Liver Retransplantation

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24.1 Introduction

Since the early days of liver transplantation (LT), retransplantation (reLT) has been recognized as a medical, surgical, and ethical challenge.

The first reLT was performed in Pittsburg in 1968 and reported by Thomas Starzl in the 1980s [1].

After an initial progressive increase, the European Liver Transplant Registry (ELTR) [2, 3] reported in the last 10 years a decrease in the use of re-LT that accounts recently about 5% of the registry cases. More generally, the prevalence of the procedure ranges between 5% and 15% of all transplants in the different series reported.

ReLT represents the only life-saving option for patients with a failed graft. However, it has been clearly shown that it produces inferior survival outcomes compared to primary LT, despite recent improvements.

According to ELTR data [2] (1988–2009), 5-year graft survival after reLT recently increased to 52%, although the gap between primary LT (68% at 5 years) and re-LT remains. Similarly, OPTN/SRTR reported in 2010, 5-year survival of 70% for primary LT compared to 55% for re-LT.

However, a recent study [4] reported similar survivals between reLT and primary transplantation after the introduction of DAA, underlining the relevant role of HCV in worsening the results of reLT in the pre-DAA era.

On the contrary, results of reLT are significantly lower in patients primarily transplanted for NASH cirrhosis if compared to the other ethiologies [5].

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Allocation has a relevant role in early and middle-term results. The "Share 35" policy (prioritization of donors to regional candidates with MELD ≥ 35 over local low MELD candidates) implemented in United States in 2013 showed an improved 2-year graft (67% vs. 21.1%) and patient (69.2% vs. 33.1%) survival after reLT compared to the Pre-Share period [6]. According to ELTR (2018 annual report [3]), reLT is mostly used in young patients, showing a numerical decline in the last decade.

The use of a graft for reLT costs for patients in the waiting list the chance of getting their first liver transplant. That generates an ethical issue especially when considering the shortage of organs. If the need of reLT in emergency condition as hepatic artery thrombosis is not a matter of dispute, the use of a graft for a primary disease recurrence or a chronic rejection remains controversial.

On these bases, there are no uniform guidelines for relisting; consequently, the decision is at the discretion of physician and transplant centers.

24.1.1 Indication to Retransplant

When in the 1980s, the University of Pittsburgh and Colorado published their first experiences with reLT, the main indication was rejection. In the past two decades with the introduction of cyclosporine and general improvements in immunosuppression, a shift has been recorded in the main indications to reLT, from rejection to early graft loss for PNF or vascular issues.

Indications are divided according to the time of the event in:

1. Early causes: Early graft failure is a usually dramatic condition that occurs in the first days or weeks after LT (typically within the first month). In 49% of cases, reLT is indicated in the first month whereas 65% of reLTs occur within 6 months after LT [2]. Early reLT is mainly due to:
   (a) Primary non-function (PNF).
   (b) Vascular complications (hepatic artery thrombosis, portal vein thrombosis, hepatic vein thrombosis)
   (c) Acute rejection
2. Late causes: Chronic graft dysfunction is the result of a progressive worsening of liver function for which all therapeutic efforts had failed. Diagnosis may be sometimes difficult and a multidisciplinary team is needed to share the decision. The main causes include:
   (a) Chronic rejection
   (b) Recurrence of primary liver disease (viral infections, autoimmune disease, others)
   (c) Biliary complications/ischemic cholangiopathy

In the ELTR study [2], collecting data in Europe from 1998 to 2009, the main indications for reLT were vascular complications (27%), PNF (25%), rejection (19%— chronic in 14%), and biliary complications (10%). Recurrent diseases were the indication in only 11% of cases.

PNF is an irreversible graft failure defined by hepatic cytolysis, severe coagulation deficit, high lactate levels, hypoglycemia, absence of bile production, and hepatic hemodynamic instability in the early postoperative course of liver transplantation [7]. The reported incidence ranges from 4% to 8% [8] of primary transplants. ReLT represents the only therapeutic option. Five-year survival after reLT for PNF is similar to other causes (60% vs. 51%, $p = 0.63$ in a Uemura et al. series) [7] but with survivals reaching comparability to primary transplantation if the reLT is performed within the first week. The increased acceptance of marginal grafts over the past decades has raised the rates of PNF in many transplant centers. PNF can be attributed to multiple causes related to donors (i.e., steatosis, older donors, use of split graft, or from DCD) and possibly to recipients (i.e., prolonged cold ischemia time, comorbidities, high MELD) [9].

Early hepatic artery thrombosis (HAT) is a serious technical complication, occurring in approximately 3% of adult LT and 8% of pediatric transplants [10]. HAT is typically more frequent in the first week after LT.

Risk factors of early HAT can be related to surgical procedure (intimal dissection, vessel kinking, small caliber, use of arterial conduit, variant arterial anatomy) or to donor/recipient characteristics (elderly donors, hypercoagulable state, cytomegalovirus infection, ABO incompatibility, acute rejection, previous LT, pre-LT portal vein thrombosis).

Early HAT resulted in an overall reLT rate of 62% in children and 50% in adults, with an overall mortality rate of 33.3% in a systematic review by Bekker et al. [10]. More recent case series [11, 12] confirm these results. Graft salvage approaches such as surgical or radiological thrombectomy or thrombolysis can be attempted; nevertheless, reLT is the gold standard of therapy for HAT especially due to the frequent middle-term consequences of temporary arterial occlusion with particular reference to ischemic cholangiopathy-related events. Patients retransplanted due to HAT have better outcomes (graft and patient survival) than those retransplanted for other indications [13].

HAT may also occur in a later phase and sometimes years after the procedure. Late HAT has a different and usually milder evolution probably due to the development of arterial peribiliary collaterals capable to maintain various degrees of arterial vascularization. The outcome of late HAT is variable mainly depending on the degree biliary damage associated with ischemia. It often results in ischemic cholagiopathy almost invariably requiring a reLT.

Portal vein thrombosis (PVT) and **hepatic vein outflow obstruction** are uncommon complications after LT; a portal thrombectomy or graft interposition is often needed in case of PVT whereas a balloon angioplasty or stenting may be an option in the presence of hepatic vein outflow obstruction. ReLT is considered only in case of failure of conservative approaches and after an accurate balance between severity of liver dysfunction and related symptoms on the one side and the risks of a reLT on the other.

After the introduction of calcineurine inhibitors in regular practice, **acute cellular rejection (ACR)** is a relatively rare indication to reLT. On the other hand, antibody-mediated rejection (AMR) has emerged as the pathophysiologic mechanism of some previously unexplained graft dysfunctions needing reLT.

The exact incidence of AMR is unknown because the diagnosis is difficult to establish [14]. O'Leary et al. [15] reported for recipients with high mean fluorescence intensity (MFI) preformed donor-specific HLA alloantibodies (DSA) a significant greater risk of early allograft injury and possibly loss (<90 days) often in combination with ACR. The development of DSA (IgG3) is reported to have a hazard ratio for graft loss of 3.35 [16]. Therefore, in order to start the treatment, the dosage of DSA is mandatory every time an unexplained graft dysfunction is present.

Similarly to acute rejection, the incidence of **chronic rejection** seems to be diminishing in the contemporary era according to ELTR data [2]: from 36% of all reLTs at the end of the 1990s to 14% during the last years. However, chronic rejection remains one of the most relevant causes of graft dysfunction/loss frequently representing a clinical challenge. A significant proportion of patients do no respond to increased immunosuppression needing a reLT: High mortality is reported in the absence of reLT.

Biliary complications (Ischemic type biliary lesions) are often the results of earlier HAT, prolonged WIT, or CIT. Graft from donor after cardiac death (DCD) also representing a common cause of reLT in the first months after LT when endoscopic treatment failed. Some patients have been undergoing to endoscopic or PTBD approaches to try a conservative solution. Not infrequently these efforts may induce septic complications worsening the picture and making the reLT option more complex.

In a recent series [17], it has been shown that reLT for ischemic type biliary lesions (leading cause of reLT, 23% of cases) was associated with a better middle- and long-term survival if compared to the other indications to reLT.

The profile **recurrent disease** as indication to reLT has changed relevantly in the last years.

Recurrent HCV infection has been a clinical challenge in LT until recently being responsible for up to 30% of all reLT [18]. The introduction of DAA-based therapy in 2011 led to a successful treatment of most recurrence after LT and reduced relevantly the number of patients HCV positive at the moment of transplant. Therefore, an incremental decline in HCV-related reLT has been reported from 20.4% in 2005 to 1.2% in 2014 [19].

Recurrent autoimmune disease leads to liver failure prompting the need for a reLT in 5–10% of cases.

Primary sclerosing cholangitis recurrence (rPSC) occurs in 8.6–27% [20] of LT recipients within 5 years and it is related to an increased risk of graft failure and mortality. Graft loss due to rPSC is higher compared to other AI liver disease and reLT is common (8.4% [21]]. The UNOS database [22] emerged that PSC patients retransplanted for disease recurrence have a similar survival compared to primary LT recipients at 5 years. This finding supports the indication to reLT for recurrence PSC.

Recurrent primary biliary cholangitis (rPBC) after LT is reported ranges between 10.9% and 42% [20] but differently than other autoimmune diseases graft loss due to recurrent disease is not a major issue [23].

Autoimmune hepatitis can recur in the graft despite immunosuppressive medications; recurrence rate reported is 7–42% [20] with a median of 26 months after LT. Graft loss occurs in a more expedited fashion than in recurrence of other AI diseases and re-recurrence in the retransplanted graft has been observed in 50–67% of cases [20].

Nonalcoholic steatohepatitis representing nowadays the fourth leading cause of LT IN United States has a high rate of recurrence (0–33% [24, 25]) but rarely leads to reLT.

24.1.2 Multiple Transplants

More studies reported worse outcomes with repeat retransplants. The need for reLT can also lead to further retransplantation. In some series, more than five grafts for the same recipient have been reported. A series analyzing 25-year experience [26] reported 1- and 3-year survival rates of 66% and 61% for first reLT, 45% and 40% for second reLT, and 24% and 0% for third reLT. Memeo et al. [27] reported his experience with reLT in 1985–2012; the rate of reLT was 8.4% ($n = 399$). The main indication for third LT was arterial thrombosis, for fourth LT was chronic rejection. Patient overall survival since third transplant was 82%, 80%, 75%, and 71% at 1, 3, 5, and 10 years, while for the fourth transplant was 42%, 42%, 42%, and 42%, respectively. The patient who received five LT (due to Budd-Chiari syndrome) died at 20 months after last LT. Early patients mortality (90 days) since third LT is higher than after first LT; factors affecting mortality are found in extra hepatic sepsis and need for vasoactive drug support [27]. The 2018 ELTR annual report [3] provided a 5-year survival following a second and a third LT of 48% and 42%, respectively, that is significantly lower than after primary LT (66%, $p < 0.0001$).

Results of reLT at our center stratified according to reason for transplant and number of procedures are shown in Fig. 24.1.

24.1.3 Factors Affecting Outcome

Research work has been done to find prognostic factors for patient survival to carefully select patients who might benefit from reLT and to better allocate organ resource. Main independent predictors of poor survival after reLT are high MELD, recipients' age, use of older donors (age >60), HCV infection, timing of re-LT, and number of transplants.

Candidates to liver reLT have higher mean MELD at the time of retransplant than recipients of primary liver graft [28]. As expected, sicker patients with higher creatinine and bilirubin level, need for mechanical ventilation or renal replacement therapy tend to have significantly inferior outcomes.

Recently, it has been shown that the reported MELD threshold for survival benefit in reLT is 21; risk of death or failure after reLT is 3.5–8.3 times greater than risk of death without LT for candidates with MELD <21 [29]. This implies that timing and therapeutic window for retransplant are key issues and may turn out to be extremely challenging.

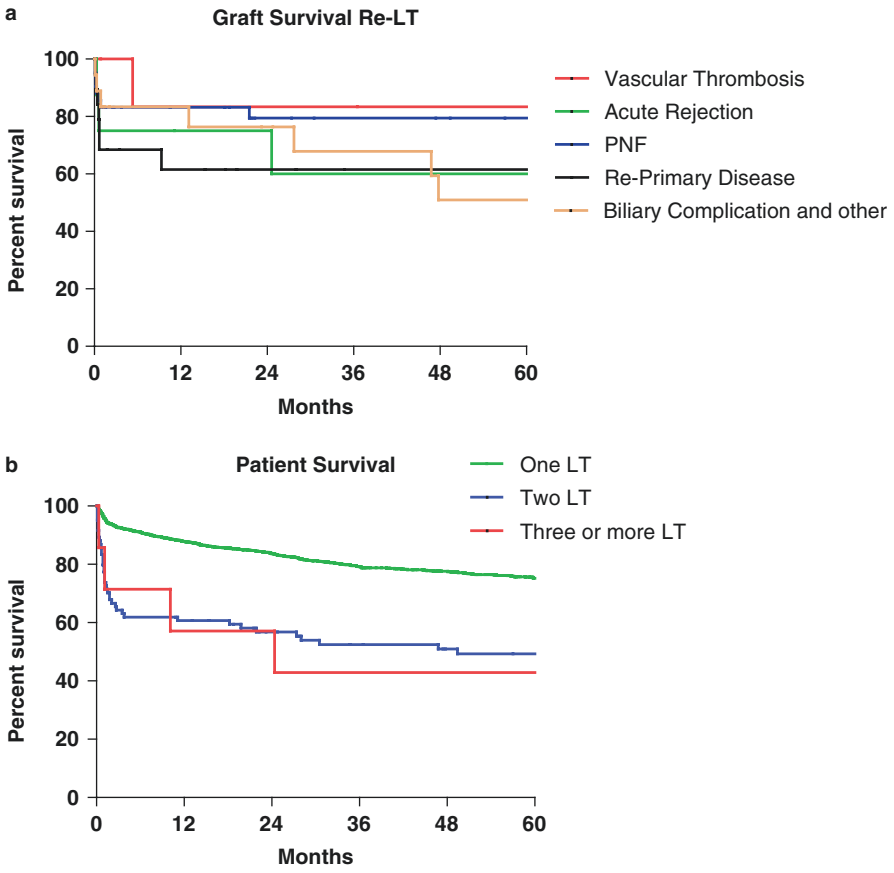

Fig. 24.1 Graft and patient survival after reLT at our center stratified according to reason (**a**) for transplant and number of procedures (**b**)

As far as timing of reLT is concerned, the best survivals were found after very early reLT (<7 days) and late transplant (>365 days). Some studies showed an increased mortality rate for reLT between 8 and 30 days after primary LT [30]. Such a higher mortality may be the result of delay due to unsuitable graft or late decision by the clinicians. As a result, patients may arrive at the reLT in worst conditions and with a higher degree of multiple organ dysfunction.

In such a context, recipient age relevantly affects survival being associated with higher prevalence of comorbidities and age-related limited functional reserve.

It has been reported an increase of 1.52 in the risk of death every 20 years of recipient age [31]. However, even though UNOS dataset confirmed this tendency but showed that in recipients of re-LT >60 years, increasing age was not associated with an increased 90-day and 1-year mortality ($p = 0.88$, $p = 0.74$) [32].

A good matching between donor and recipient is key for a successful liver transplant. Unfortunately, the state of urgency that often leads to the need of retransplant

(PNF, HAT) prompts the decision to use the first available graft to save patient's life despite graft quality. In contrast, in a setting of non-urgent reLT, a better perioperative patient management positively influences post reLT graft survival even in the presence of high-risk donors [33].

The use of grafts from donors >60 years is reported to adversely affect survival after reLT [33–35]. Donor quality has been shown to be important especially when matching with HCV-infected old recipients in the pre-DAA era. Indeed, UNOS analysis resulted that, in HCV-negative patients, a broader range of donors can be used for live-saving reLT if compared to HCV-positive ones [36].

The use of split graft should be discouraged for reLT due to the higher risk of reLT [37] and the worst survival in several case series [38]. Finally, the use of grafts from DCD is not recommended [39], especially for high MELD recipients.

ReLT represents a surgical challenge; nevertheless, the improvement in reLT outcomes can be attributed in advances in operative and anesthesiologic techniques. Surgical choices adopted during primary LT guide reLT approach and need to be known in detail preoperatively. The complexity of the operation is mainly related to the time elapsed between LT and reLT; if performed early reLT hepatectomy results quick and relatively straightforward because most of dissection is already done and portal hypertension is usually inferior than first transplant. When reLT occurs late, dense adhesions and scar tissue complicate dissection and identification of structures. An en-block clamp of hilar structures may be necessary when identification of single element is impossible. This allows to transect en-masse the hilum and then proceed with the hepatectomy. Subsequently, each structure has to be careful identified and prepared for the anastomosis. In some instances, portal stump may result too short to allow a secure clamping and an adequate anastomosis. In these cases, we have used an intravasal clamping with a Foley balloon allowing the anastomosis with an interposition donor venous iliac graft to achieve an adequate portal stump as shown in Fig. 24.2.

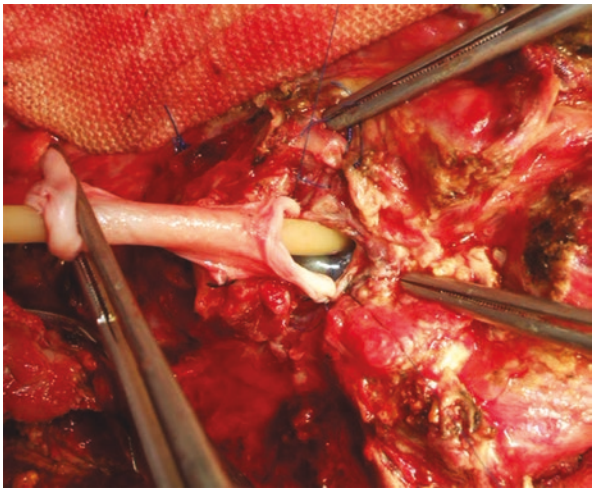

Fig. 24.2 Intravasal clamping using a Foley balloon during hepatectomy at reLT

Venovenous bypass is often required and a vena cava complete replacement is performed when caval preservation resulted too dangerous. Vascular reconstructions are usually complex; the presence of HAT in the recipient may dictate an alternative method for arterial reconstruction. The use of the recipient splenic artery or the creation of an aortic conduit for hepatic graft arterialization are frequently adopted solutions. A Roux-en-Y choledochojejunostomy is mandatory in the presence of questionable recipient duct quality or anastomotic tension. In a French series [27] of multiple reLTs, venovenous bypass was required in 82.2%–100%, caval replacement in 66.6%–100%, and bilio-enteric anastomosis in 93.3% of the cases.

24.1.4 Models to Predict Outcome

Although a consensus is not yet be reached in the definition of futile reLT, a minimum 1-year expected survival of 50% after reLT has been arbitrarily proposed. To avoid futile reLT and to facilitate decision-making for the best utilization of a scarce donor resource, risk predictor models have been proposed over the years (Table 24.1). The most commonly used risk score for reLT was the Rosen score proposed in 1999 and validated in 2003 [40]. This score defined three different levels of risk (low, medium, and high) on the basis of four prognostic factors (recipient age, bilirubin level, creatinine level, interval between primary transplant, and reLT). The 5-year survival was 68% for low risk, 62% for intermediate risk, and 38% per high risk. Criticisms have emerged over the years for this score since it was formulated in the pre-MELD era, it does not consider donor variables and it required mathematical calculation. Subsequently, specific models were developed for pediatric [38] and HCV-positive [34] recipients. The UCLA group [35] recently published a new risk stratification scoring. This system assigns one or two points for preoperative clinical variables as recipient age >55 years., MELD > 27, history of prior reLT, serum albumin level <2.5 g/dL, timing of reLT between 15 and 180 days, requirement for ventilator at the time of reLT, donor age >45 years. and intraoperative variable as pRBC transfusion >30 units during reLT. The assigned points are added together to stratify patients into four risk categories (RC). The 5-year patient survival reported was 79% for RS I, 59% for RS II, 49% for RS III, and 22% for RS IV.

24.1.5 The Ethical Issue

As already mentioned, the opportunity to use the scarce donor resource to offer a second chance to a transplant patient is still under debate. Even after the reduction of HCV-related transplants due to the introduction of DAA, mortality in waiting list still ranges between 4% and 10%. As far as ethical principles governing liver transplant allocation are concerned, the rationale to assign an organ for a reLT lays in the potential to increase the utility of the first transplantation improving patient

Table 24.1 Predictor models for liver retransplant. *Modified From Kitchens WH, Yeh H, Markmann JF. Hepatic retransplant: what have we learned? Clin Liver Dis 2014;18*(3)*:741–2.* Copyright Elsevier

Author	Predictor model	Risk categories	1-year survival (%)
Rosen et al. (2003) [40]	$R = 10 \times (0.0236 \times$ [recipient age] $+ 0.125 \sqrt{}$[bilirubin in mg/dL] $+ 0.438 \times$ [loge Cre in mg/dL] $- 0.234$ [interval to retransplant, 0 for 15–60 days, 1 for >60 days])	Low risk: $R < 16$ Medium risk: $R = 16–20$ High risk: $R > 20$	75% 58% 42%
Davis et al. (2009) [38]	**Pediatric retransplant** Assign 1 point for neonatal cholestasis/ paucity of bile ducts, being on life support at time of retransplant, receiving a split-liver graft Subtract 1 point for: Age 5–18 years at time of retransplant, acute rejection as indication for retransplant	Low risk: <0 points Medium risk: 0 points High risk: 1–3 points	82% 62% 49%
Hong et al. (2011) [35]	Assign 2 RS points for: – I.O pRBC >30 units – prior liver transplant >1 – mechanical ventilation at the time of reLT – interval from prior transplant to retransplant of 15–30 days Assign 1 RS point for: – interval from prior transplant to retransplant of 31–180 days – donor age >45 years – MELD score >27 – serum albumin level <2.5 g/dL at time of reLT – recipient age >55 years	PIC I: RS = 0 Category II: RS = 1–2 Category III: RS = 3–4 Category IV: RS = 5–12	84% 75% 63% 33%
Andres et al. (2012) [34]	**HCV-positive** retransplant RS = 0.23 × (donor age) + 4.86 log (Cre) − 2.45 × log (interval between transplants in days) + 2.69 × INR + 0.1 × (recipient age) − 3.27 × (serum albumin) + 40	Low risk: RS <30 Medium risk: RS 30–40 High risk: RS >40	72.2–87.3% 62.5–71.7% 50%

Cre Creatinine, *PIC* Predictive index category, *I.O* Intraoperative, *pRBC* Packed red blood cells, *RS* Risk score

survival. At the same time, every single donor organ allocated to a previously transplant patient generates a harm on the waiting list. In line with Merion [41] and Schaubel [42] seminal considerations, we should evaluate the indication to reLT through the lens of transplant benefit [43]. ReLT provides an increase of individual benefit but a questionable impact on population benefit due to the harm on the waiting list. Population benefit may increase only through an accurate selection of recipients and timing in order to optimize the difference between the expected survival with reLT versus that expected without reLT.

In this view, accurate prediction of irreversible liver failure, early model-assisted decision to relist the patient and adequate donor-recipient matching are key issues to ethically and clinically justify a reLT.

Key Points

- Liver retransplant is associated with inferior survival compared to primary transplant but outcomes have improved over time.
- Indications for reLT vary depending on the interval between prior transplant and retransplant. Early retransplants are mainly due to PNF and vascular thrombosis while late retransplants are commonly causes by chronic rejection or recurrent primary disease.
- Factors affecting poor outcomes after reLT are high MELD, donor and recipient old age, use of split graft or graft from donors after cardiac death and timing of reLT.
- To avoid futile retransplant, several risk predictors model have been developed
- Retransplant remains a surgical and ethical challenge

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