transplantation, intraoperative hemodynamic complications, massive transfusions of hemocomponents, intraoperative vascular clamping with hypotension, and many other postoperative events such as infections, surgical reinterventions and frequent imaging studies with contrast medium. [11]Other important conditions for the establishment of renal failure are the previous existence of renal dysfunction, use of nephrotoxic drugs, especially calcineurin inhibitors, sepsis, *shock,* and liver graft dysfunction. [10]

The only two infectious complications during the immediate postoperative period reported in the present study were bacteremia and nosocomial pneumonia, affecting 8 % and 5 % of patients, respectively. These data are in agreement with an Italian study conducted in 2017, in which the main infectious complications were nosocomial pneumonia and bacteremia, and the main infectious agents isolated during the immediate postoperative period in liver transplant patients were *Escherichia coli* and *Klebsiella pneumonia* followed by *Pseudomonas aeruginosa* and *Staphylococcus aureus*. [9]

Other similar studies have also documented a predominance of Gram-negative bacteria in this group of patients. [11-13] Therefore, the use of prophylactic antibiotics targeting Gram-negative and Gram-positive bacteria is indicated and is the usual practice in the center where this research was carried out. Given the high levels of immunosuppression in the first days after transplantation and the contact with nosocomial pathogens, it is in this period when the risk of infection is higher [14]and this was reflected in the data obtained.

The incidence of arterial hypertension following liver transplantation varies between 50% and 70% worldwide.[15] It is mainly due to the adverse effects of chronic steroid and calcineurin inhibitor therapy. [16] In the present study, 27 patients were transplanted who were not known to be hypertensive before transplantation, of whom six had systolic blood pressure greater than 130 mmHg or a diastolic blood pressure greater than 90 mmHg at the last measurement recorded in the file. This is an inaccurate and unreliable measurement of the development of

post-transplant arterial hypertension since these patients were not necessarily subsequently diagnosed with hypertension. It is important to note that in 51% of the cases no blood pressure measurements were taken during ambulatory follow-up.

According to international statistics, obesity is a very frequent complication in transplant patients with incidence ranging from 15% to 40% at one-year post-transplantation. Therefore[10], the increase in mean body mass index observed in this study is not surprising. It is presumed that this difference is underestimated in the present study, as weight and height were not available for all patients before and after transplantation. In addition, many are only a few years post-transplant and have not yet reached their peak BMI.

The majority of patients who had at least one episode of graft rejection documented by biopsy had acute cellular rejection, which is consistent with international statistics reporting that 20-40% of patients have at least one episode of acute rejection following transplantation. On the other hand, [16] chronic rejection, which occurs in only 10 to 20%, according to international [16]statistics, occurred in only one patient in the sample, which corresponds to 2.2%.

Patients who are candidates for liver transplantation should be referred early to a specialized solid organ transplantation center for comprehensive and multidisciplinary care to diagnose and manage comorbidities and complications of the primary liver disease to optimize the results of the transplant.

After transplantation, patients must follow a chronic control in the specialized liver transplant center, given the complex therapy they require. This is because metabolic complications are highly prevalent in the transplanted population and widely influence post-transplant mortality. In this context, strict weight control and a specialized nutritional approach are fundamental aspects in the management of transplant recipients to avoid subsequent complications of metabolic syndrome.

This is a single-center study that involved only patients who received liver grafting. Therefore, the findings described here are not extrapolated to other populations of patients who have received liver transplantation, and due to the size of the sample should be interpreted with caution. Larger, multicenter studies are important for the adequate characterization of these patients.

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