Liver Re-transplantation in Adults: Indications and Outcomes Analysis of a 23-year Experience in a Single Center in Argentina

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ABSTRACT

Background: Liver retransplantation (re-LT) represents the only treatment for patients with irreversible graft failure.

Objective: The aim of the current study was to describe the outcomes of both, patient and graft, after re-LT, at a high-volume referral center.

Methods: Our population consisted of patients, with liver disease, who underwent re-LT in our institution between January 1996 and December 2019.

Results: 49 patients met the inclusion criteria. The patient's overall survival (OS) for the first year was 85% (Confidence Intervals (CI) 71-92) and 70% at five years (CI 53-82). In our population, three (6.12%) patients presented loss of graft and were included again in the transplant list; of these, one agreed to a new transplant while the remaining two died. This gave us graft survival results similar to those obtained for the re-LT patient; 85% at one year (CI 71-92) and 70% at 5 years (CI 53-82).

Conclusion: Our study shows that re-LT is a valid and safe treatment for both early graft dysfunction and for transplanted patients who again present end-stage liver disease, showing a satisfactory long-term evolution, with parameters comparable to primary transplantation.

KEYWORDS: Liver transplantation; Surgery; Liver disease

INTRODUCTION

Continuous advances in surgical techniques, anesthetics, and pharmacological resources favored the increase in the overall survival (OS) of patients with liver transplantation (LT) [1, 2]. However, 5-20% of transplant recipients will again develop end-stage liver disease [3, 4]. In the United States [1] between 7-10% of all liver transplants constitute retransplants, while in our country this group represents 5-7% [5]. Since the beginning of LT, liverretransplantation (re-LT) has been recognized as a challenge, not only for its technical complexity but also for all the aspects involved in the evolution of the patient. Considering that it represents an increase in the demand for organs, over a supply that is always limited, it is essential to demonstrate that this practice is justified, by proving that the results obtained are at the same level as for primary transplantation.

According to the available evidence, the prognosis for both graft and receptor is poorer for re-LT. The latest OPTN/SRTR 2018 Annual Data Report: Liver [1] reported that the OS of patients who undergo a primary transplant varies from 72-84% at 5 years; whereas, groups like Doyle et al. report a 5-year OS of 59.5% for re-LT [6]. Similar results were found by Azoulay and colleagues at the Paul Brousse Hospital where the 5-year OS rates

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were 54% and 42.5% respectively [7].

Given these results, the aim of the current study was to describe patient and graft OS after re-LT, in a high-volume referral center in Argentina.

MATERIALS AND METHODS

Patients

A retrospective observational cohort study was carried out, based on a prospective database, on adult patients (over 16 years old), who underwent a re-LT in our center between January 1996 and December 2019. The data collected included demographic characteristics, etiopathogenic factors, clinical and biochemical characteristics, morbidity, and mortality.

Definitions

For the analysis, the period between primary LT and re-LT was divided into two groups: early re-LT, those performed within the postoperative year (0-365 days), and late re-LT, those performed after one year (> 365).

Primary dysfunction is defined as loss of graft requiring re-LT within the first postoperative week. Primary disease recurrence is defined as the diagnosis of the return of the pathology that caused the first transplant.

Postoperative complications were divided into three groups: immediate complications (within the first week), mediate complications (before 90 days), and late complications (after 90 days).

Clavien–Dindo classification was used to graduate postoperative morbidity. Grades III–V were considered as major complications.

Loss of the graft is considered to be an indication of readmission to the waiting list or the death of the patient.

Follow up

All patients received the same postoperative care provided by the same medical team, it included clinical evaluation and blood test 7-10 days after discharge, and then subsequently after 1, 3, and 6 months. All patients were followed up from the date of re-LT to either the date of death or the date of the last contact.

Ethical Considerations

This study was approved by the Institutional Ethics Committee (Protocol number 3989) and is in consonance with the Helsinki Declaration.

Statistical Analysis

For the descriptive analysis, continuous variables were expressed as mean and standard deviation or median and interquartile range according to the observed distribution. The categorical variables were expressed in absolute frequencies and percentages. OS of the patient and the graft was estimated using the Kaplan-Meier method. Confidence intervals (CI) for OS were calculated using the Greenwood method. For the analysis of the factors associated with patient and graft OS, a simple and adjusted Cox proportional hazard model was constructed, reporting the raw Hazard Ratio and adjusted with its CI. The assumption of proportionality of the risks and the interaction of the variables with time were tested graphically (graph of the risk functions and their logarithms, comparison of predicted and observed values) and statistically (Schoenfeld test), and the ability to discriminate of the crude and adjusted model using Harrell's C index. For the statistical analysis, the STATA 13 program (StataCorp, College Station, TX, USA) was used.

RESULTS

Between 1996 and 2019, 877 liver transplants were performed in adult patients at our Hospital, 49 of which (5.6%) were re-LTs.

The demographic and etiological data are shown in Table 1. The main cause of LT was Hepatitis C Virus (HCV) in 17 (35%) patients, while Autoimmune Hepatitis (AIH) was second in frequency, with 9 patients (18.4%). Regarding the causes that led to re-LT, the most frequent was primary disease recurrence in 16 (32.7%) cases.

Table 1: Recipient baseline characteristics.

Variables	Total
Age (years)	47 (36-60)
Male sex (male/female)	26 (53%) 1.13
Primary diagnosis	
HCV	17 (34.69%)
AIH	9 (18.40%)
PBC	7 (14.28%)
Alcohol	4 (8.16%)
Cryptogenic	3 (6.12%)
BA	3 (6.12%)
Hemochromatosis	2 (4.08%)
Others	4 (8.16%)
Causes of graft loss	
Primary disease recurrence	17 (34.69%)
Arterial thrombosis	14 (28.57%)
Biliary stricture	10 (20.40%)
Rejection	5 (10.20%)
Primary graft dysfunction	3 (6.12%)
Others	3 (6.12%)

HCV: hepatitis C virus; AIH: autoimmune hepatitis, PBC: primary biliary cholangitis; BA: biliary atresia

Of the 49 re-LT, 16 (32.7%) were early re-LT, while 33 (67.3%) were late. The main indications of early re-LT were arterial thrombosis 9 (56.3%) and primary graft dysfunction 3 (18.8%). For late re-LT, the most frequent causes were primary disease recurrence 15 (45.5%) and biliary stricture 9 (27.3%). The rest of the indications are summarized in Table 2.

Table 2: Causes of early and late re-LT.

Indications	Early re-LT= 16	Late re-LT= 33
Primary graft dysfunction	3	0
Biliary stricture	1	9
Arterial thrombosis	9	3
Venous thrombosis	2	0
PBC	0	1
AIH	0	1
Primary disease recurrence	1	15
Rejection	0	4

PBC: primary biliary cholangitis; AIH: autoimmune hepatitis,

The median time to re-LT was 35 months (CI 5-98).

38 patients presented a total of 58 postoperative complications, 21 (36%) of these were immediate, 14 (24%) mediate, and 23 (39%) presented late complications. The most frequent was hemorrhagic shock 7 (33%) in the immediate period, rejection 5 (35.7%) in the mediate stage, and primary disease recurrence 10 (43.5%) in the late stage. Postoperative complications are summarized in Table 3.

With a mean follow-up of 3.08 years, we had a total of 13 (26%) deaths, 6 of which (46%) were within the first 90 days of surgery and 4 (66.7%) during the first 24 hours. Patients' OS at one year was 85% (CI 71-92) and 70% (CI 53-82) at 5 years (Fig 1).

In our population, 3 (6.12%) patients presented loss of graft and were readmitted to the transplant list; one accessed a new transplant, while the remaining two died. This shows similar graft OS results to the ones obtained for the re-LT patient; 85% at one year (CI 71-92) and 70% at 5 years (CI 53-82) (Fig 2).

Table 3: Complications.

Variable	Total
Complications < = 7 days	
Hemorrhagic shock	7 (33,3%)
Reperfusion injury	4 (19.04%)
Kidney failure requiring dialysis	2 (9.52%)
Intra-abdominal abscess requiring percutaneous drainage	2 (9.52%)
Long-term ventilator support requiring tracheostomy	1 (4.7%)
Intestinal perforation	1 (4.70%)
Others	4 (19.04%)
Complications > 7 < = 90 days	
Rejection	5 (35.70%)
Biliary stricture	2 (14.30%)
Arterial thrombosis	2 (14.30%)
Primary disease recurrence	2 (14.30%)
Intra-abdominal abscess requiring percutaneous drainage	2 (14.30%)
Others	1 (7.14%)
Complications > 90 days	
Primary disease recurrence	10 (43.5%)
Rejection	6 (26.10%)
Biliary stricture	5 (21.70%)
Others	2 (8.70%)

DISCUSSION

The current study shows the outcomes of the longest re-LT series carried out in Argentina, with 49 cases of re-LT in adults out of a total of 877 LT, with an OS of 85% at 1 year and 70% at 5 years. These results are significantly higher than those presented by Masior et al. in 2016 [8-9-10], but similar to those published in more recent works such as Takagi et al, Holland 2020 and the one presented by Jeffrey et al, in 2019, where a total population of 278 re-LT, performed in New Zealand and Australia, they obtained patient OS rates of 89% at 1 year and 81% at 5 years [3, 11-12].

The median age in our population was 47 years, similar to reports of the USA [13], Italy [11-14], and the Netherlands [11]. Although the recipient's age over 60 years has been reported as a poor prognostic factor in works like Hong 2011 and others [15-16], in our series we found no association between age at re-LT and OS of the patient or graft.

With regard to the indications for re-LT, we find differences with previous reports. In one of the main studies performed in the United States, from 1999 to 2003 [17], the majority of transplants were due to primary graft dysfunction (37.5%), hepatic artery thrombus (20%), primary disease recurrence (17.5%) and graft rejection (12.5%). Other groups report similar results [17, 18].

On the contrary, in our series, the main cause of re-LT was primary disease recurrence (32.7%), while graft dysfunction only explained 6% of re-LT. The remarkable decrease in cases of primary graft dysfunction could be associated with advances in surgical techniques, pharmacological resources, management of critical patients, intensive care units, etc.

Among the resources that could reduce the need for retransplantation due to vascular complications, it is worth highlighting our policy of monitoring all patients with doppler ultrasound, every 12 hours for the first 3 days and then daily; detecting early vascular complications and allowing us to act on them, with the possibility of preserving the graft.

The rise in the curve of transplanted patients with primary disease recurrence is a trend already reported in studies such as that of Zarrinpar, from the University of California [16], and is clearly related to the increase in patients' OS after the first transplant; the longer the OS, the greater the possibility of primary

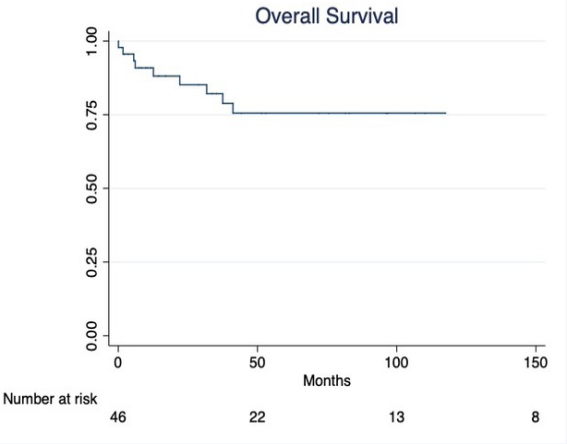

Figure 1: Kaplan-Meier overall re-LT patients' survival. Numbers at risk indicate the total patients at risk.

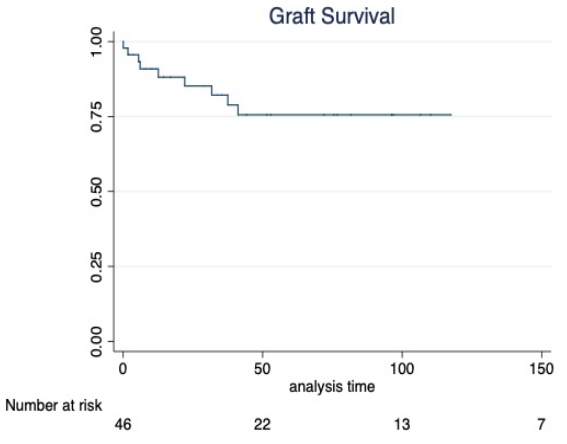

Figure 2: Kaplan-Meier graft survival. Numbers at risk indicate the total patients at risk.

disease recurrence and, consequently, the need for re-LT [19].

Regarding the period LT and re-LT, several studies have reported worse results among early re-LT. In The European Liver Transplant Registry (ELTR), early re-LT has a significantly lower, 5-year graft survival, than that observed with late re-LT (45% vs. 50%) [4]. In concordance, The United Network for Organ Sharing (UNOS) reports that re-LT, practiced within the first year, shows below-standard results [20]; similar conclusions are found in other studies [21]. However, in our series, we did not find differences in long-term patient or graft survival rates between early or late re-LT recipients, in agreement with other groups such as that of Moon et al, from Kosin University Gospel Hospital, Korea [22] or Kamei, from the University Hospital of Western Ontario, Canada [23].

An estimate of survival was calculated, based on the presence of independent predictors of survival following the modified Rosen and UCLA scores [24, 25], none of them resulted in statistically significant.

The limitations of our work are inherent in its retrospective design and the small size of the analyzed population. However, it is important to highlight that it was carried out in a single center, specialized in LT, run by a stable team, and with a mean follow-up of 3.08 years. In addition, it should be noted that, so far, it is the largest series presented in Argentina.

Although re-LT continues to be a matter of controversy for the medical community, between 5-20% of patients with LT will present loss of graft, and for them, this practice will constitute the only alternative treatment.

In conclusion, the current study shows that re-LT is a valid and safe treatment for both early graft dysfunction and for already transplanted patients who again present end-stage liver disease, reflecting a satisfactory long-term evolution, with parameters comparable to primary transplantation.

CONFLICTS OF INTEREST: None declared.

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