UNIVERSITÀ DEGLI STUDI DI PADOVA

CORSO DI LAUREA IN MEDICINA E CHIRURGIA

Dipartimento di Scienze Chirurgiche Oncologiche e Gastroenterologiche

Direttore: Prof. Fabio Farinati

UOC di Chirurgia Generale 2

Direttore: Prof. Umberto Cillo

TESI DI LAUREA

OUTCOMES OF LIVER RE-TRANSPLANTATION AND VALIDATION OF PREDICTIVE MODELS OF GRAFT FAILURE ON SINGLE HIGH-VOLUME CENTER

Relatore: Prof. Enrico Gringeri

Correlatore: Dr. Jacopo Lanari

Laureanda: Marzia Franzò

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RIASSUNTO

Presupposti dello studio. Attualmente, il trapianto di fegato rappresenta la terapia di scelta per i pazienti con epatopatie croniche in fase terminale e insufficienza epatica acuta di qualsiasi eziologia. In caso di mancato funzionamento dell'organo dopo il trapianto, il retrapianto di fegato rappresenta l'unica opzione terapeutica. Con l'aumento del numero di pazienti sottoposti a trapianto epatico, una percentuale sempre crescente di pazienti con disfunzione del graft necessita di un nuovo trapianto di fegato. Oggi, il 5-22% di tutti i riceventi va incontro a perdita del graft e necessità di retrapianto. La carenza di donatori idonei è il problema più urgente che si pone oggi nell'ambito dei trapianti epatici, e in questo contesto l'utilizzo di organi da una ridotta riserva per il retrapianto rimane controverso, anche a causa degli outcome inferiori rispetto ai primi trapianti. Ciononostante, è stato ripetutamente dimostrato che il retrapianto di fegato rappresenta una valida opzione terapeutica per quei pazienti che subiscono una irreversibile perdita del graft, in quanto esso fornisce risultati positivi a lungo termine, il che giustifica il reiterato uso di organi per uno stesso paziente. Per aiutare i trapiantologi a selezionare l'accoppiamento donatore-ricevente con la più alta probabilità di sopravvivenza a lungo termine dopo trapianto, sono stati sviluppati modelli predittivi di perdita del graft, così da poter identificare gruppi di pazienti ad alto rischio dopo il primo trapianto. Inoltre, allo scopo di contribuire alla decisione clinica nell'eseguire o meno un secondo trapianto e in quali tempistiche, sono stati sviluppati modelli predittivi di sopravvivenza dopo il retrapianto di fegato. L'implementazione di questi score di rischio sarebbe auspicabile, in modo da continuare a migliorare e ottimizzare gli outcome del retrapianto, arginando le problematiche sollevate dall'uso di un secondo organo a partire da una già ridotta riserva di organi da donatore.

Scopo dello studio. Lo scopo dello studio è valutare gli outcome di trapianto e retrapianto di fegato nel nostro centro ad alto volume e validare gli esistenti score predittivi di perdita del graft dopo il trapianto.

Materiali e metodi. Studio retrospettivo condotto su un database aggiornato prospetticamente di pazienti sottoposti a trapianto di fegato in un singolo centro dal 01/01/2010 al 31/12/2019. I criteri di esclusione sono stati: età del ricevente inferiore a 18 anni, trapianto da donatore vivente, trapianto domino e trapianto combinato. Sono stati applicati quattro modelli di sopravvivenza sulla popolazione del primo trapianto: Donor Risk Index (DRI), Donor-Model for End Stage Liver Disease (D-MELD), Eurotransplant DRI (ET-DRI) e Model for Early Allograft Function Scoring (MEAF). Sono stati calcolati due modelli di sopravvivenza sul gruppo dei retrapianti: Survival Model for Liver Retransplantation (SMLR) e Liver Retransplantation Risk Score (LRRS).

Risultati. A 1, 3 mesi e 1, 5 anni la sopravvivenza del graft nella coorte di studio è stata rispettivamente 95,4%, 93%, 82% e 70%. I pazienti con un D-MELD >= 1600 o un MEAF >= 8 hanno mostrato una sopravvivenza del graft significativamente inferiore rispetto ai pazienti a basso rischio. Con la regressione logistica multivariata sono stati identificati 6 predittori indipendenti di scarsa sopravvivenza del graft dopo il trapianto di fegato: PNF (HR, 44,7; 95% CI, 24,1, 83,0; p < 0,001). Clavien >= 3b (HR, 2.72; 95% CI, 2.00, 3.70; p < 0.001), EAD (HR, 1.38; 95% CI, 1.01, 1.90; p = 0.045), ITBL (HR, 3.17; 95% CI, 1. 79, 5.63; p < 0.001). 79, 5,63; p < 0,001), PVT (HR, 1,95; 95% CI, 1,13, 3,36; p = 0,016) e D-MELD >= 1600 (HR, 1,45; 95% CI, 1,05, 2,01; p = 0,025). La sopravvivenza del graft dopo il retrapianto a 1 e 3 mesi, 1 e 5 anni è stata rispettivamente 92,1% e 87,3%, 49,2% e 44,2%. Né SMLR né LRRS sono stati in grado di discriminare con sufficiente significatività statistica i pazienti ad alto rischio di perdita del graft dopo il retrapianto. Sono stati identificati 5 predittori indipendenti di scarsa sopravvivenza del graft dopo il retrapianto: PNF (HR, 7.74; 95% CI, 1.58, 37.8; p = 0.011), ITBL (HR, 226; 95% CI, 4.62, 11030; p = 0.006), pRBC trasfusi (HR, 1.10; 95% CI, 1. 01, 1.19; p = 0.006). 01, 1.19; p = 0.028), Clavien >= 3b (HR, 5.12; 95% CI, 1.12, 23.5; p = 0.036) e LRRS (HR, 2.08; 95% CI, 1.08, 4.01; p = 0.029).

Conclusioni. Il re-trapianto epatico può essere offerto ai riceventi che subiscono un fallimento dell'organo dopo trapianto con risultati ottimali. Gli score

prognostici sono utili per identificare i riceventi ad alto rischio di fallimento del graft, ed hanno l’obiettivo di ottimizzare il matching fra donatore e ricevente e guidare i clinici nell'allocazione delle scarse risorse del trapianto.

ABSTRACT

Background. Currently, liver transplantation (LT) represents the standard treatment for patients with end-stage liver disease and acute liver failure of all etiologies. In case of irreversible graft failure after primary LT, liver retransplantation (re-LT) is the only therapeutic option. As the number of recipients undergoing LT grows, an increasing proportion of patients with graft dysfunction require re-LT. Today, 5-22% of all recipients experience graft loss and need for re-LT. The shortage of suitable donor livers is the most pressing problem facing LT today, and in this setting the utilization of scarce donor organs for re-LT remains controversial because of its inferior outcomes compared to primary LT. Nevertheless, re-LT has been consistently shown to be a viable therapeutic option for patients who have undergone irreversible graft failure since it provides positive long-term outcomes, which justifies the use of donor livers.
In order to help LT providers select the donor-recipient match with the highest probability of long-term graft survival, predictive models of graft failure have been developed to identify high-risk groups of patients after first LT. Furthermore, to assist clinicians in deciding whether and when to perform a second transplant, survival models after re-LT have been developed. The implementation of these risk scores would be recommended in order to continue improving and optimizing the results of re-LT while minimizing the issues of using a second graft from a scarce organ pool.

Aim of the study. The aim of the study is to assess the outcome of LT and re-LT in our high-volume cohort and validate the current predictive score for graft failure.

Materials and methods. This is a retrospective study carried out on prospectively maintained databases identifying patients who were submitted to LT in a single center from 01/01/2010 to 31/12/2019. The patient exclusion criteria were a recipient age less than 18 years, living-donor LT (LDLT), domino and combined LT. Four prediction models were calculated on primary LT population: the donor risk index (DRI), the Donor-Model for End Stage Liver Disease (D-MELD), the

Eurotransplant DRI (ET-DRI) and the Model for Early Allograft Function Scoring (MEAF). Two prediction models were calculated on the re-LT group: the survival model for liver retransplantation (SMLR) and the liver retransplantation risk score (LRRS).

Results. At 1, 3 month and 1, 5 years the graft survival in the study cohort was 95.4%, 93%, 82% and 70% respectively. Patients with a D-MELD >= 1600 or a MEAF >= 8 showed a graft survival significantly lower compared to low risk patients. 6 independent predictors of poor graft survival after LT were identified with multivariable logistic regression: PNF (HR, 44.7; 95% CI, 24.1, 83.0; p < 0,001). Clavien >= 3b (HR, 2.72; 95% CI, 2.00, 3.70; p < 0.001), EAD (HR, 1.38; 95% CI, 1.01, 1.90; p = 0.045), ITBL (HR, 3.17; 95% CI, 1.79, 5.63; p < 0.001), PVT (HR, 1.95; 95% CI, 1.13, 3.36; p = 0.016) and D-MELD >= 1600 (HR, 1.45; 95% CI, 1.05, 2.01; p = 0.025). Graft survival after re-LT at 1 and 3 months, 1 and 5 years was 92.1% and 87.3%, 49.2% and 44.2% respectively. Neither SMLR nor LRRS were able to discriminate with enough statistical significance patients at high risk of graft failure after re-LT. 5 independent predictors of poor graft survival after Re-LT were identified: PNF (HR, 7.74; 95% CI, 1.58, 37.8; p = 0.011), ITBL (HR, 226; 95% CI, 4.62, 11030; p = 0.006), pRBC transfused (HR, 1.10; 95% CI, 1.01, 1.19; p = 0.028), Clavien >= 3b (HR, 5.12; 95% CI, 1.12, 23.5; p = 0.036), and LRRS (HR, 2.08; 95% CI, 1.08, 4.01; p = 0.029).

Conclusions. Re-LT can be offered to recipients who experience graft failure after LT with optimal results. Graft survival risk scores are useful to identify recipients with high risk of graft failure, aiming for the optimization of graft-recipient matching and guiding clinicians in the allocation of scarce graft resources.

1. INTRODUCTION

1.1. Liver transplantation

1.1.1 History of Liver transplantation

Just a few short decades ago, there were no possibilities for patients dying of end-stage organ failure. One of the shining achievements of modern medicine is the development of clinical transplantation and transplant immunology.

The transplantation of organs became practicable only when the French surgeon Alexis Carrel developed his technique of vascular anastomosis in the late 19th century. However, the issue of organ rejection had to be solved.

Forty years later, Peter Medawar and Frank Macfarlane Burnet began to define the process by which one individual, the recipient, rejects a donor's tissue, by developing a general theory on the immunologic nature of *self* and the concept of immunologic tolerance. The results of their studies allowed Joseph Murray to perform the first renal transplant between identical twins in 1954. Afterwards, the discovery of immunosuppressive drugs led to the success in allograft survival that we enjoy today (1).

The first reported liver transplantation (LT) was in 1952, when Vittorio Staudacher from the University of Milan first described the technique of LT in four dogs. It was an orthotopic LT, where the donor allograft completely replaced the host liver. His work went basically unnoticed for almost six decades.

In 1955 Stuart Welch of Albany Medical College outlined the first heterotopic LT, while in 1956 Jack Cannon of University of California published an experimental description of orthotopic LT in animals. In the meantime, two centers, the Peter Bent Brigham Hospital in Boston and Northwestern University in Chicago, both independently started working at LT on experimental dogs. Most of the transplanted dogs survived only for a few days, mainly because of rejection.

The first human LT was attempted by Thomas Starzl at University of Colorado in 1963, in a 3-year-old boy with biliary atresia. The patient did not survive the surgery due to massive bleeding. Four more LT were performed by Starzl's group,

one in Boston and one in Paris, but they were all unsuccessful, mainly because of technical surgical problems, inadequate immunosuppression and graft preservation.

Thanks to the improvement in immunosuppression regimens and the techniques of graft procurement and preservation, the first successful human LT was performed by Starzl in 1967. The patient was a 18-month-old child diagnosed with hepatoblastoma who survived more than a year. The first LT in Europe was attempted in 1968 by Sir Roy Calne starting his LT program at the University of Cambridge.

It was only in 1979 that the revolutionary discovery of cyclosporine improved the outcomes and the 1-year survival rates passed the 50%. These results led to a consensus committee for LT at the National Institute of Health in 1983, which established the use of LT in clinical practice.

Over decades, major advancements in LT history were:

- the definition of brain death criteria in 1967;
- the development of preservation solutions;
- The piggyback operation that allows to preserve the recipient retrohepatic vena cava in 1968;
- The systematic use of pump-driven venovenous bypasses which greatly diminished intraoperative bleeding;
- the introduction of tacrolimus as immunosuppressant in 1993;
- the use of marginal donors, split liver procedures and living donor LT (LDLT) to face the problem of graft shortage (2).

1.1.2. Liver transplantation activities today

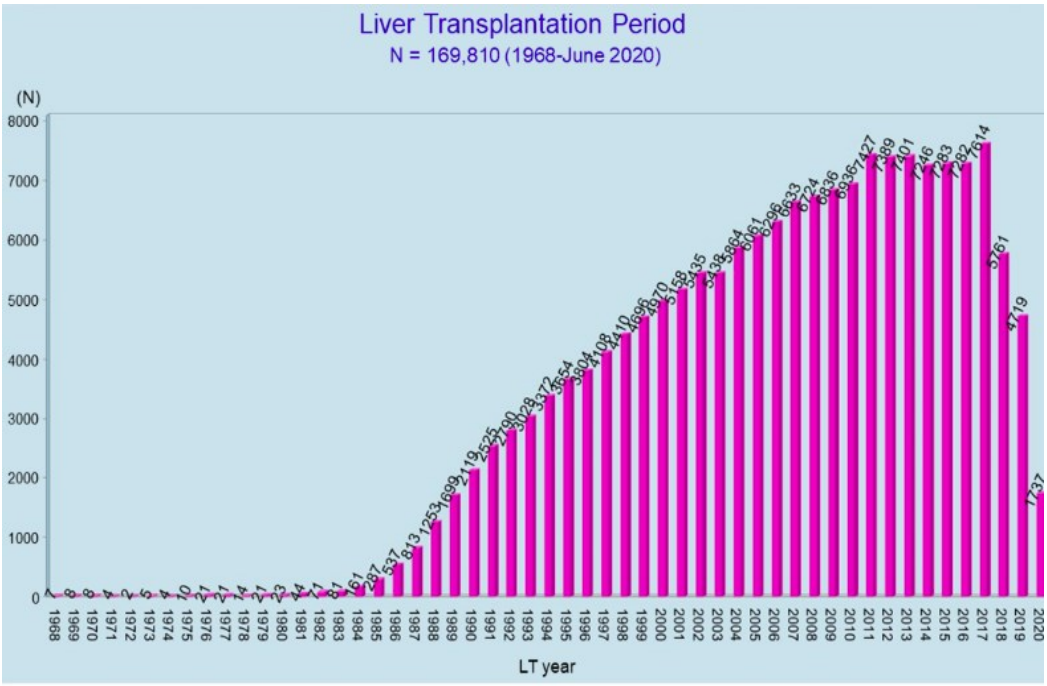


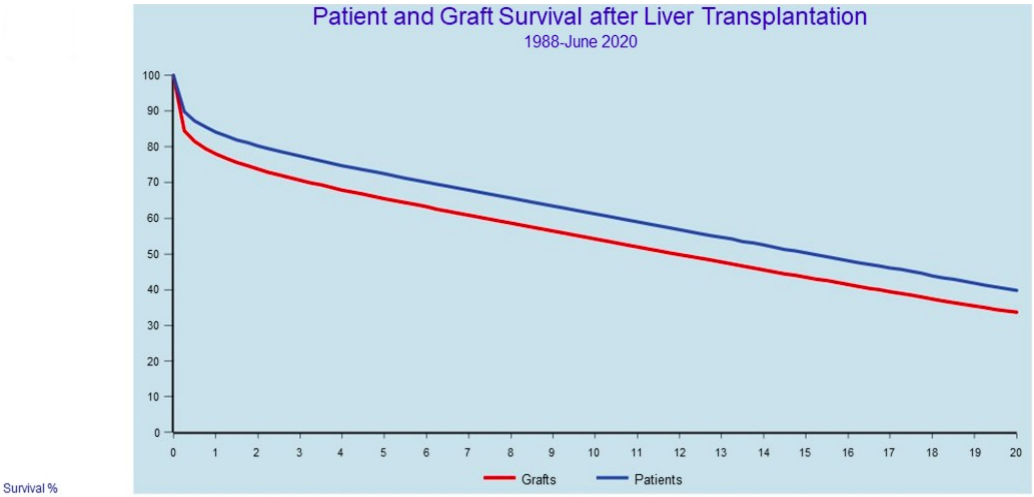
Figure 1. Evolution of LTs in Europe per year from 1968 to 2020, N=169,810 (1968-June2020). ELTR data.

Since 1967, LT has quickly become the standard therapy for acute and chronic liver failure of all aetiologies.

According to the European Liver Transplant Registry (ELTR), which collects prospectively the data of LT in 145 centers all over Europe since 1968, 169,819 procedures have been performed from May 1968 to June 2020 in Europe (Fig. 1).

ELTR data collected between 1988 and 2020 report patient overall survival (OS) rates of 84%, 71% and 61% at 1, 5 and 10 years after LT, respectively. Graft survival rates at 1, 5 and 10 years are 78%, 66% and 54% respectively (Fig. 2).

The first months after LT are the most critical for patient and graft survival, being the 59% of re-LT performed within 6 month and 44% within 1 months (namely early re-LT). After 6 months the prevalence of re-LT drops and so does the prevalence of death (Fig. 3).



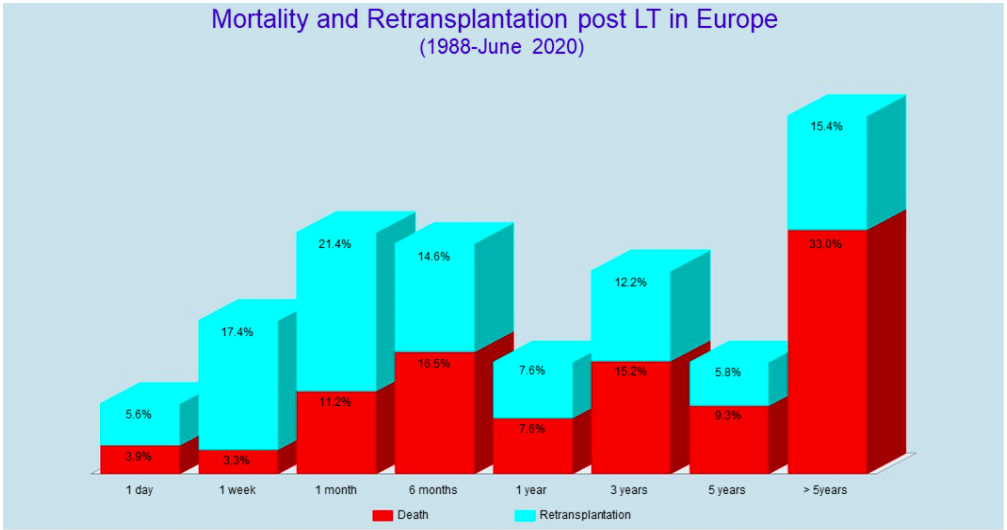
Population	1 yr	3 yrs	5 yrs	8 yrs	10 yrs	12 yrs	14 yrs	16 yrs	18 yrs	20 yrs
Grafts	78%	71%	66%	59%	54%	50%	46%	41%	37%	34%
Patients	84%	77%	72%	66%	61%	57%	52%	48%	44%	40%

Number of exposed patients

	Total	1 yr	3 yrs	5 yrs	8 yrs	10 yrs	12 yrs	14 yrs	16 yrs	18 yrs	20 yrs
Grafts	163722	110411	83328	65681	45487	34956	26485	19664	14110	9613	6316
Patients	147392	106953	81807	65102	45710	35465	27136	20321	14759	10197	6808

Figure 2. Patient and Graft survival rates after LT (1988-June2020). ELTR data.

The first months after LT are the most critical for patient and graft survival, being the 59% of re-LT performed within 6 month and 44% within 1 months (namely early re-LT). After 6 months the prevalence of re-LT drops and so does the prevalence of death (Fig. 3).



Cumulative proportions	1 day	1 week	1 month	6 months	1 year	3 years	5 years	>5 years
Death	4%	7%	18%	35%	42%	58%	67%	100%
Retransplantation	6%	23%	44%	59%	67%	79%	85%	100%

Figure 3. Mortality and Retransplantation after LT (1988-June 2020). ELTR data.

1.1.3. Indications and contraindications

LT represents a valuable therapeutic option for a wide range of pathologies that lead to acute or chronic terminal liver failure, as well as for genetic diseases characterized by an intrinsic deficit of hepatic metabolism or involving the liver. It is also considered a validated procedure for carefully selected patients with primary or secondary liver tumors who cannot undergo hepatic resection. Main diseases leading to LT in Europe are shown in Figure 4.

LT should be considered in any patient with end-stage liver disease, whose life expectancy would be increased beyond what the natural history of their underlying condition would predict or in whom LT is likely to improve the quality of life.

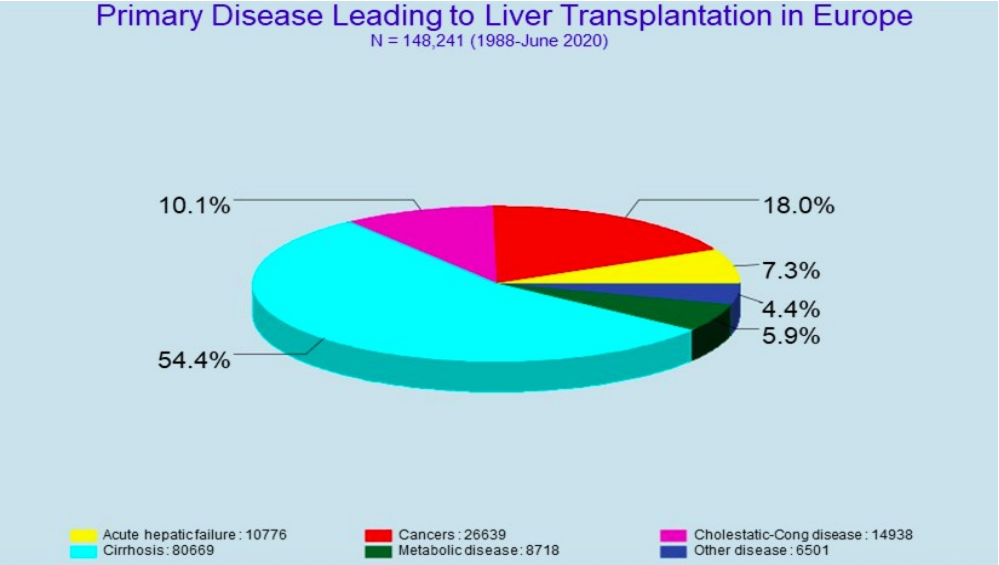


Figure 4. Indications to LT in Europe, N=148,241 (1988-June 2020). ELTR data.

A- Chronic viral hepatitis

Viral hepatitis (HBV, HCV and HBV + HDV) represents the most frequent indication for LT both in the acute-fulminant form and, mostly, in the chronic form. The main problem is the reinfection of the graft, as these viruses have extrahepatic replication sites, thus preventing the complete eradication of the virus with transplantation.

Regarding hepatitis B virus (HBV), as the use of the vaccine, which is effective in inducing the formation of antibodies, increases worldwide, it is possible that the

incidence of HBV infection decreases over time. A careful patient selection before transplantation is pivotal for the outcome of LT itself. The most important element to evaluate is the state of pre-transplant virus replication through the quantification of HBV-DNA, using highly sensitive tests such as PCR (polymerase chain reaction) and E antigen positivity (HBeAg) (3).

The absence of active replication of the pre-transplant virus significantly reduces the probability of viral recurrence. This goal can be achieved by undertaking, when possible, an adequate antiviral therapy of the duration of at least three to six months based on drugs such as lamivudine, adefovir or new agents such as entecavir, tenofovir which, by inhibiting viral replication, also improve liver function. The prophylaxis of post-transplant viral recurrence is based on the combination of anti-HBs immunoglobulins (HBIG) (4) and lamivudine, which drastically reduces the graft reinfection rate, the risk of developing resistance to both drugs and costs.

Hepatitis C virus (HCV) recurrence after transplantation is very common. A histological picture of acute hepatitis appears in 25-45% of patients starting from four to six months after transplantation, while a pattern of chronic hepatitis, with a very broad spectrum of severity, is evident starting from one year in 50-97% of patients, depending on the various case series. 8-44% of patients develop cirrhosis within 5-7 years of transplantation and 40% of these have hepatic decompensation within one year of the onset of the condition. Thus, the natural history of graft reinfection is significantly more aggressive than HCV infection in non-transplanted patients. Predictive factors of the aggressiveness of recurrent hepatitis C include donor age, treatment for acute rejection, and level of hepatitis C viremia at the time of transplantation (5). The introduction of direct-acting antiviral agents has changed the therapeutic landscape, reducing the need for transplantation in patients with hepatitis C, as well as the risk of retransplantation for recurrent infection.

B-Alcoholic liver disease

Alcoholic liver disease is one of the most common indications to LT in western countries. The pre-transplant evaluation of these patients focuses on social and psychological aspects, in order to ascertain total abstinence from alcohol for at least 6 months before inclusion on the waiting list, and the presence of family and social support before and after LT. It is also essential to identify the possible coexistence of additional alcohol-related diseases such as cardiomyopathy, chronic pancreatitis, peripheral polyneuropathy, cerebral atrophy that increase the perioperative risk or compromise the patient's quality of life post-transplant.

C- Non-alcoholic steatohepatitis

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are becoming increasingly prevalent medical issues in the developed world as they are part of the metabolic or insulin resistance syndrome. These patients may have histological necrotic-inflammatory alterations and fibrosis that may lead to end-stage liver disease and need for LT. The existence of comorbid conditions associated with metabolic syndrome, which may raise the risk of complications after surgery, is one particular aspect that needs to be carefully assessed. It's possible that many NASH patients who may benefit from LT are excluded because of concomitant diseases associated with the metabolic syndrome. Morbid obesity in particular may be a barrier to transplantation since it increases infections and the length of stay at the hospital and intensive care unit.

D- Cholestatic cirrhosis

Primary biliary cholangitis (PBC). In this chronic cholestatic liver disease, prognostic indices have been developed to establish the right timing for transplantation. In addition, other factors such as unbearable itching and resistance to medical therapy, osteoporosis with pathological fractures, severe and worsening asthenia and recurrent cholangitis are also correct indications for LT. PBC can relapse after transplantation even if the differential diagnosis is often complex, particularly with chronic rejection; the recurrence rate varies from 10 to 25% of patients 5 years after transplantation and reaches 30% at 10 years.

However, severe recurrent PBC liver disease is extremely rare and therefore generally not a clinical problem. The serum positivity of AMAs (anti-mitochondrial antibodies) (6) seems to have no role in the recurrence, while a risk factor is represented by tapering up to discontinuation of steroid therapy.

Primary sclerosing cholangitis (PSC). The indications for LT and the prognostic indices used in PSC are very similar to those of PBC. This liver disease, however, has a more rapid clinical course, it is more frequent in man, particularly at a young age, it is often associated with chronic inflammatory bowel diseases (especially ulcerative rectum-colitis, found in 70% of cases) and represents the main risk factor for cholangiocarcinoma, observed in 10-20% of cases. While the simultaneous presence of ulcerative colitis does not represent a contraindication to LT, since only an adequate colonoscopic follow-up is required for the early diagnosis of colorectal adenocarcinoma, the presence of cholangiocarcinoma represents a contraindication for the high rate of recurrence. Furthermore, the current screening methods of cholangiocarcinoma such as tumor markers (CA 19.9 and CEA), ERCP with biliary tract brushing and MRI cholangiography, although widely practiced, fail to reach a preoperative diagnosis in a substantial percentage of patients. The recurrence of PSC appears approximately 25 months after the transplant. The diagnosis requires the use of cholangiography (evidence of stenosis of the biliary tract intra and / or extrahepatic) and/or biopsy (histological picture of fibro-obliterative lesions of the bile ducts with possible ductopenia). It must be differentiated from chronic rejection or chronic ischemic damage of the biliary tree due to thrombosis or stenosis of the hepatic artery. The recurrence of sclerosing cholangitis, however, does not change the 5-year survival after LT.

<u>E-Autoimmune hepatitis</u>

This liver disease accounts for 2.6% of LT in Europe and 5.9% in the United States. Compared to other indications for LT, it is necessary to maintain a more aggressive immunosuppressive therapy, generally based on the combination of corticosteroids, calcineurin inhibitors (tacrolimus or cyclosporine) and m-TOR inhibitors or mycophenolate-mofetil, because of the highest incidence of acute

and chronic rejection and the recurrence of the disease. Acute cellular rejection can occur even up to 80% of patients and it is frequently steroid-resistant, making it necessary to use second-line therapy.

The recurrence of autoimmune hepatitis affects 12-36% of transplanted patients, it generally occurs at least 12 months after surgery and it is often related to suboptimal immunosuppressive therapy. Diagnosis is based on clinical, laboratory (AST, ALT, circulating autoantibodies), and histological parameters (portal and/or lobular hepatitis with lymphoplasmacytic infiltrates).

In the majority of patients, the clinical course of recurrence is mild to moderate and it solves with adequate therapy adjustments. The only known risk factor is the positivity of some histocompatibility antigens in the recipient (HLA DR3-DR4).

F-Genetic diseases

The genetic defect can involve a function or synthesis deficit of a hepatic protein, which may lead to acute liver disease up to the fulminant or chronic form up to a picture of cirrhosis and possible repercussions also on other organs or systems. This is the case of Wilson's disease (autosomal recessive defect of copper excretion with accumulation in the liver, brain, kidney and bone) in which the indications for LT are represented by the fulminant form or by progressive liver and/or neurological damage in the absence of response to medical therapy. Another example is alpha1-antitrypsin deficiency, an autosomal recessive inherited defect characterized by low circulating levels of the protease inhibitor with consequent development of pulmonary emphysema at young age, and protein accumulation in hepatocytes with the development of chronic liver disease. In both of the aforementioned diseases, LT allows the genetic defect to be completely resolved.

In other cases, the genetic defect is present in extra-hepatic sites but causes concomitant liver disease. Examples are hemochromatosis (autosomal recessive disease characterized by hyperaccumulation of iron in the liver, heart, pancreas, skin and adenohypophysis, secondary to an increased absorption of iron from the small intestine) in which transplantation is indicated when refractory to medical therapy, usually in case of late diagnosis, and erythropoietic protoporphyria in

which the enzyme defect is located in bone marrow resulting in accumulation of protoporphyrin IX in the liver, peripheral nervous system and skin leading to cirrhosis, neuropathy and photosensitivity respectively. In these two diseases, LT does not eliminate the metabolic defect and does not represent the ultimate healing. Finally, the genetic defect can reside in the liver, but the damage involves other organs as in hereditary amyloidosis (congenital disease leading to cardiomyopathy, renal failure, neuropathy and gastrointestinal symptoms secondary to amyloid substance deposition) in which the transplantation leads to regression of organ damage in many patients, except for heart disease.

G-Hepatocellular carcinoma

80-90% of patients with hepatocellular carcinoma (HCC) have concomitant and underlying liver cirrhosis. Liver resection and LT can be two therapeutic options. Transplantation has numerous advantages over resection, as the latter cannot always be practiced due to the risk of development of irreversible post-operative hepatic insufficiency in cirrhotic livers, while transplantation allows to remove at the same time the neoplasm and the underlying chronic liver disease, also considering the frequent multifocality of HCC. In recent years, therapeutic advances and better selection of cancer patients (7) have significantly improved the outcome of LT in the presence of HCC, leading to a 5-year survival of around 60%. As regards the selection of patients, currently the most used criteria are those of Mazzaferro (8), according to which a patient is eligible for transplantation if they have a single lesion with a diameter of less than 5 cm or, in case of multifocality, 3 nodules maximum, with a diameter not exceeding 3 cm. Despite this, the recurrence of HCC, primarily in the graft and then in other sites such as the lung or bone marrow, can affect a fair percentage of patients up to 15-20%. The neoplastic recurrence is due to the presence of micrometastases in the loco-regional lymph nodes or in extrahepatic sites that escape current diagnostic techniques or that are not identified at the operating table. In this case, it is necessary to undertake aggressive chemotherapy. Furthermore, the immunosuppressive therapy itself accelerates the growth rate of micrometastases.

H-Acute liver failure

Acute liver failure (ALF) represents an urgent indication to LT. Viruses (especially hepatitis viruses A and B), drugs and toxic agents are the most common causes of acute liver failure, with the proportions varying between countries. Seronegative hepatitis is also an important cause of LT for acute liver failure. LT has revolutionized the prognosis of acute liver failure, causing survival to increase from 10–20% to 75–80% at 1 year and 70% at 5 years (9).

Patients with liver disease undergo extensive evaluation to establish their eligibility for transplantation. Cardiac, pulmonary, and renal functions are examined. A social worker or other mental health specialist may also visit the patients for a psychosocial assessment. The risk-benefit ratio of undergoing transplantation is assessed individually for each patient.

There are absolute and relative contraindications (9) to transplantation (Tab. I).

Table I. Absolute and relative contraindications to LT (9)

Absolute contraindications	**Relative contraindications**
Uncontrolled medical condition (cardiopulmonary, neurologic etc.)	Psychosocial conditions
Extrahepatic malignancies (without disease-free survival of 2-5 years)	Sever hepatopulmonary or hepatorenal syndrome
Sepsis or uncontrolled infection	Severe obesity
Active alcohol or drug abuse	Severe malnutrition
Lack of social support	

Generally, contraindications are conditions that either make the risk of surgery prohibitive or anticipate that long-term survival or quality of life after transplantation are low. End-stage liver disease alone is an operative risk factor, so it is important to select patients who do not have too much additional comorbidity that would increase mortality and operative risk. Life-limiting medical conditions, such as severe cardiopulmonary or neurologic disease, are absolute contraindications. In patients with prior extrahepatic malignancies, a disease-free survival of 2-5 years is required before transplantation. Once patients are placed on immunosuppression after transplantation, they are at higher risk for

de novo malignancies and may be at increased risk for recurrent malignancy. Sepsis or active, uncontrolled infection is another contraindication. Inadequate psychosocial support systems suggest poor prognosis post transplantation: patients must have a care partner outside the medical team. Since many patients with liver disease have a history of significant substance abuse, strict abstinence for a minimum of 6 months from addictive drugs and alcohol is required.

Relative contraindications hinder optimal allograft and patient outcome, they can vary widely between different transplant centers and are sometimes modifiable before transplantation (10).

Relative contraindications may be psychosocial conditions resulting in poor compliance, advanced age (in general over 70 years), and severe hepatopulmonary or hepatorenal syndrome that may not be cured or improved after LT, as well as severe obesity or severe malnutrition. Here, the indication must be assessed individually for each patient (11).

Patients diagnosed with HCC exceeding the Milan criteria (8) can still be candidates for LT. Over the last decades, many extended criteria for LT on HCC patients have been adopted, mostly based on tumor volume and alpha-fetoprotein. Moreover, it has been demonstrated that HCC patients initially outside criteria can be successfully transplanted after downstaging treatments (9,11,12).

1.1.4. Organ donation and allocation

Donation after brain death (DBD) is the most common type of deceased donation, while donation after circulatory death (DCD) is increasingly used as an additional source of organs for transplantation (9). Living-donor LT (LDLT) is a well-established procedure that is becoming more common globally. The benefits of LDLT include the use of an excellent healthy donor, little ischemia time, elective operation, and timing of the transplant based on the recipient's need and medical stability rather than the availability of deceased organs. However, LDLT is more difficult to perform than whole-organ transplantation, and living donation carries some risk for healthy donors. The recipient's risk must be higher or equal to the donor's risk.

The administration of waiting lists falls under national jurisdiction. It defines the criteria used to add patients to waiting lists and remove them from these lists.
In the United States, the organization which administers the Organ Procurement and Transplantation Network (OPTN) is United Network for Organ Sharing (UNOS), whereas organ allocation policies are not uniform across Europe: for different nations and geographical areas, there are several organ exchange organizations and organ allocation can be either patient-directed or center-directed.
Today, an extension of indications has been perceived, whereas the number of available cadaveric donor livers remains low. Actually, limited organ supply and an increasing demand for organ transplantation has increased transplant waiting times. As a result, the quantity of patients dying while on the liver waiting list has been rising recently. Since optimal patient selection and timing are crucial to obtain a successful outcome, which patients to list for LT and when to transplant patients on the waiting list has generated significant concern. Patients with end-stage liver disease need to be transplanted before they undergo life-threatening systemic complications. They should not be transplanted too soon since the risks of the procedure and lifelong immunosuppression might outweigh the benefits of transplant.
In the past, livers were allocated to potential liver recipients based on the Child-Turcotte-Pugh (CTP) score, ABO blood type compatibility, and overall waiting time. Categories for liver allocation included the following: status 1, patients with acute fulminant hepatic failure or patients with primary graft dysfunction or hepatic artery thrombosis occurring within the first week posttransplantation, or pediatric patients who de-compensate and require continuous care in the intensive care unit. Status 1 patients received priority for liver allocation over all patients with chronic liver disease. Patients with chronic liver disease were classified and ranked as status 2A, 2B, or 3 according to CTP score, ICU care, estimated survival, complications of portal hypertension and presence of HCC. The “tiebreaker” within each of these broad disease severity categories was waiting time (UNOS criteria for patients with chronic liver disease) (13).

By default, waiting time was the primary determinant in liver allocation. Recent research, however, has shown that longer waiting periods are not linked to a higher chance of dying while on the waiting list (14). With experience, it became clear that the previous allocation mechanism, which included waiting time and the CTP score, had additional limitations. The CTP score's most significant issue is that it bases its computation on two very subjective criteria, portosystemic encephalopathy and ascites severity.

Since 2002, the Model for End-Stage Liver Disease (MELD) score has been used to establish patient priority on the waiting list. MELD was first created to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts (TIPS) (15). The model's validity was subsequently tested in 4 independent data sets, including patients hospitalized for hepatic decompensation, ambulatory patients with non cholestatic cirrhosis, patients with primary biliary cirrhosis and unselected patients from the 1980s with cirrhosis. The MELD scale proved to be a reliable measure of mortality risk in patients with end-stage liver disease and suitable for use as a disease severity index to determine organ allocation priorities (16). MELD score is based on serum bilirubin, creatinine levels and International Normalized Ratio (INR) for prothrombin time. It is a slight modification of the risk score used in the original TIPS model. The original mathematical formula for MELD is: $9.57 \times \log_e(\text{creatinine}) + 3.78 \times \log_e(\text{total bilirubin}) + 11.2 \times \text{Log}(\text{INR}) + 6.43$.

The MELD score is based entirely on variables that are objective and inherently defined by patient condition. Because of this, the MELD based liver allocation system allows for much more precise and objective measurement of results of liver allocation and transplantation and enables comparison of allocation systems across regions and countries (17). Implementation of MELD led to an immediate reduction in liver transplant waiting list registrations for the first time in history of LT. In contrast to the clear benefit of accurately estimating mortality on the waiting list, MELD has not been found to be as useful in predicting mortality following LT. Mortality in the post transplantation period is related not only to the degree of liver dysfunction prior to transplantation, but to other factors, such as donor characteristics, experience of the transplantation team, and postoperative

complications (18). Patients with end-stage liver disease should be listed if their MELD score is less than 15. However, with the exception of patients with extremely high MELD scores over 35, it does not give a prediction of mortality after LT (19). There are exceptional conditions where MELD alone may be inadequate for prioritization for LT, including ascites, hepatic encephalopathy, polycystic liver disease, cholangiocarcinoma, hepatopulmonary syndrome etc. In these cases, extra points could be given to patients in order to give them priority to transplantation (20).

1.1.5. Extended Criteria Donors

The scarcity of suitable donor livers is the most critical problem of LT today. LDLT and split LT have been used to face the donor shortage, but they have ethical and technical issues that make them less than optimal ways to expand the donor pool. Another way to increase the pool of potential donors is to liberalize the standard acceptance criteria. Extended criteria donors (ECD) are allografts that do not meet traditional criteria for transplantation. The concern over the increased risk of primary nonfunction (PNF) or early poor function, possibly leading to graft failure and need of re-LT, limits the use of extended criteria liver donors.

Ischemia-reperfusion injury (IRI) is the primary causative mechanism of graft dysfunction that is seen in the marginal organ. On restoring the blood supply, the liver is subjected to insult, aggravating injury already caused by the initial ischemia. IRI to endothelial cells disrupts the sinusoidal microcirculation by up-regulating the attraction, activation, adhesion, and migration of neutrophils causing local tissue destruction by release of proteases and oxygen-free radicals. IRI in LT leads to PNF and increased rejection and contributes to high morbidity (21).

There is not a uniform definition of ECD livers. ECD grafts generally fall into two main risk categories: poor graft function and potential for disease transmission.

Donor characteristics demonstrated to yield an increased risk of delayed graft function or primary nonfunction include age older than 60 years, hypernatremia exceeding 155 mEq/L, macrovesicular steatosis exceeding 40%, cold ischemia

time exceeding 12 hours and donors after cardiac deaths (DCD). The Eurotransplant definition of ECD also includes elevated transaminases (ALT >105 U/L, AST >90 U/L), serum bilirubin >3 mg/dl, ICU stay with ventilation >7 days, BMI>30.

Donor age 65 years and older represents the largest expanding component of the current donor pool. The allograft performance is acceptable for donors in their seventh, eighth, and ninth decades, with a typical incidence of PNF of less than 10%. Hypernatremia is a frequent clinical finding within the donor population and impairs allograft function through a process whereby hepatocytes increase their intracellular osmolality to minimize cellular damage associated with the extracellular hypertonic state. During normalization of hypernatremia, intracellular water may rapidly accumulate, resulting in cell swelling and injury (22).

Of ECD classified livers, hepatic steatosis is a frequent finding and continues to rise with non-alcoholic fatty liver disease (NAFLD) having a prevalence of 30-40% in the US and European population. Clinical experience suggests significant risk for early graft dysfunction and poor outcome at >30% macrovesicular steatosis, though reports vary considerably. Given that hepatic IRI is a major cause for initial graft dysfunction, hepatic steatosis may well aggravate it. Kulik et al. reported that fatty liver allografts are a major cause for PNF with excessive mortality in case of retransplantation (23).

The use of livers obtained from DCD donors in the early 1990s was a pioneering effort to reduce the gap between available organs recipients in need for transplant. The early experience with DCD livers was not good because of the high risk of allograft failure secondary to the prolonged donor warm ischemia period and IRI. However, as expertise has grown, aspects linked to better outcomes have been determined, and more centers have started using these donors (24).

In 2018, a DCD graft was used in 38% and 9% of all deceased donor LT in the Netherlands and United States of America, respectively. In the United Kingdom, 26% of deceased donor LT were performed with DCD grafts. LT with DCD grafts (DCD-LT) is considered to be inferior compared to LT with grafts donated after brain death (DBD-LT), due to the increased risk of complications such as early

allograft dysfunction (EAD) and biliary complications. Among biliary complications, non anastomotic strictures (NAS) are the most feared as they often require multiple interventions for biliary drainage, are largely irreversible and are known to have a negative impact on recipient and graft survival. The incidence of NAS, also known as ischemic cholangiopathy or ischemic-type biliary lesions (ITBL), after DCD-LT varies between 3% and 39% (25).

The reported incidence of PNF was 15.5% after the introduction of DCD organ donation. Increased knowledge about the pathophysiology of DCD donation and transplantation, especially the introduction of machine perfusion, have contributed to better outcomes, and at present the incidence of PNF in DCD grafts matches those in DBD grafts (2.1%) (26).

The most recent decade has seen the introduction of preservation techniques such as hypothermic oxygenated perfusion (HOPE), subnormothermic machine perfusion and normothermic machine perfusion (NMP). Rather than relying on donor aspects alone, machine perfusion allows for graft reconditioning and functional assessment before LT. The physiological conditions provided by ex vivo NMP allow graft viability assessment through measurement of lactate clearance, flow rates, bile production, and biliary biochemistry. Despite the nonphysiologic conditions of subnormothermic machine perfusion and HOPE, previous authors have reported viability testing to be possible through measurement of perfusate alanine aminotransferase, aspartate transaminase (AST), and lactate dehydrogenase levels. Viability testing has become an integral part of machine perfusion technology and has the potential to reduce the risk of PNF while providing more confidence to use marginal grafts (26).

Marginal grafts with an increased risk of disease transmission include those with serologic positivity (HCV, hepatitis B virus, human T cell lymphotropic virus (HTLV-I/II) or carcinoma outside the liver. The utilization of HCV+ allografts for HCV- recipients or HCV+ recipients with an undetectable viral load should be reserved for extreme necessity. In contrast, utilization of HCV+ allografts among HCV+ recipients who are active viral replicators of genotype 1 or 4 should be encouraged (22).

A study that compared the graft and patient survival between standard donors and ECD concluded that liver grafts from ECD can be used to drastically reduce wait list time with outcomes comparable to those for standard donors. Of the multiple ECD criteria examined, only donor age >60 years and cold ischemia time >12 hours resulted in reduced graft and patient survival (27).

1.1.6. Technical aspects of LT

The most frequently performed type of LT in Europe and USA, the so-called "conventional" or "standard" LT, employs the whole liver graft. However, in Asian nations, where deceased donation is rare, the use of partial grafts from living donors is more common, with quite satisfactory outcomes even compared to Western cadaveric transplantation (28).

The "Standard" LT requires the explanation of the diseased liver and the implantation on the graft in the right upper quadrant, in the place formerly occupied by the recipient liver. The surgical technique varies depending on or whether or not the recipient's inferior vena cava (IVC) is preserved. The surgical procedure involving the preservation of the native IVC is called *piggy-back* technique, which is used in most European countries. The preservation of the IVC of the recipient allows for hemodynamic stability and decrease in blood component requirements during the surgical procedure, thus it significantly reduces the magnitude of LT (29). Furthermore, the piggy-back technique does not require dissection of the retrocaval compartment, thus reducing retroperitoneal bleeding. This technique also makes it easy to solve problems posed by size mismatch between recipient and donor IVC (30).

When the recipient's IVC cannot be preserved, end-to-end anastomoses between the donor's IVC and the recipient's supra- and infrahepatic IVC is made (so-called *classic* technique).

The hepatectomy implies the interruption of caval flow during the anhepatic phase, which results in a reduction in venous return to the heart and a decrease in renal perfusion, as well as splanchnic hyperemia secondary to portal clamping. Venovenous bypass improves hemodynamic stability and allows decompression of the occluded splanchnic venous system. However, the use of venovenous

bypass is associated with other complications, such as hypothermia and pulmonary thromboembolism. Adding a temporary portocaval shunt to the piggy-back technique can minimize hemodynamic instability, avoid retroperitoneal bleeding (and intraoperative transfusion requirements) secondary to portal hypertension and preserve renal function during the anhepatic stage. Clinical benefits of this technique, however, are more evident in patients with a baseline portal flow of 1,000 mL/min or greater and those with severe portal hypertension and a portocaval gradient of 16 mmHg or greater (30).

Right after IVC anastomosis, end-to-end portal vein anastomosis is performed. The graft is flushed and then reperfused by portal blood. LT is then completed with end-to-end hepatic artery and bile duct anastomosis.

Because donor liver shortage is the limiting step in the expansion of LT, several innovative techniques have been developed to enlarge the pool of organs. Recently advanced procedures have focused on using a part of the liver graft for transplantation, especially for pediatric LT. In fact, the number of whole-organ cadaveric grafts size-matched for the pediatric population has always been inadequate. With the split LT, the whole adult cadaveric liver is divided into two functioning allografts, increasing the total number of available grafts (31). The left part (segment II and III without caval vein) can be transplanted into a child, the right part (segment I, IV, V to VIII) into an adult successfully (Fig. 5).

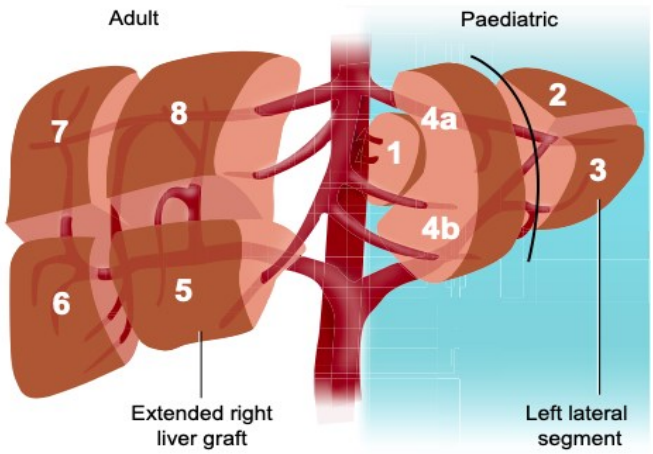


Figure 5. Split liver transplantation with adult and child as recipients (9)

Common bile duct and common hepatic artery remain with the left part of the liver, portal vein with the right one. In the recipient of the left part of the liver the own caval vein is preserved and anastomosed with the left hepatic vein. In the recipient of the right part of the liver the right hepatic artery of the graft is anastomosed with the recipient's common hepatic artery. Two separate intrahepatic bile ducts are anastomosed with a Roux-en-Y loop of the jejunum (32).

Splitting the liver into full right (segments V to VIII) and full left (segment I to IV) lobes offers an additional opportunity of LT for two adult patients. The limits of this type of LT are that splitting the liver into full right and full left lobes is technically demanding, and normally the left lobe has a weight of about 450 g, which only allows it to be implanted in low weight patients (33).

Living donor LT (LDLT) has also been accepted as an established treatment modality of end-stage liver diseases to alleviate the shortage of cadaveric donor organs. There have been noticeable improvements in recipient outcomes, but apprehension remains regarding the safety of living donors (34).

Left lateral lobe of a living donor graft is transplanted into pediatric patients. In adults, living donation generally uses the donor’s right liver lobe, which comprises segments V to VIII. Right hepatectomy requires meticulous dissection on which the right hepatic artery, right portal vein, right bile duct and right suprahepatic vein are isolated. Aside from the technical difficulties in the donor hepatectomy, there is a significant morbidity that affects 38% of donors and a mortality rate estimated to be around 0.18%. Furthermore, the recipient procedure is also challenging, due to the size of the anastomoses, especially of the artery and bile duct. Nevertheless, outcomes are good and at present they are similar to those obtained with whole grafts from deceased donors. Donor hepatectomy entails morbidity and mortality risks. Approximately one third of the patients experience some kind of complication (9).

1.1.7. Complications of LT

The morbidity and mortality associated with LT continues to decrease thanks to refinements in surgical technique, immunosuppression, and early diagnosis. Post-operative complications that lead to graft failure and patient morbidity/mortality can be generally classified as vascular, biliary, parenchymal, and malignant.
Vascular complications include:

- hepatic artery thrombosis (HAT) or stenosis, portal vein thrombosis (PVT), hepatic vein thrombosis (HVT);
- hepatic artery pseudoaneurysm;
- arteriovenous fistula;
- celiac stenosis.

Biliary complications include:

- anastomotic biliary strictures and stenosis;
- Ischemic-type biliary lesions (ITBL);
- bile leak;
- cholestatic disease recurrence;
- infections (35).

1.2. Retransplantation of the liver

1.2.1. Definition and indications for liver retransplantation

When irreversible graft failure occurs, liver retransplantation (re-LT) is the only therapeutic option.
LT leads to graft loss and re-LT in 5-22% of all recipients (36). In many cases, patient survival may be assured by offering a retransplantation. However, re-LT increases the need for donor organs and may only be allowed if the outcome legitimizes repetitive placement on the wait-list of patients in need for a new liver graft. As the demand for re-LT may increase due partly to the utilization of ECD, we may expect a further shortage of liver grafts. Therefore, using graft for re-LT can only be justified if the outcome is successful and may compete with primary LT. The use of ECD has been instrumental in expanding the available donor pool.

In the European countries, DCD is developed to overcome the organ shortage, and the number of DCD donations has been increasing. However, DCD grafts are reported to have higher incidences of PNF and ITBL with subsequent poor graft survival (37).

There is also the ethical question remaining about whether it is justifiable to use multiple grafts for the treatment of a single patient. From a socio-economic point of view, the question arises whether these scarce organs were used optimally. One might argue that a substantial number of these grafts could have been donated to patients in need of a first graft (38). Also the costs involved in re-LT are higher compared to primary LT (39).

67% of re-LT occur within the first year after LT, and 44% within the first month after primary LT (Fig. 3). Nonetheless, during the last decades re-LT have dropped (Fig. 6) (40).

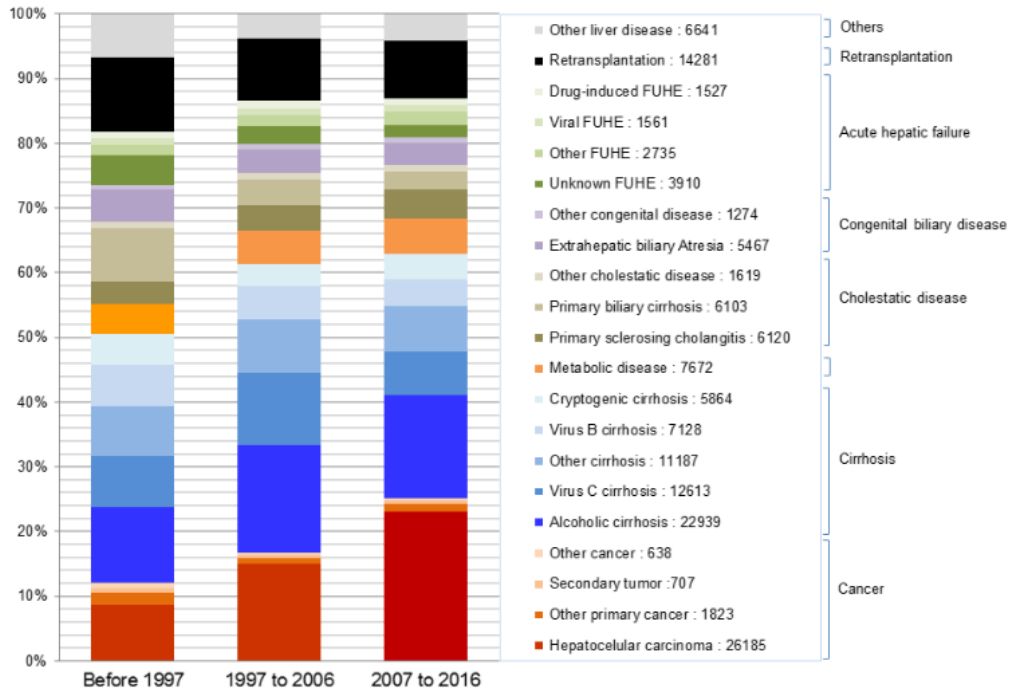


Figure 6. Evolution of indications to LT according to three eras (40)

Re-LT can be defined as *early* if it takes place during the first month after the first LT, and *late* if it is performed afterwards.

Early re-LT can be classified as *urgent* when it takes place in the first week or *elective* when it is performed between 7 and 30 postoperative days (POD). Early

re-LT is technically easier because the recipient hepatectomy does not require dissection. The principal concerns for determining the utility or futility of re-LT in the early post-transplant are the consequence of the graft failure such as brain herniation, refractory sepsis, or severe hemodynamic impairment. As little data exist to guide decisions for re-LT in such settings, the experience and judgment of the surgical team is of paramount importance.

In the late post-transplant period, re-LT is considered by most to be high-risk surgery and is therefore only practiced by experienced surgeons in specialized centers. Late re-LT poses several challenges. First, due to the ever-present shortage of organs, patients must achieve a high degree of illness to be eligible for organ allocation. Concurrent medical comorbidities such as renal failure, coagulopathy, recurrent infection, and the chronic use of immunosuppression contribute to the medical complexity of these patients. Second, in the later post-transplant period, anatomy is often distorted and surgical dissection is made difficult by dense, vascular adhesions (41).

Annual report of the ELTR in 2018 (40) showed that early re-LT is mainly indicated for primary non-function (PNF) and technical complications (biliary or vascular). Whereas, rejection and disease recurrence are the most frequent indications for late re-LT (Fig. 7).

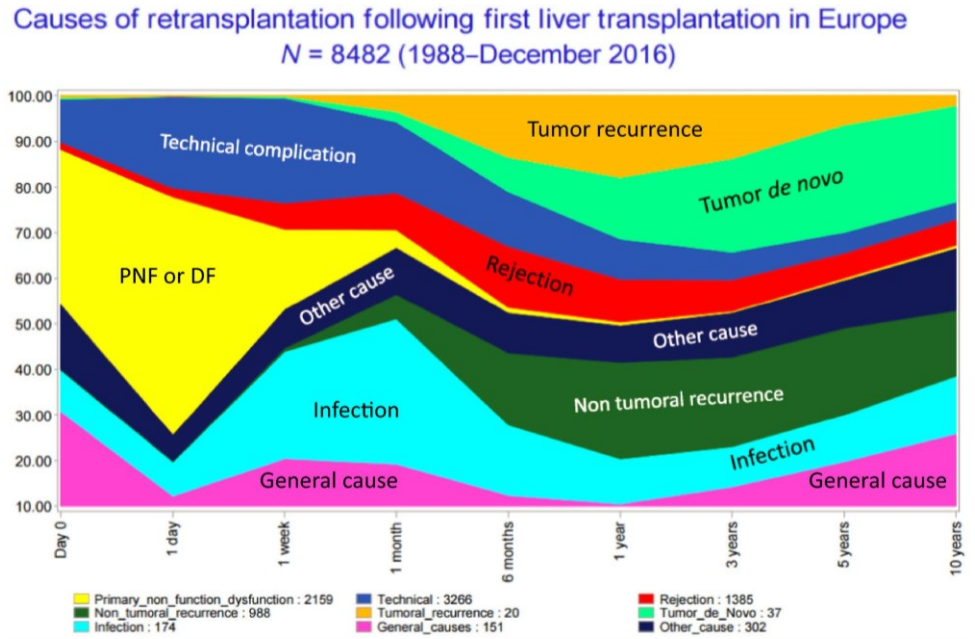


Figure 7. Causes of retransplantation following first liver transplantation in Europe, N = 8482 (1988-December 2016) (40).

PNF is the most common indication for re-LT (42,43), and the impact on patient and healthcare teams, as well as the burden on the organ pool in case of the need for re-LT, should not be underestimated. Liver allograft dysfunction can be primary or secondary. Early allograft dysfunction (EAD) is a reversible condition of poor initial graft function and the patient needs intensive care support through the early postoperative period. PNF could be described as the irreversible extreme of EAD when the extent of cellular injury is not compatible with graft survival. PNF can only lead to patients' death or re-LT. Primary allograft dysfunction occurs when the main abnormality involves altered metabolism at the cellular level due to the process of transplantation. The identification of graft dysfunction due to secondary causes is essential, as most common causes, such as sepsis or vascular complications, are amenable to intervention that may rescue the graft (26).

Unfortunately, a universally accepted description of PNF is lacking. Initial definitions of PNF include a non-life-sustaining function of the liver after LT leading to death or re-LT within 7 days (44). Exclusion of other possible known causes leading to re-LT or death (45) and the absence of technical complications has been also used to define PNF. The associated clinical picture included coagulopathy, failure to wake up, renal dysfunction, failure of the liver to initiate or maintain bile production, lactic acidosis, and hemodynamic instability. Histopathologically, the grafts usually showed small infarcts and/or zonal hepatocellular coagulative necrosis (centrilobular or periportal) or severe cholestasis subsequently without evidence of rejection (46). The transplant authorities in the United Kingdom and United States described two different sets of diagnostic criteria for PNF that could guide listing for urgent re-LT. Listing criteria for urgent re-LT by NHS Blood and Transplant Liver Advisory Group (United Kingdom) for PNF require at least 2 of the following criteria in the first 7 postoperative days: AST >10 000 IU/l, International normalized ratio (INR) >3.0, Serum lactate >3 mmol/L, Absence of bile production. OPTN (United States) urgent re-listing criteria within 7 days posttransplant define PNF as the presence of AST ≥3000 and one or both of the following: INR ≥2.5; acidosis, defined as having an arterial pH ≤ 7.30 or venous pH of 7.25 and/or lactate ≥4 mmol/L (47).

Less-well-recognized as a form of PNF is initial poor function (IPF) of the liver, which is a borderline function of the liver requiring prolonged treatment in the intensive care unit associated with substantial morbidity. Although not as devastating as PNF, it is associated with significantly higher mortality, graft failure rate and re-LT rate than observed in patients with immediate liver function (44).

PNF raised as an indication for re-LT over the years, mainly because of increasing acceptance of older donors and more marginal donor organs. This aspect plays a decisive role for patients with acute liver failure who have a high incidence of PNF and who urgently require a graft (36). In the past, marginal grafts were used for high-risk recipients, and this approach was associated with poor graft and patient survival, particularly in the presence of multiorgan system failure. More recently, these grafts have been used in less sick recipients with satisfactory results, effectively expanding the donor pool, but representing a risk factor for PNF/IPF (48).

Technical complications are common indications for liver re-LT and mainly consist of vascular or biliary complications. Vascular complications include mainly HAT, PVT and HVT. Intractable biliary complications can also be an indication for re-LT and occasionally induce life-threatening sepsis (49).

Chronic rejection as a cause of graft failure has diminished through the years as a result of improved immunosuppression (48), but early acute allograft rejection remains an important issue. The rare cases of therapy resistance may be another cause of graft failure (50).

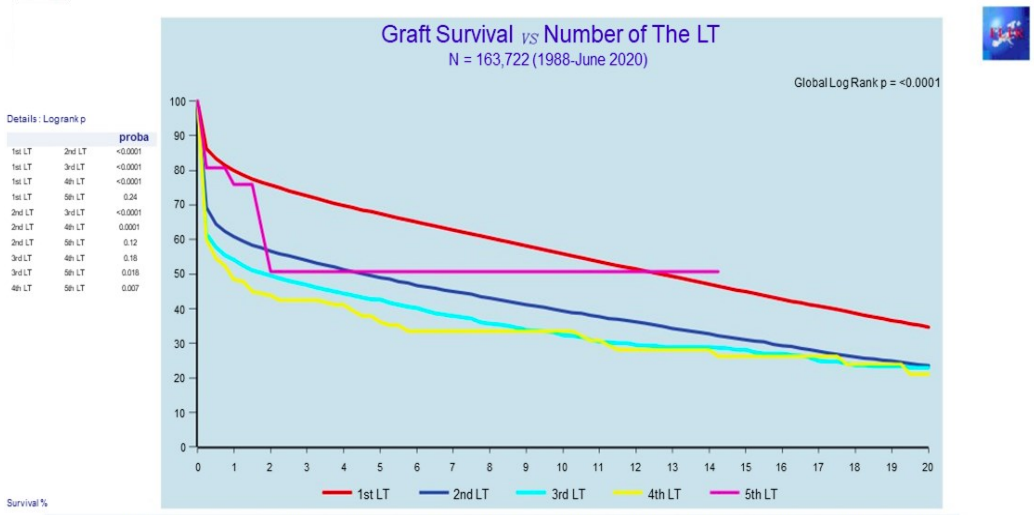
All liver diseases that necessitate LT can virtually recur (mostly HCV, autoimmune hepatitis [AIH] or cholestatic diseases). Although some interventions have been shown to alter the natural history of recurrent disease, most of these disease processes are not modified by currently available therapies (51).

Two different studies show the evolution of indications for re-LT in Italy: the main causes of graft failure between January 1987 and February 2003 were surgical complications, PNF, chronic rejection and HCV recurrence (52); between 1998 and 2010, major indications for re-LT were PNF and HAT (53). In

particular, PNF increased from 25% to 64%, whereas HCV recurrence declined from 14% to 4%.

1.2.2. Outcomes after liver retransplantation

Reported graft survival rates after re-LT are 61%, 49% and 39% at 1, 5 and 10 years respectively, significantly lower than survival rates reported after primary LT that are 80%, 67% and 56% at 1, 5 and 10 years respectively ($p < 0.001$) (40) (Fig. 8).



TH rank	1 yr	3 yrs	5 yrs	8 yrs	10 yrs	12 yrs	14 yrs	16 yrs	18 yrs	20 yrs
1st LT	80%	73%	67%	60%	56%	51%	47%	43%	39%	35%
2nd LT	61%	54%	49%	43%	39%	36%	33%	29%	26%	24%
3rd LT	54%	47%	43%	36%	32%	30%	29%	27%	24%	23%
4th LT	48%	43%	36%	33%	33%	28%	28%	26%	24%	21%
5th LT	76%	51%	51%	51%	51%	51%	51%			

Number of exposed patients

	Total	1 yr	3 yrs	5 yrs	8 yrs	10 yrs	12 yrs	14 yrs	16 yrs	18 yrs	20 yrs
1st LT	147626	101940	77018	60744	42139	32394	24560	18217	13082	8907	5830
2nd LT	14034	7538	5646	4413	2989	2285	1703	1270	889	610	415
3rd LT	1749	829	602	481	326	250	201	159	128	86	64
4th LT	268	93	60	41	32	26	20	17	11	10	7
5th LT	45	11	2	2	1	1	1	1	0	0	0

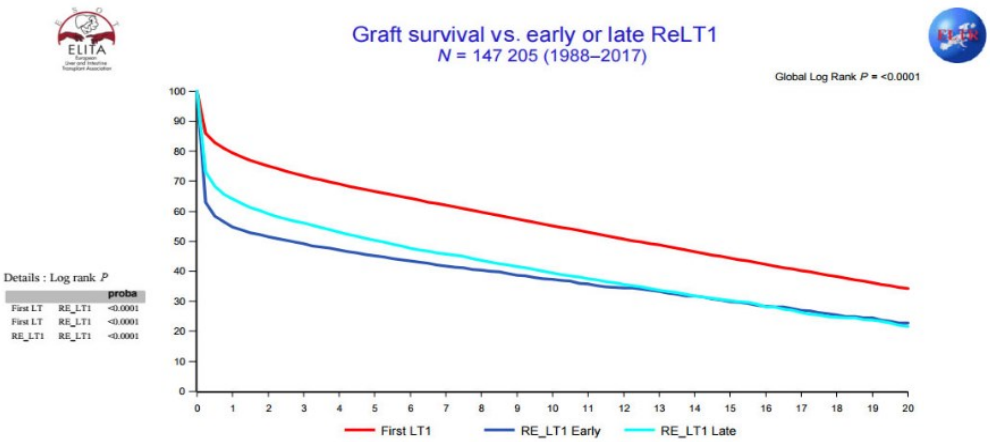
Figure 8. Graft survival according to number of the LT, N=163,722 (1988-June 2020). ELTR data.

Takagi et al. observed an overall patient survival rate of 70.8% at 5 years and 60.7% at 10 years after first re-LT, relatively better compared to previous reports (37). Their findings suggested that although these survival rates were lower than primary LT, re-LT is an effective strategy for patients with irreversible graft failure and offers good long-term outcome, which justifies the use of donor livers. Pérez-Saborido et al. concluded that re-LT is a good option for patients with

failure of the first graft, with 5-year patient and graft survival rates about 65% (54). Marudanayagam et al. found that the overall 1-, 5- and 10-year survival rates following first re-LT were 66%, 57% and 47%, respectively, confirming that re-LT is an effective treatment modality for patients with primary graft failure and offers good long-term survival (55).

Five-year graft survival rates following a second, a third and a fourth LT are 49%, 43% and 36% respectively (Fig. 8). As previously mentioned, during the last decade, the donor shortage has worsened. Therefore, it remains debatable whether the use of multiple grafts for individual recipients is justified. For the first re-LT, when performed after selecting patients with prognostic indicators for success, this question is not relevant anymore because of acceptable survival results. It has been demonstrated that even with repeated re-LTs, up to 3, an acceptable long-term patient survival can be obtained (38).

The MELD scale has been shown to be a good predictor of pre-transplant mortality, although it is a poor indicator of the outcome of the transplantation itself. Contrary to this, various studies found that the outcome of liver re-LT might be predicted by MELD score: a cut-off value of 25 (52) or 23 (53,55) is a predictor of survival following re-LT.



Survival %

Rang_TH	1 year	3 years	5 years	8 years	10 years	12 years	14 years	16 years	18 years	20 years
First LT1	79%	72%	67%	60%	55%	51%	47%	42%	38%	34%
RE_LT1 Early	55%	49%	45%	40%	37%	34%	32%	28%	25%	23%
RE_LT1 Late	64%	56%	50%	44%	39%	36%	32%	28%	25%	22%

Number of exposed patients

	Total	1 year	3 years	5 years	8 years	10 years	12 years	14 years	16 years	18 years	20 years
First LT1	134598	91280	67979	53467	36507	27557	20414	14645	10107	6596	4039
RE_LT1 Early	5579	2670	1998	1549	1044	779	563	410	285	187	131
RE_LT1 Late	7028	3928	2878	2199	1461	1083	778	539	355	239	149

Figure 9. Graft survival versus early or late ReLT, N = 147 205 (1988–2017) (40).

ELTR data show that late re-LT has a significantly better graft survival than early re-LT, as much as 50% vs. 45% at 5 years (Fig. 9) (40). Nonetheless, discordant results have been reported in literature so far (43,56–58). Markmann et al. found that patients retransplanted more than 30 days after LT showed better outcomes than those retransplanted between 8 and 30 days. The survival in patients retransplanted within 1 week was intermediate in the overall population (56). Bellido et al. observed significant differences between overall survivals among urgent versus elective retransplant patients (81% vs 51.1%) (57). The results of a previous study suggested greater mortality during the first month after both elective and urgent re-LT. However, it was demonstrated that urgent re-LT is very different thereafter: the mortality was significantly lower for those undergoing urgent procedures. In contrast with primary transplantation, where the overall survival in the group of urgent LT patients was poor, survival was high among those with urgent indications for re-LT (59). Azoulay et al. also found that the elective group of re-LT patients exhibited survival curves similar to the first LT group. Hence, re-LT was fully justifiable when performed electively. Conversely, they showed a different picture for emergency re-LT: the results were worse than those obtained for urgent single transplant patients. However, despite its inferior results, re-LT cannot be totally abandoned for ethical and practical reasons (39). Consistent with other studies, Sun et al. observed that all mortalities in their series occurred within 1 year from re-LT, reflecting the importance of extensive monitoring as well as aggressive treatment during the early postoperative period (60).

Many studies show that patient survival after re-LT strongly depends on the indication for re-LT. Yoo et al. found that graft survival of patients who underwent re-LT for PNF was significantly lower than that of patients who underwent re-LT for other reasons; those who underwent re-LT for PNF were 20% more likely to lose their graft at 1 year compared with those who underwent re-LT for other reasons. Renal failure was very common in patients who underwent re-LT for PNF, and this may explain in part the lower graft and patient survival (61). The decision to retransplant patients with recurrent HCV remains

questionable. Although some studies have shown poor outcome in HCV-infected transplant recipients after re-LT (36,61), other studies have shown similar results for patients with and without HCV infection (56). Improving antiviral therapy in the future would significantly influence the long-term course of HCV reinfection and re-cirrhosis (36).

Pfitzmann et al. observed that patients with ischemic-type biliary lesion (ITBL) and rejection have the best survival within the first months and during the long-term course. The successes in ITBL and rejection are due to improved preservation procedures, especially the arterial pressure perfusion, the progress and advanced experiences in endoscopic treatment, and improvement of immunosuppressive therapy. In most patients with ITBL or rejection, elective re-LT is possible, whereas in the case of PNF or HAT, re-LT depends on the prompt availability of donor organs due to severe clinical course (36).

Causes of death after re-LT can be infection (36,43), bleeding or recurrence of the disease (36). Markmann et al. indicated the possibility that heavy immunosuppression contributes to the reduced survival in retransplanted patients because of a higher incidence of death due to sepsis. Furthermore, death resulting from fungal infection was relatively common in retransplanted patients (56). Montenovo et al. confirmed that sepsis is associated with a significantly increased risk of death when developed after re-LT (62).

1.2.3. Early retransplantation

Early re-LT accounts for 35-44% of re-LTs (58,63). Recipient and technical factors differentiate early from late re-LT (41,58). Referring to Moon et al. most of the early re-LT patients are in the intensive care unit (ICU) before the re-LT procedure, with half of them on continuous venovenous hemofiltration and on mechanical ventilation at the time of re-LT. Accordingly, ICU stay before re-LT is longer in cases of early re-LT than in cases of late re-LT. In addition, INR, Child-Turcotte-Pugh and MELD scores of early re-LT patients were relatively higher than those of late re-LT patients. A poorer preoperative general condition may lead to high 30-day postoperative mortality rates in early re-LT (58).

PNF and vascular complications are the most common indications for early re-LT (58,63). Bitterman et al. compared the outcomes of re-LT after initial living donor LT (LDLT) with those after initial deceased donor LT (DDLT). Timing of re-LT was significantly associated with the cause of initial graft failure in both re-LDLT and re-DDLT groups. In re-LDLT recipients, the most frequent reason for graft failure associated with re-LT ≤14 days was vascular thrombosis, whereas primary graft failure was most common in re-DDLT recipients (64). Furthermore, it was reported a significantly inferior long-term survival in patients who had re-LT for PNF and vascular complications. In both the United States and the United Kingdom, in recognition of the severity of illness and the high mortality associated with PNF and early HAT without re-LT, is given an urgent priority for re-LT (65).

HAT is a serious complication of LT which leads to an increased risk of morbidity and graft loss. HAT is typically more frequent in the first week after LT, but it can occur even years after the procedure. HAT can be classified as early (within 30 days post-LT) and late HAT (after 30 days post-LT). The etiology of HAT is probably multifactorial, including both surgical and medical risk factors. Technical aspects of the arterial anastomosis are important particularly for early thrombosis, but the improvement of surgical technique has lessened this problem. Apart from technical causes, other risk factors include a variety of conditions such as immunologic factors, clotting abnormalities, tobacco use and infections (66). Prompt identification of HAT may allow for urgent revascularization options, including surgical thrombectomy, and arterial reconstruction or thrombolysis. Re-LT is frequently required, especially in patients with severe ischemic cholangiopathy. Lui et al. compared patients undergoing re-LT for HAT with patients retransplanted for other indications. HAT recipients were significantly older, with a higher preponderance of males. The incidence of hepatitis C viral infection and the MELD score were significantly lower in the HAT cohort, while pre-transplant PVT was significantly higher. Patients undergoing re-LT for HAT had 13% decreased risk of graft loss and increased patient survival. Moreover, patients who underwent late re-LT for HAT had increased risk of early graft loss (67).

PNF of a liver graft remains the one of the worst complications after LT because of its dismal outcomes. A recipient with a primary failing liver graft will not survive without emergency re-LT. Unfortunately, not every patient facing this complication will remain physiologically stable enough to be retransplanted, and some of them will not survive after re-LT. If re-LT fails to rescue the patient, a single case of PNF may result in the death of the recipient and loss of 2 grafts. Although the benefits of expanding the donor pool include decreasing waitlist morbidity and mortality, using more grafts with characteristics linked to a higher incidence of complications and graft failure may expose an individual recipient to an increased risk of poor outcome. As previously mentioned, the lack of a universal definition of PNF remains a problem. This contributes to the uncertainty of its real incidence and leads to lack of shared protocols for re-LT. The ischemia-reperfusion injury process (IRI) is the main cause of EAD, and PNF manifests when this damage is severe. The susceptibility of a particular graft to IRI varies, however marginal grafts are more vulnerable. Risk factors for PNF include: donor age, donor intensive care unit stay, cold ischemic time (CIT), graft steatosis and severity of recipient illness. Strategies to mitigate risk factors have evolved over the years. Advanced donor age was identified as a risk factor in a previous era where the majority of deceased donors were younger, but donor characteristics have changed today, and all transplant programs rely on much elderly donors. The exclusion of concomitant conditions reduces the risk derived from the advanced donor age. Both warm ischemic time (WIT) and CIT are factors that can be partially modified. WIT should ideally not exceed 60 min. CIT for DCD, marginal DBD and non-marginal DBD grafts should be less than 6, 8, and 12 hours respectively. Machine perfusion is a strategy to prevent IRI or reduce steatosis before implantation. Intensive management of patients and prevention of other organs failure before re-LT is crucial to face severe recipient illness (26).

Despite DCD liver grafts being widely accepted, the use of DCD for re-LT is actually avoided, because of the increased risk of complications, such as early allograft dysfunction. However, since the availability of DBD grafts has decreased, the waiting time for an optimal DBD liver to become available for a re-LT candidate could be too long with subsequent risk of deterioration of patient's

condition. Van Reeven et al. compared the outcomes of re-LT with DCD grafts with that of matched DBD cases and concluded that re-LT with a DCD graft can provide similar patient and graft survival rates as DBD re-LT (25). Due to the advances in organ preservation and transplantation, in the current era the incidence of PNF in DCD grafts is similar to that of DBD grafts (2.1%) (26).

1.2.4. Late retransplantation

Late re-LT accounts for 55-65% of re-LT. It is surgically more difficult than early re-LT, with longer operative time, modified anatomic landscape and adhesions close to vascular structures that complicate the procedure. Previous adhesions and fibrosis are a huge obstacle for the hepatectomy of primary LT. In addition, after removal of the graft, a sufficient length of the vena cava, hepatic artery, and distal bile duct should be preserved. Thus, experienced surgical skills are crucial for success during re-LT (58). Appropriate management of inferior vena cava (IVC) is essential to ensure safe removal of the graft and optimal outflow for the new graft. Laroche et al. demonstrated that caval preservation during the initial transplantation may facilitate re-LT by allowing repeat preservation of the native IVC and avoiding complete caval occlusion during second graft implantation. Caval preservation also limits the risk of renal dysfunction after re-LT and should be promoted whenever technically possible (68).

The most common causes of late re-LT are disease recurrence and chronic rejection. It is therefore important to implement immunosuppressive protocols with the objective of gaining immunotolerance. In the recent literature, ischemic-type biliary lesion (ITBL) has become a more frequent indication for late re-LT, increasing from 10% to 30% over time. Patients with ITBL develop progressive graft failure despite aggressive treatment with endoscopic and interventional radiology, and mortality without re-LT can be very high. ITBL has a multifactorial origin. Ischemic, genetic and immunological factors, and bile salt-induced injury are known risk factors. Schielke et al. reported that patients with ITBL usually had good and stable graft function for many years, with survival rates significantly higher than those patients retranslated for other indications.

This subgroup of patients might greatly benefit from elective re-LT and achieve an excellent long-term outcome (69).

Autoimmune liver diseases (ALD) can recur after LT with a reported rate of 18% for PBC, 11% for PSC, and 22% for AIH. Potentially modifiable risk factors for recurrence of ALD are: colectomy before LT; cholangiocarcinoma before LT; donor age; multiple episodes of acute cellular rejection; MELD score (70). Notably, it was reported that late re-LT performed specifically for PSC recurrence showed 5-year graft and patient outcomes that were significantly better than all other causes of late re-LT and were comparable to outcomes after primary transplantation (71)

HCV recurrence is almost universal and is still a leading indication for late re-LT. Up to 40% of HCV-infected transplant recipients develop cirrhosis within 5 years after LT, often requiring re-LT (72). Many studies demonstrated that transplant recipients with HCV infection who underwent re-LT had significantly lower graft and patient survival compared with those who underwent re-LT for other reasons (36,61). Considering these factors and the current organ shortage, re-LT for HCV appeared controversial. However, various studies demonstrate that the approval of first-generation direct-acting antiviral (DAA) agents in 2011 (boceprevir and telaprevir) and second-generation DAAs in 2013 (sofosbuvir and simeprevir) has changed the approach. DAA therapy has provided a viable option in reducing the need for re-LT in the setting of recurrent HCV infection and the total number of re-LT declined 5.2% annually following re-LT trends secondary to recurrent HCV infection (72). According to Belli et al., the percentage of primary LT in patients with HCV infection has declined since DAA became available (73). Young et al. also found that in the DAA era patients who underwent LT experienced lower likelihood of graft failure, post-LT death and re-LT (74). An analysis of re-LT outcomes before and after DAA introduction showed that patient and graft survival rates after re-LT were better in HCV patients in the post DAA era. The outcome after re-LT became similar between patients with and without HCV infection. Furthermore, in the post-DAA era, compared to the pre-DAA era, HCV patients had lower rates of biliary complications, disease recurrence, primary graft failure, and vascular thrombosis as contributing factors of primary graft failure. In

contrast, HCV patients in the post-DAA era had higher rates of diffuse cholangiopathy and PNF as contributing causes for graft failure after primary transplant. In HCV patients who had graft failure after re-LT, the rates of disease recurrence and graft failure were lower in the post-DAA era. In the post-DAA era, causes for graft failure after re-LT were similar between HCV and non-HCV patients (75). Croome et al. reported that graft survival was also not significantly different after re-LT (performed for all indications) compared with primary LT after the introduction for DAA (76).

1.3. Predictive models for survival

In the last decades, there have been many studies to assess the outcomes of both primary LT and re-LT. Predictive models of graft failure have been developed to identify high-risk groups of patients after first LT and, above all, to help LT providers in selecting the best donor-recipient match, namely the match with the best probability of long-term graft survival.
Furthermore, survival models after re-LT have been defined to guide clinicians choosing who and when to retransplant. In order to keep improving and optimizing the outcomes of re-LT, overcoming the issues deriving from the use of a second donor graft, the implementation of these risk scores would be advisable.

1.3.1. Survival models after primary LT

Some research groups identified risk factors of graft failure and developed models to predict the outcomes after first LT.
Feng et al. (77) defined donor characteristics that affect the risk of post-transplant graft failure, identifying seven donor and graft characteristics that are significantly and independently associated with increased failure of deceased donor LT. These included 3 donor demographic characteristics (age, race and height), 3 relating to cause of death (COD) (trauma, cerebrovascular accident (CVA), anoxia and other) and type of donor death (DCD), and a split/partial graft. The factors required to determine the relative risk associated with a particular graft are known at the time

of organ offer. This enables transplant physicians to share information regarding the risk posed by any graft offer in juxtaposition to the candidate's disease severity at that moment. Their study provides a risk assessment for every potential liver graft compared to the ideal liver graft:

Donor risk index (DRI) = exp[(0.154 if 40≤ age <50) + (0.274 if 50≤ age <60) + (0.424 if 60≤ age <70) + (0.501 if 70 ≤ age) + (0.079 if COD = anoxia) + (0.145 if COD = CVA) + (0.184 if COD = other) + (0.176 if race = African American) + (0.126 if race = other) + (0.411 if DCD) + (0.422 if partial/split) + (0.066 ((170–height)/10)) + (0.105 if regional share) + (0.244 if national share) + (0.010 × cold time)].

Halldorson et al. (78) developed a statistic, D-MELD, the product of donor age and preoperative MELD, to stratify posttransplant survival. It was hypothesized that D-MELD, being the product of two continuous variables (donor age and calculated preoperative MELD), would result in an incremental gradient of risk for postoperative mortality and complications estimated as length of hospital stay (LOS). Using a cutoff D-MELD score of 1600, a subgroup of donor–recipient matches with significantly poorer short- and long-term outcomes was defined. Patient and graft survival rates were significantly worse at 1 year for D-MELD ≥ 1600 in the validation cohort (Fig. 10). Identification of poor donor/recipient matches could guide allocation of organs into recipients in which the benefit from the limited resource of donor livers can be maximized.

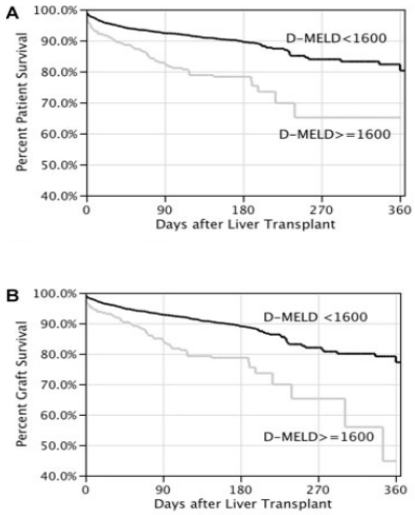


Figure 10. Validation of D-MELD ≥1600: (A) Patient survival, (B) graft survival (78)

Braat et al. (79) validated the DRI (77) and conducted a study aimed to design a risk scoring system tailored for the Eurotransplant region. In their analysis, DRI, latest donor's gamma glutamyl transpeptidase (GGT) and rescue allocation remained significant factors that were used to create the Eurotransplant Donor Risk Index (ET-DRI). The risk index is obtained by the following equation:

ET-DRI = exp[0.960((0.154 if 40≤age<50)+(0.274 If 50≤age<60)+(0.424 if 60≤age<70)+(0.501 if 70≤age)+(0.079 if COD = anoxia)+(0.145× if COD = cerebrovascular accident)+(0.184 if COD = other)+(0.411 if DCD)+(0.422 if partial/split)+(0.105 if regional share)+(0.244 if national share))+(0.010×(cold ischemia time−8 h)) +0.06((latest lab GGt (U/L)- 50)/100)+(0.180 if rescue offer)]

This ET-DRI might be used for risk indication and possibly for allocation purposes within the Eurotransplant region.

Pareja et al. (80) developed and validated a model for the quantitative assessment of early allograft function after transplantation, the Model for Early Allograft Function Scoring (MEAF). Their analysis selected a small number of postoperative variables that adequately describe EAD and a score was assigned for each variable value. The maximum alanine aminotransferase (ALT) and international normalized ratio (INR) values during the first 3 postoperative days ($ALT_{max3POD}$ and $INR_{max3POD}$) and the bilirubin value on day 3 after LT ($bilirubin_{3POD}$) were the most suitable variables for modeling EAD.

To facilitate model interpretation, the final MEAF score range was arbitrarily set at 0 to 10 points. Therefore, the $ALT_{max3POD}$, $INR_{max3POD}$ and $bilirubin_{3POD}$ scores were set from 0 to 3.33. The MEAF score consists of adding the 3 scores corresponding to each value:

$$\text{score } ALT_{max3POD} = \frac{3{,}29}{1+e^{-1.9132\ (lnALTmax3POD-6.1723)}}$$

$$\text{score } INR_{max3POD} = \frac{3{,}29}{1+e^{-6.8204\ (lnINRmax3POD-0.6658)}}$$

$$\text{score } bilirubin_{3POD} = \frac{3{,}29}{1+e^{-1.8005(lnbilirubin3POD-1.0607)}}$$

The MEAF score showed a significant association with patient and graft survival.

Agopian et al. (81) constructed a model for individualized risk estimation of graft failure after LT and then compared the model's prognostic performance with the existing EAD definition (bilirubin level of ≥10 mg/dL on postoperative day 7, INR of ≥1.6 on postoperative day 7, or AST or ALT level of >2000 U/L within the first 7 days) and the MEAF score (79). Their analysis found that factors associated with 3-month graft failure–free survival included post-LT AST level, INR, bilirubin level (TBIL), and platelet count (PLT), measures of which were used to calculate the Liver Graft Assessment Following Transplantation (L-GrAFT) risk score. The L-GrAFT model showed a significantly superior discrimination of 3-month graft failure–free survival compared with the existing EAD definition and the MEAF score. The formula for risk-score calculation is:

L-GrAFT risk score = 11.27 – 0.429 × (AUClogAST) + 0.005 × (AUClogAST^2) + 4.607 × (early slope logAST) + 4.413 × (early slope logAST^2) + 0.890 × (logmaxINR − 0.049 × (AUClogTBIL) + 0.004 × (AUClogTBIL^2) + 5.336 × (slopelogTBIL) − 0.046 × (AUClogPLT) − 5.249 × (slopelogPLT) + 13.086 × (slopelogPLT^2).

The L-GrAFT scores correspond to 5 risk groups of 3-month graft failure: very low risk (<−3.23), low risk (≥−3.23 to<−1.18), moderate risk (≥−1.18 to<−0.57), moderate-to-high risk (≥−0.57 to <1.3), and high risk (>1.3).

Avolio et al. (82) developed and validated a simplified comprehensive model estimating at day 10 after LT the early allograft failure (EAF) risk at day 90: the Early Allograft Failure Simplified Estimation (EASE) score. Early allograft failure was defined as graft failure (codified by retransplant or death) for any reason within 90 days after transplant. The EASE score outperformed L-GrAFT, MEAF, EAD, ET-DRI, D-MELD and DRI scores, estimating EAF on day 90 with 87% accuracy. Patients could be stratified in 5 classes, with those in the highest class exhibiting unsustainable EAF risk and being suitable for re-LT. The EASE score was derived by the following equation:

EASE score = 0.958 + (0.044 × MELD score at transplant) + (0.065 × PRBC) + (2.567 × thrombosis on days 1-10) + [0.000534 × AUC^2 for ln(AST level) on days 1, 2, 3, 7, and 10] + [−0.093 × AUC for ln(platelet count) on days 1, 3, 7, and 10] + [−7.735 × slope for ln(platelet count) on days 1, 3, 7, and 10] + (0.735 × slope

for bilirubin level on days 1, 3, 7, and 10) + (−0.402 × high-volume center), where PRBC stands for packed red blood cell.

1.3.2. Survival models for liver retransplantation

Studies focused on the development of risk scores to determine survival after re-LT may serve as a guidance for clinical decisions of liver acceptance for re-LT.
Rosen et al. (83) developed a prognostic model to predict survival following re-LT, based on recipient age, total serum bilirubin, creatinine and interval to re-LT. This model was constructed by combining data from a U.S. and an international cohort to improve its generalizability. Because PNF as an indication for re-LT historically has been viewed as ethically obligated, the predictive model was based on patients who underwent re-LT at least 2 weeks after their primary transplant. The survival model for liver retranspltantion (SMLR) Rwas derived from the following equation:
SMLR = 10 [0.0236 (recipient age) + 0.125 √bilirubin) + 0.438(log (creatinine) - 0.234(interval to reLT)]
with zero for 15 to 60 days and 1 for patients undergoing re-LT more than 60 days beyond their primary transplantation.
Two risk-score cutoff values (16 and 20) were chosen to assign 3 risk groups, low, intermediate-, and high-risk groups, in relation to the number of deaths within the first 90 days following re-LT (Fig. 11). Interestingly, it was also reported that the etiology of non-PNF graft failure, including HCV recurrence, did not impact outcome after regrafting. This model therefore appears generalizable to patient populations with graft failure of diverse etiologies and wide ranges of severity. This study also evaluated the validity of MELD score in predicting survival after re-LT and found that it properly correlated with outcome following re-LT, but the cut-offs assigning relative risk are different from those that have been traditionally used in patients awaiting primary LT.

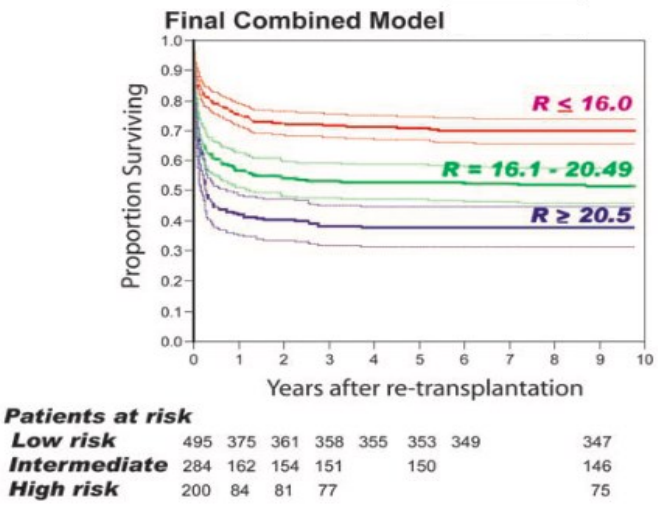


Figure 11. Kaplan-Meier survival according to risk groups assigned by final predictive model, Rosen et al. (83)

Linhares et al. (84) tried to develop a method for identifying subgroups of patients whose prognosis was insufficiently acceptable for justifying liver re-LT. They proposed a mathematical model based on the recipient's age at the time of re-LT, serum creatinine, interval between the initial transplantation and re-LT (early failure of the first graft) and the urgency of re-LT. This model was able to predict the length of survival of re-LT patients (Tab. II).

Table II. Final result of the predictive model for long-term survival among liver re-LT patients, Linhares et al. (84)

Variables	**Score**
Urgency of retransplatation	14
Recipient's age (per 10-year increment)	4
Creatinine (per 100-unit increment)	4
Early failure of the first graft	-10

Northup et al. (85) investigated the effects of ECD grafts on re-LT and developed a predictive mortality index in liver re-LT based on the previously established DRI (77). The addition of the cause of recipient graft failure to the DRI formed the retransplant donor risk index (ReTxDRI). The ReTxDRI was predictive of overall recipient survival and was a strongly independent predictor of death after re-LT. The use of the ReTxDRI may improve recipient and donor matching and help to optimize posttransplant survival in liver re-LT.

The equation for the ReTxDRI is: exp[(0.154 if 40≤ age <50) + (0.274 if 50≤ age <60) + (0.424 if 60≤ age <70) + (0.501 if 70 ≤ age) + (0.079 if COD = anoxia) + (0.145 if COD = CVA) + (0.184 if COD = other) + (0.176 if race = African American) + (0.126 if race = other) + (0.411 if DCD) + (0.422 if par- tial/split) + (0.066 ((170 – height)/10)) + (0.105 if regional share) + (0.244 if national share) + (0.010 × cold time) + (0.119 if graft failure: biliary) + (0.094 if graft failure: recurrent disease) + (0.063 if graft failure: rejection) + (0.187 if graft failure: vascular thrombosis) + (0.017 if graft failure: all other)].

Hong et al. (86) also developed a prognostic scoring system for risk stratification of post- LT patients with graft failure who might benefit from re-LT. They identified independent recipient's and donor's risk factors for graft failure after re-LT. Each independent predictor was assigned risk score (RS) points of 1 or 2. Graft failure predictive index (PI) was established by the sum of all RS for each patient (Tab. III). The patients were assigned to 4 PI risk categories (PIC) based on the similarity of observed graft failure-free survival outcome: 0 for PIC I, 1 to 2 for PIC II, 3 to 4 for PIC III, and 5 to 12 for PIC IV. The PIC was highly predictive of long-term patient and graft survival outcome. Patients in categories I to III are acceptable candidates for ReLT. Pursuing re-LT in transplant candidates determined to fall in the high- risk category (PIC IV) is not recommended.

Table III. Independent predictors and assigned risk score points (86)	
Variables	Risk score points
Intraoperative PRBC>30 units	2
Prior OLT>1	2
Requirement for ventilator at the time of ReLT	2
Interval to ReLT: 15-30 d 31-180 d	2 1
Donor age>45	1
MELD>27	1
Albumin<2.5g/dL at the time of ReLT	1
Recipient age>55	1

Brüggenwirth et al. (87) aimed to develop and validate a risk model which identifies high-risk combinations of recipient- and graft-related factors prognostic for long-term graft survival after re-LT. The so-called liver retransplantation risk score (LRRS) model included 7 predictors of graft survival: recipient age, MELD score, indication for re-LT, recipient hospitalization, time between primary LT and re-LT, donor age, and cold ischemia time (CIT). By assigning risk points to each variable, a simplified risk score was created ranging 0–10 (Tab. IV). Low-risk (0– 3), medium-risk (4–5), and high-risk (6–10) groups were identified with significantly different 5-year survival rates.

Table IV. Recipient- and graft-related variables prognostic for graft failure after liver re-LT and points according to the liver retransplantation risk score (LRRS) (87)			
Recipient-related		**Graft-related**	
Variables	Points	Variables	Points
Age		Donor age	
≤40	0	≤40	0
40-60	0	40-60	1
≥60	1	≥60	1
MELD		Time between primary LT and reLT	
≤9	0	Very early (<2 weeks)	0
10-19	0	Early (2 weeks-3 months)	1
20-29	0	Late (>3 months)	0
30-39	2	CIT	
≥40	2	≤6	0
Indications for reLT		6-12	1
Rejection	0	≥12	1
Vascular complications	0		
Primary non-function	1		
Recurrent HCV	1		
Recurrent liver desease	0		
Biliary complications	0		
Bacterial Infection	3		
Other	0		
Recipient medical condition			
Home	0		
Hospitalized	1		

2. AIM OF THE STUDY

The aim of the study is to assess the outcome of LT and re-LT in our high-volume cohort and validate the current predictive score for graft failure.

3. MATERIALS AND METHODS

This is a retrospective study carried out on prospectively maintained databases identifying patients who were submitted to LT in a single center. The present study has been conducted in compliance with regional ethics committees and national laws of the participating institution: no patient approval was needed for retrospective studies. Patients gave written consent for every procedure performed in the hospital, including use of data for medical purposes, which was obtained in a manner that was consistent with the Declaration of Helsinki, and all procedures were performed in accordance with the Declaration of Istanbul. No one received compensation or was offered any incentive for participating in this study.

The study cohort included all consecutive LT performed from 1 January 2010 to 31 December 2019. The patient exclusion criteria were a recipient age less than 18 years, living-donor LT (LDLT), domino and combined LT.

Data collected for analysis included the following: (1) recipient demographic characteristics (age, sex), primary end-stage liver disease diagnosis, diabetes, chronic kideny disease (CKD), perioperative laboratory results (Model for End-stage Liver Disease [MELD] score at transplant, bilirubin level, creatinine level and post-operative day [POD] 1 to 10 AST level, ALT level, bilirubin level, lactate level and platelet count), pretransplant hospitalization or mechanical ventilation, packed red blood cell (PRBC) transfusions at LT, and conditions complicating the postoperative course (ie, vascular thrombosis, biliary complications, primary non-function [PNF], early allograft disfunction [EAD] acute rejection, acute kidney injury [AKI], intensive care unit [ICU] staty and length of stay [LOS]), indication to Re-LT and time between primary LT and Re-LT; (2) donor demographic characteristics (age, sex, height, body mass index [BMI], ethnicity, cause of death and allocation, last GGT level); (3) grafts (donation after cardiac death [DCD], donation after brain death [DBD], split liver, MP grafts, and macrosteatosis); and (4) surgical procedure characteristics (cold ischemia time [CIT]).

Four models were calculated on primary LT population:

1. The Donor Risk Index (DRI), as previously described (77) using 8 variables: donor age, donor cause of death, donor ethnicity, donor type, partial graft, donor height, allocation and CIT. DRI was stratified according to 3 category:
    a. DRI <= 1,5 (low risk)
    b. DRI > 1,5 and < 2 (intermediate risk)
    c. DRI >= 2 (high risk)
2. The D-MELD score is the product of donor age and preoperative MELD (78); D-MELD score >= 1600 defines high risk of poor patient and graft survivals.
3. The Eurotransplant Donor Risk Index (ET-DRI), as previously described (79) using 8 variables: donor age, donor cause of death, donor type, partial graft, allocation, CIT, latest donor GGT level and kind of offer. ET-DRI was stratified according to 3 categories:
    a. ET-DRI <= 1,5 (low risk)
    b. ET-DRI > 1,5 and < 2 (intermediate risk)
    c. ET-DRI >= 2 (high risk)
4. Model for Early Allograft Function Scoring (MEAF) that was developed on our study population as described by Pareja et al. (80) using 3 variables: maximal ALT and INR level until POD 3 and bilirubin level at POD 3. MEAF score >= 8 defines high risk of poor patient and graft survivals. Of note, for the calculation of this model, the study was restricted only to the patients whose postoperative ALT, INR and bilirubin levels were available.

Two models were calculated on re-LT population:

1. The Survival Model for Liver re-LT (SMLR) was calculated as described by Rosen et al. (83) using 3 variables: bilirubin level, creatinine level and time between primary LT and re-LT. SMLR has three category:
    a. SMLR < 5 (low risk)
    b. SMLR >= 5 and <= 9.5 (intermediate risk)
    c. SMLR > 9.5 (high risk)

2. Liver Retransplantation Risk Score (LRRS) was calculated as described by Brüggenwirth et al. (87) using 7 variables: recipient age, MELD at re-LT, indication for re-LT, recipient medical condition at re-LT, donor age, time between prumary LT and re-LT, and CIT. LRRS has three risk category:
    a. LRRS 1 - 3 (low risk)
    b. LRRS 4 - 5 (intermediate risk)
    c. LRRS >= 6 (high risk)

Our center policy for leading to retransplant is based on evidence of biochemical signs of a non-functioning graft, or expected deterioration of other vital functions leading to death, or expected substantial change of prognosis after the second graft.

3.1. Statistical analysis

Statistical models used to develop the DRI, D-MELD, ET-DRI, MEAF, SMLR and LRRS was previously described (77–80,83,87).

Values for categorical variables were expressed as totals and percentages whereas for continuous variables they were expressed as medians and standard deviations. Statistical analyses were performed using the Pearson's chi-squared test or Fisher's test for categorical variables and the Kruskal–Wallis rank sum test for continuous variables.

The length of follow-up was calculated from the date of LT to the date of patient death (overall survival—OS) or the latest follow-up. The graft survival was calculated from the date of LT to the date of re-LT. The durations of follow-up and survival were expressed as medians (standard deviation [SD]). Patients and grafts survival curves were calculated using the Kaplan–Meier technique and compared with the log-rank test.

4. RESULTS

From 1 January 2010 to 31 December 2019, a total of 783 LT were performed at Hepatobiliary pancreatic surgery and LT Unit of Padua University Hospital, Padua, Italy. Seven hundred nineteen were primary LT and 64 were re-LT. Overall, 21 patients were excluded for the following reasons: pediatric recipients (6), LDLT (2), domino (5) and combined LT (8). After the exclusion criteria were applied, 762 LT recipients were enrolled in our study: 699 91.7%) were primary LT and 63 (8.3%) re-LT. Median follow-up was 42.5 (+/- 34.6) months. Among the 699 patients primarily transplanted during the study period, 49 (7%) underwent re-LT, whereas 14 re-LT patients were primarily transplanted before 2010. Notably, median follow-up in the re-LT cohort was 9.3 (+/- 34.2) months.
The median age at LT was 57.1 (+/- 9.8) years and median MELD at LT was 17 (+/- 9). HCV positive patients were 262 (37%) and 320 (45.8%) had HCC.
Median time to re-LT was 7 (+/- 1640.2) days, 40 (63.5%) were early re-LT and 23 (36.5%) late re-LT. Median MELD at re-LT was 28 (+/- 8.4). The main indication for re-LT was PNF (27 [43%] over 63 re-LT) followed by vascular complications (22.2%).
Table V resumes the characteristics of study populations.

Table V: Study population characteristics

	Re-LT, N = 63[1]	**First LT**, N = 699[1]
Partial/Split Graft	4 / 63 (6.3%)	37 / 699 (5.3%)
Cirrhosis (y)	6 / 63 (9.5%)	650 / 699 (93%)
Indication to LT		

Table V: Study population characteristics		
	Re-LT, N = 63[1]	**First LT**, N = 699[1]
- HCV		262 / 699 (37%)
- HBV		150 / 699 (21%)
- HDV co-infection		62 / 699 (8.9%)
- Alcohol		222 / 699 (32%)
- NAFLD / NASH		47 / 699 (6.7%)
- ALF		23 / 699 (3.3%)
- Other		126 / 699 (18%)
HCC	0 / 61 (0%)	320 / 699 (45.8%)
Indication for Re-LT		
- Bacterial infection	5 / 63 (7.9%)	
- Biliary complications	7 / 63 (11%)	
- HCV recurrence	4 / 63 (6.3%)	
- PNF	27 / 63 (43%)	
- Recurrent liver	2 / 63 (3.2%)	

Table V: Study population characteristics		
	Re-LT, N = 63[1]	**First LT**, N = 699[1]
disease		
- Rejection	4 / 63 (6.3%)	
- Vascular complication	14 / 63 (22.2%)	
Age at procedure	52.9 (12.7)	57.1 (9.8)
Sex (Female)	27 / 63 (43%)	170 / 699 (24.3%)
Weight (*missing)	65.0 (14.2) *12	75.0 (13.7) *164
Height (*missing)	170.0 (7.8) *13	172.0 (8.1) *176
BMI (*missing)	23.4 (4.4) *14	25.5 (3.8) *181
Diabetes (*missing)	0 / 19 (0%) *44	112 / 443 (25%) *256
CKD (*missing)	2 / 20 (10%) *43	21 / 436 (4.8%) *263
MELD (*missing)	28.0 (8.4) *3	17.0 (9.0)
Patient location		
- Home	20 / 63 (31.8%)	561 / 699 (80.3%)

Table V: Study population characteristics		
	Re-LT, N = 63[1]	**First LT**, N = 699[1]
- Hospital	5 / 63 (7.9%)	131 / 699 (18.7%)
- ICU	38 / 63 (60.3%)	7 / 699 (1%)
Postoperative course		
Postoperative Clavien >= 3b	46 / 63 (73%)	213 / 699 (30.5%)
CCI	52.1 (34.4)	24.2 (27.6)
LOS (days)	28.0 (29.1)	17.0 (23.0)
ICU stay (days) *missing	9.0 (17.0) *31	4.0 (11.5) *251
PNF	3 / 63 (4.8%)	32 / 699 (4.6%)
EAD	18 / 63 (29%)	131 / 699 (19%)
Biliary complications	10 / 63 (15.9%)	144 / 699 (20.6%)
- Biliary stenosis	6 / 63 (9.5%)	101 / 699 (14.4%)
- ITBL	1 / 63 (1.6%)	20 / 699 (2.9%)
- Biliary leak	3 / 63 (4.8%)	31 / 699 (4.4%)
PVT	2 / 63 (3.2%)	26 / 699 (3.7%)

Table V: Study population characteristics		
	Re-LT, N = 63[1]	**First LT**, N = 699[1]
HAT	5 / 63 (7.9%)	32 / 699 (4.6%)
HA Stenosis	1 / 63 (1.6%)	6 / 699 (0.9%)
Acute rejection	10 / 63 (16%)	89 / 699 (13%)
Banff score (*missing)	*1	*18
- RAI 2 -3	2 / 9 (22%)	16 / 71 (23%)
- RAI 4 -6	4 / 9 (44%)	34 / 71 (48%)
- RAI 6 -8	3 / 9 (33%)	21 / 71 (29.5%)
HCV recurrence		57 / 262 (22%)
Re-LT	3 / 63 (4.8%)	49 / 699 (7.0%)
Indication for Re-LT		
- HAT		6 / 49 (12%)
- HVT		2 / 49 (4.1%)
- ITBL		5 / 49 (10%)
- PNF		26 / 49 (53%)

Table V: Study population characteristics		
	Re-LT, N = 63[1]	**First LT**, N = 699[1]
- PVT		5 / 49 (10%)
- Rejection		1 / 49 (2.0%)
- Sepsis		4 / 49 (8.2%)
Days from primary LT	52.0 (793.9)	4.0 (189.4)
Donor characteristics		
Allocation (*missing)	*4	*12
- Extra-regional	36 / 59 (61%)	249 / 687 (36%)
- Local	3 / 59 (5.1%)	95 / 687 (14%)
- Regional	20 / 59 (34%)	343 / 687 (50%)
DCD	0 / 63 (0%)	2 / 699 (0.3%)
Donor Age (*missing)	56.0 (19.3) *3	64.0 (17.0) *10
Sex (female) *missing	24 / 54 (44%) *9	252 / 605 (42%) *94
Donor Height (*missing)	170.0 (7.3) *1	170.0 (9.3) *8
Donor Weight (*missing)	71.0 (12.3) *9	75.0 (13.4) *38

Table V: Study population characteristics		
	Re-LT, N = 63[1]	**First LT**, N = 699[1]
Donor BMI (*missing)	24.9 (3.5) *9	25.4 (5.9) *38
Donor COD (*missing)	*3	*11
- Anoxia	2 / 60 (3.3%)	53 / 688 (7.7%)
- CVA	40 / 60 (67%)	496 / 688 (72%)
- Other	4 / 60 (6.7%)	6 / 688 (0.9%)
- Trauma	14 / 60 (23%)	133 / 688 (19%)
Macrovesicular steatosis	5.0 (6.1) *31	5.0 (9.8) *185
Operative variables		
CIT (*missing)	458.0 (79.5) *4	485.0 (95.8) *17
pRBC (*missing)	7.0 (5.9) *6	5.0 (5.8) *21
Scores calculated on primary LT population		
DRI (*missing)		*121
- DRI <= 1,5		89 / 578 (15%)
- DRI > 1,5 and > 2		317 / 578 (55%)

Table V: Study population characteristics		
	Re-LT, N = 63[1]	**First LT**, N = 699[1]
- DRI >= 2		172 / 578 (30%)
D-MELD >= 1600 (*missing)		142 / 689 (21%) *10
ET-DRI (*missing)		*105
- ET-DRI <= 1,5		419 / 594 (71%)
- ET-DRI > 1,5 & > 2		69 / 594 (12%)
- ET-DRI >= 2		106 / 594 (18%)
MEAF >= 8 (*missing)		74 / 204 (64%) *495
Scores calculated on Re-LT population		
SMLR		
- SMLR < 5	1 / 63 (1.6%)	
- SMLR >= 5 & <= 9.5	2 / 63 (3.2%)	
- SMLR >= 9.5	60 / 63 (95%)	
LRRS		
- LRRS 1 - 3	15 / 57 (26%)	

Table V: Study population characteristics

	Re-LT, N = 63[1]	**First LT**, N = 699[1]
- LRRS 4 - 5	21 / 57 (37%)	
- LRRS >= 6	21 / 57 (37%)	
Follow-up (months)	9.3 (34.2)	44.3 (34.1)

1 Median (SD); n / N (%)

Abbreviations: NAFLD, non alcoholic fatty liver disease; NASH, non alcoholic steatohepatitis; ALF, acute liver failure; HCC, hepatocellular carcinoma; PNF, primary non function; BMI, body mass index, CKD, chronic kidney disease; MELD, model for end-stage liver disease; ICU, intensive care unit; LOS, length of stay; EAD, early allograft dysfunction; ITBL, ischemic-type biliary lesion; PVT, portal vein thrombosis; HAT, hepatic artery thrombosis; DCD, donor after circulatory death; COD, cause of death; CVA, cerebrovascular accident; CIT, cold ischemia time; pRBC, packed red blood cell; DRI, donor risk index; ET-DRI, eurotransplant donor risk index; MEAF, model for early allograft function; SMLR, survival model for liver retransplantation; LRRS, liver retransplantation risk score.

4.1. Survival analysis on the cohort of primary LT

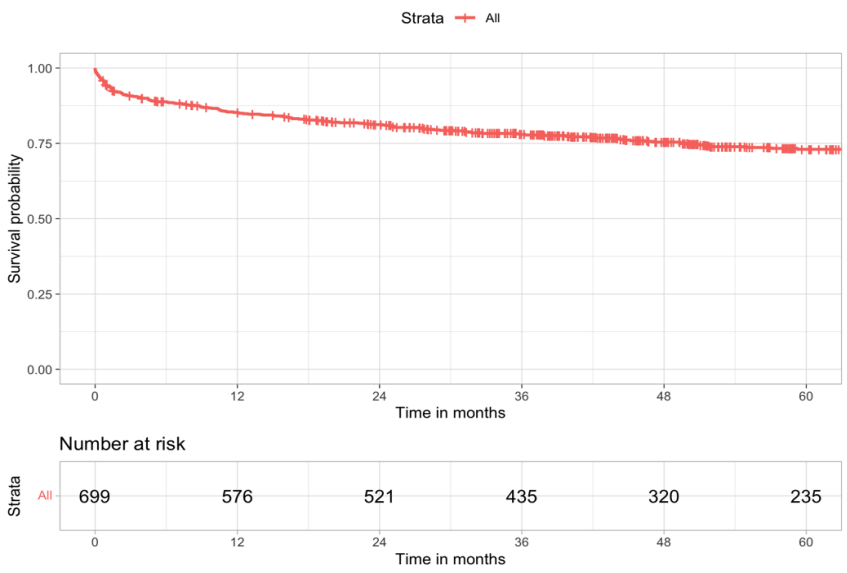


Figure 12: Kaplan–Meier overall survival curve of LT patients

In our cohort of 699 primarily transplanted patients, OS was 98.4% and 97.3%, 85.1% and 73% at 1 and 3 months, 1 and 5 years respectively (Fig. 12).

When patients were stratified according to the DRI, D-MELD, ET-DRI and MEAF models, LT with high risk of poor survival according to D-MELD and MEAF showed significantly lower OS compared to patients with low risk (Fig. 13).

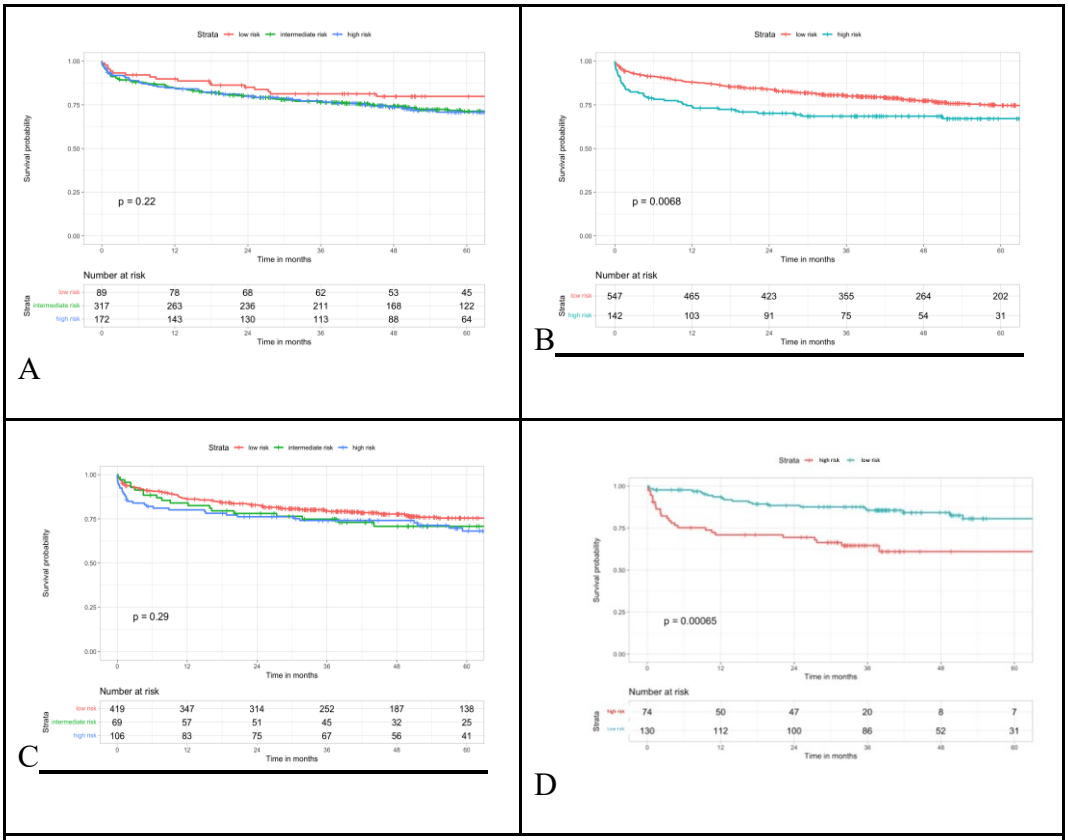


Figure 13. Kaplan–Meier overall patient survival curve of LT stratified according to A) DRI; B) D-MELD; C) ET-DRI; D) MEAF

At 1, 3 month and 1, 5 years the graft survival in the study cohort was 95.4%, 93%, 82% and 70% respectively (Fig. 14)

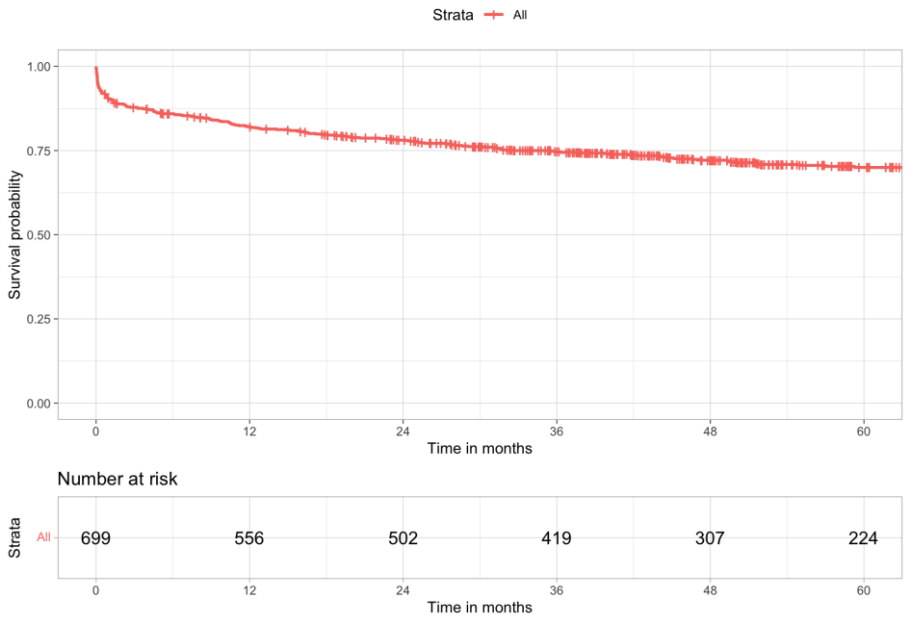


Figure 14. Kaplan–Meier graft survival curve of LT patients

Patients with a D-MELD >= 1600 or a MEAF >= 8 showed a graft survival significantly lower compared to low risk patients.

In particular, the low risk D-MELD, graft survival after at 1, 3 month and 1, 5 years was respectively 95.6%, 93.2%, 84.6% and 71.4% ; 1-, 3- and 5-year graft survival in high risk D-MELD was 95%, 92.2%, 71% and 64.9 respectively (p = 0,014 Fig. 15B). Categorizing patients according to MEAF, graft survival at 1, 3 month and 1, 5 years was 96.1%, 95.3%, 88.8% and 77.7% respectively in low risk category; whereas in high risk category graft survival at 1, 3 month and 1, 5 years was 91.8%, 85.1%, 69.9% and 58.5% respectively (p = 0.0021 Fig. 4D). Details of survival values for each model are shown in Table VI.

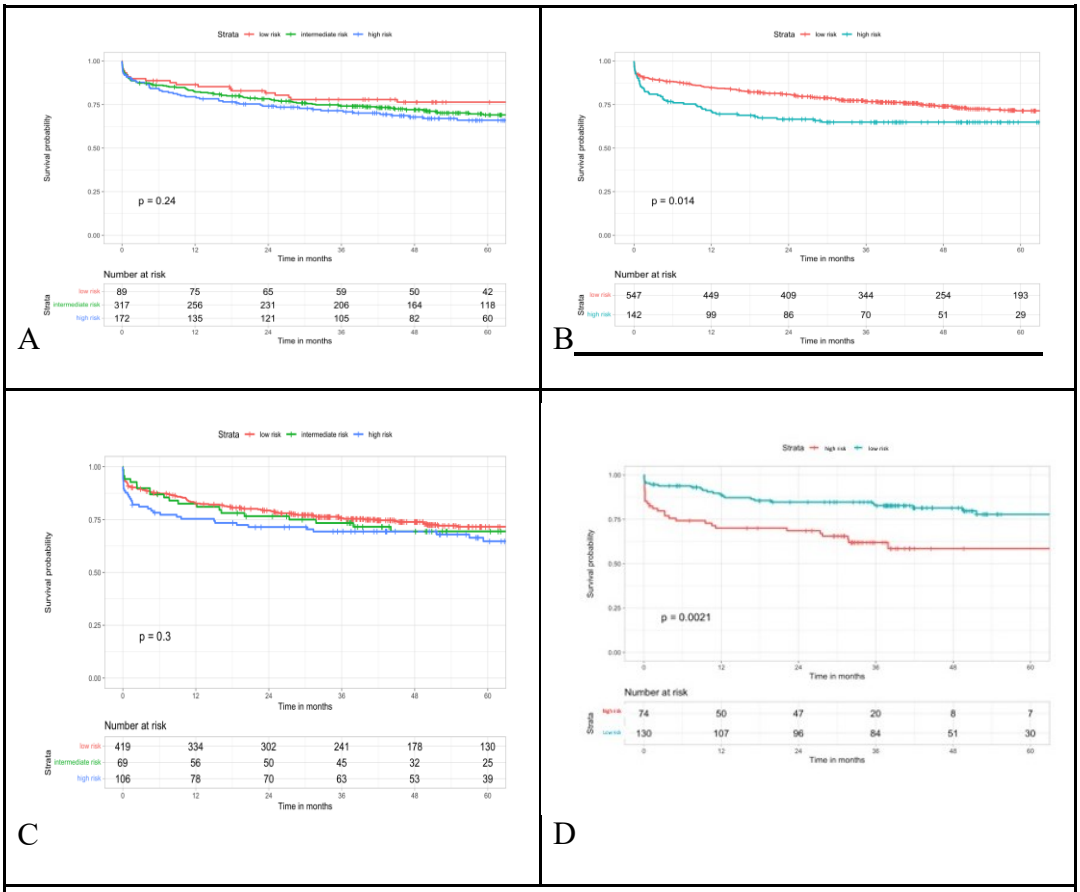


Figure 15. Kaplan–Meier graft survival curve of LT stratified according to A) DRI; B) D-MELD; C) ET-DRI; D) MEAF

Table VI. Graft survival values of LT stratified according to DRI, D-MELD, ET-DRI, and MEAF

Model	Risk	1 mo	3 mo	1 y	5 y	*p*
DRI	low	96.63%	94.38%	86.46%	76.43%	0.24
	intermediate	96.53%	94.01%	82.26%	69.07%	
	high	94.19%	92.24%	79.51%	66.0%	
D-MELD	low	95.6%	93.24%	84.69%	72.43%	0.014
	high	95.07%	92.25%	71.02%	64.94%	
ET-DRI	low	96.2%	93.79%	82.62%	71.6%	0.3
	intermediate	98.55%	94.20%	82.54%	69.43%	
	high	91.51%	88.68%	75.4%	64.74%	
MEAF	low	96.15%	95.38%	88.87%	77.75%	0.0021
	high	91.89%	85.14%	69.99%	58.50%	

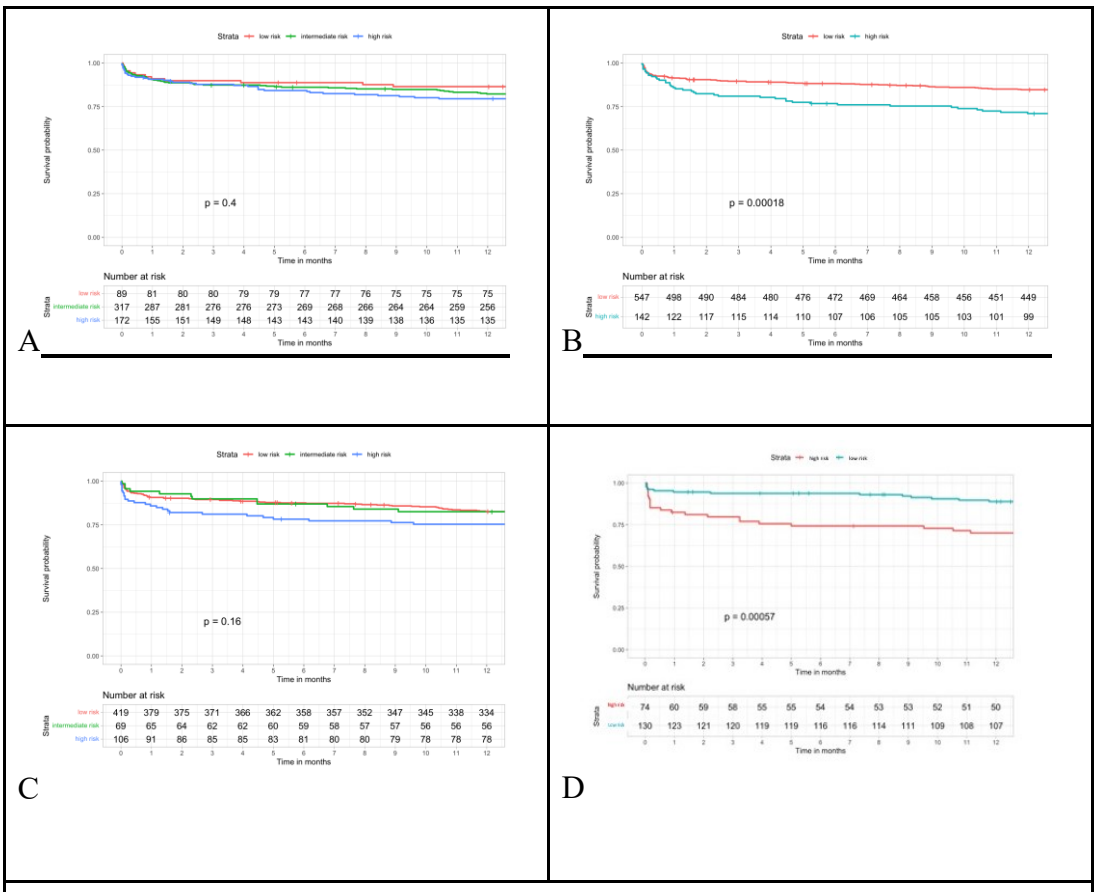


Figure 16. Kaplan–Meier 1-year graft survival curve of LT stratified according to A) DRI; B) D-MELD; C) ET-DRI; D) MEAF

1-year grafts survival curves showed similar results in terms of models' ability to identify patients at risk of graft loss (Fig. 16). Table VII shows the detailed values of 1-year graft survival according to each risk score.

Table VII. 1-Year graft survival values of LT stratified according to DRI, D-MELD, ET-DRI, and MEAF					
Model	**Risk**	**1 mo**	**3 mo**	**1 y**	***p***
DRI	low	91.01%	89.9%	86.46%	0.4
	intermediate	90.54%	87.38%	82.26%	
	high	90.69%	87.8%	79.51%	
D-MELD	low	91.4%	89.56%	84.69%	0.00016
	high	85.92%	80.99%	71.02%	
ET-DRI	low	90.69%	89.5%	82.62%	0.16
	intermediate	94.20%	89.86%	82.54%	
	high	85.85%	81.1%	75.4%	
MEAF	low	94.62%	93.83%	88.87%	0.00057
	high	82.43%	79.68%	69.99%	

Among recipient, perioperative and donor factors, a reduced graft survival was associated to male sex, prologed LOS and ICU stay, Clavien >= 3b, PNF, EAD, ITBL, PVT, HAT, donor age, pRBC transfused and D-MELD >= 1600 at univariable logistic regression. Five different independent predictors for the risk of poor graft survival after LT were identified with multivariable logistic regression. Not surprisingly, PNF was the most important independent risk factor (HR, 44.7; 95% CI, 24.1, 83.0; p < 0,001). Clavien >= 3b (HR, 2.72; 95% CI, 2.00, 3.70; p < 0.001), EAD (HR, 1.38; 95% CI, 1.01, 1.90; p = 0.045), ITBL (HR, 3.17; 95% CI, 1.79, 5.63; p < 0.001), PVT (HR, 1.95; 95% CI, 1.13, 3.36; p = 0.016) and D-MELD >= 1600 (HR, 1.45; 95% CI, 1.05, 2.01; p = 0.025) were other independent risk factors (Tab. VIII). PNF (HR, 14.2; 95% CI, 4.40, 46.1; p < 0.001) and Clavien >= 3b (HR, 6.53; 95% CI, 2.76, 15.5; p < 0.001) were the only two factors associated with graft loss within 1 year (Tab. IX).

Table VIII. Simple and Multivariable logistic regression on determinants of graft survival after LT

	Univariable			Multivariable		
Variables	**HR[1]**	**95% CI[1]**	**p-value**	**HR[1]**	**95% CI[1]**	**p-value**
Split graft	0.50	0.22, 1.12	0.092			
Cirrhosis	0.87	0.51, 1.46	0.6			
LT indications						
HCV	1.21	0.92, 1.59	0.2			
HBV	1.06	0.76, 1.46	0.7			
Alcohol	0.71	0.52, 0.96	0.028			
NASH	0.54	0.27, 1.10	0.090			
ALF	1.02	0.45, 2.31	>0.9			
Other	1.01	0.99, 1.02	0.3			
Male sex	1.55	1.09, 2.21	0.016			
Diabetes	0.98	0.67, 1.43	>0.9			
MELD	1.00	0.99, 1.02	0.6			
Pt. location						
Home	—	—				
Hospital	1.07	0.70, 1.65	0.7			
ICU	1.88	0.69, 5.09	0.2			
Clavien >= 3b	4.16	3.17, 5.47	<0.001	2.72	2.00, 3.70	<0.001
LOS (d)	1.01	1.00, 1.01	<0.001			

Table VIII. Simple and Multivariable logistic regression on determinants of graft survival after LT

	Univariable			Multivariable		
Variables	**HR[1]**	**95% CI[1]**	**p-value**	**HR[1]**	**95% CI[1]**	**p-value**
ICU (d)	1.03	1.02, 1.04	<0.001			
PNF	78.8	44.4, 140	<0.001	44.7	24.1, 83.0	<0.001
EAD	1.96	1.45, 2.66	<0.001	1.38	1.01, 1.90	0.045
Bil. stenosis	1.16	0.81, 1.65	0.4			
ITBL	2.51	1.43, 4.40	0.001	3.17	1.79, 5.63	<0.001
Biliary leak	1.16	0.63, 2.14	0.6			
PVT	3.91	2.34, 6.53	<0.001	1.95	1.13, 3.36	0.016
HAT	2.91	1.79, 4.72	<0.001			
HA Stenosis	2.02	0.65, 6.33	0.2			
Acute reject.	0.67	0.43, 1.05	0.080	0.68	0.42, 1.08	0.10
Donor age	1.02	1.01, 1.03	<0.001			
CIT	1.00	1.00, 1.00	0.15			
pRBC	1.06	1.04, 1.08	<0.001			
DRI >= 2	1.20	0.96, 1.50	0.11			
D-MELD >=1600	1.49	1.08, 2.04	0.014	1.45	1.05, 2.01	0.025
ET-DRI >= 2	1.14	0.96, 1.37	0.14			
MEAF < 8	0.45	0.26, 0.75	0.003			

[1] HR = Hazard Ratio, CI = Confidence Interval

Table IX. Multivariable logistic regression on determinants of 1-year graft survival after LT			
Variables	**HR[1]**	**95% CI[1]**	**p-value**
LT indications			
Alcohol	0.66	0.31, 1.40	0.3
Clavien >= 3b	6.53	2.76, 15.5	<0.001
PNF	14.2	4.40, 46.1	<0.001
EAD	1.60	0.73, 3.51	0.2
PVT	1.77	0.69, 4.54	0.2
HAT	1.27	0.37, 4.44	0.7
Acute rejection	0.21	0.03, 1.54	0.12
MEAF < 8	0.80	0.36, 1.77	0.6
[1]HR = Hazard Ratio, CI = Confidence Interval			

4.2. Survival analysis on the cohort of Re-LT

In our cohort of 63 Re-LT, OS was 92.1% and 88.9%, 50.8% and 45.7% at 1 and 3 months, 1 and 5 years respectively (Fig. 17A). Whereas, graft survival after re-LT at 1 and 3 months, 1 and 5 years was 92.1% and 87.3%, 49.2% and 44.2% respectively (Fig. 17B).

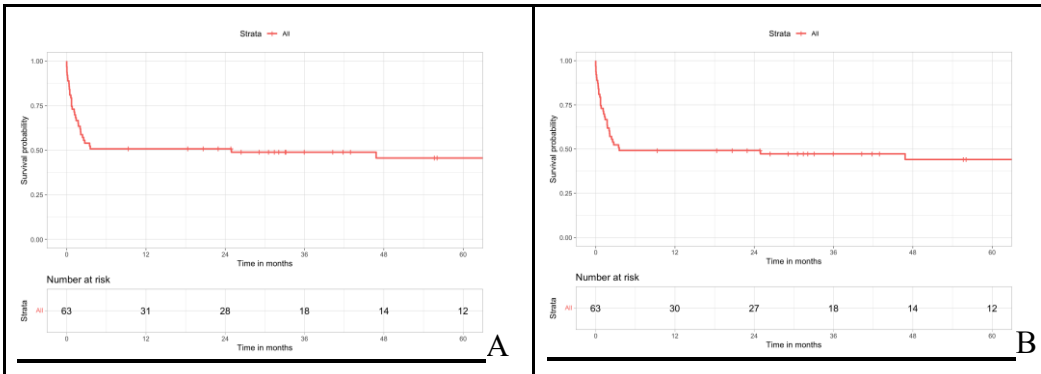


Figure 17. Kaplan–Meier survival curves of Re-LT patients. A) patient survival; B) graft survival.

SMLR and LRRS were calculated on this cohort of patients to test their capacity to identify patients with worse outcomes after re-LT. However, in our cohort, neither SMLR nor LRRS were able to discriminate with enough statistical significance for high risk against low risk patients (Fig. 18-19).

Details of graft survival values for each model are shown in Table X.

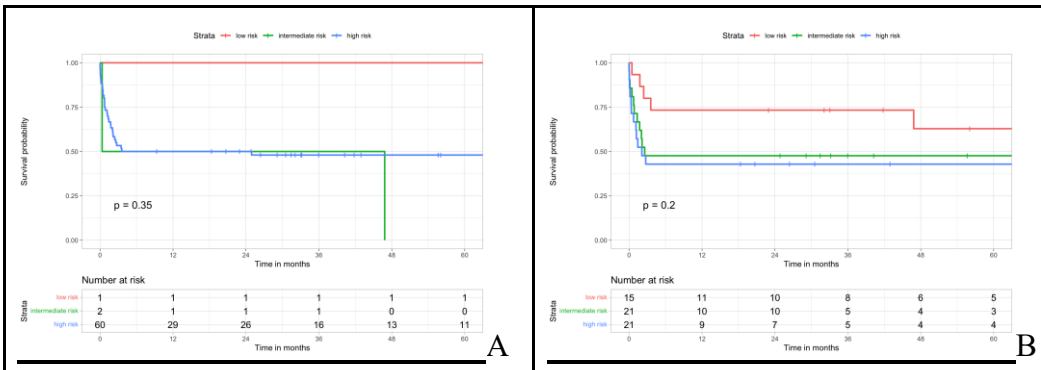


Figure 18. Kaplan–Meier overall patient survival curve of Re-LT stratified according to A) SMLR; B) LRRS.

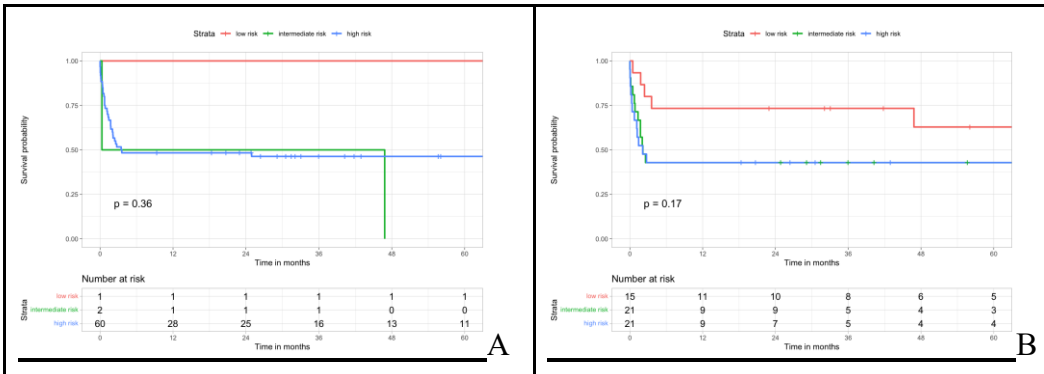


Figure 19. Kaplan–Meier graft survival curve of Re-LT stratified according to A) SMLR; B) LRRS.

Table X. Graft survival values of Re-LT stratified according to SMLR and LRRS.

Model	**Risk**	**1 mo**	**3 mo**	**1 y**	**5 y**	***p***
SMLR	low	100%	100%	100%	100%	0.36
	intermediate	100%	50%	50%	-	
	high	91.67%	88.33%	48.33%	47%	
LRRS	low	100%	100%	73.3%	62.9%	0.17
	intermediate	90.48%	85.71%	42.9%	42.9%	
	high	85.71%	76.19%	42.9%	42.9%	

Similar results were obtained with regards to 1-year graft survival as shown in figure 20 and table XI.

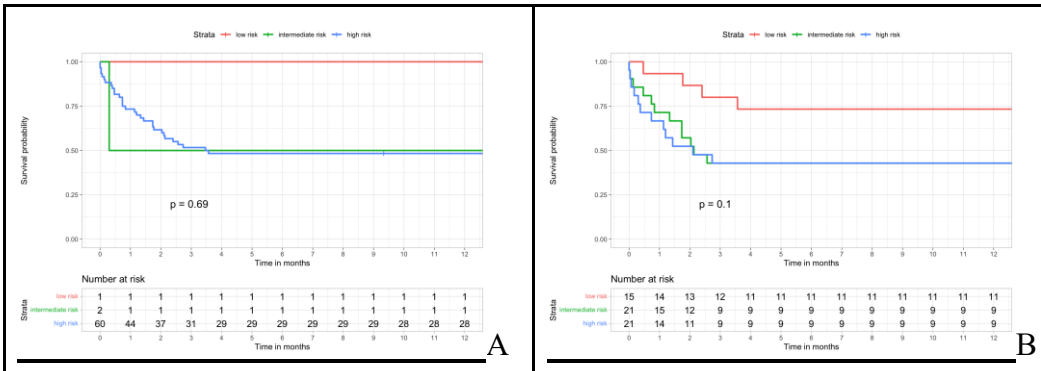


Figure 20. Kaplan–Meier 1-Year graft survival curve of Re-LT stratified according to A) SMLR; B) LRRS.

Table XI. 1-Year graft survival values of Re-LT stratified according to SMLR and LRRS.

Model	Risk	1 mo	3 mo	1 y	*p*
SMLR	low	100%	100%	100%	0.69
	intermediate	100%	50%	50%	
	high	91.67%	88.33%	48.33%	
LRRS	low	100%	100%	73.3%	0.1
	intermediate	90.48%	85.71%	42.9%	
	high	85.71%	76.19%	42.9%	

Five different independent predictors for the risk of poor graft survival after Re-LT were identified: PNF (HR, 7.74; 95% CI, 1.58, 37.8; p = 0.011), ITBL (HR, 226; 95% CI, 4.62, 11030; p = 0.006), pRBC transfused (HR, 1.10; 95% CI, 1.01, 1.19; p = 0.028), Clavien >= 3b (HR, 5.12; 95% CI, 1.12, 23.5; p = 0.036), and LRRS (HR, 2.08; 95% CI, 1.08, 4.01; p = 0.029) (Table XII). ITBL was the

strongest predictor of graft failure after re-LT, but when the analysis was limited to a shorter time horizon of 1-year, ITBL lost its significance (Table XIII).

Table XII. Simple and Multivariable logistic regression on determinants of graft survival after Re-LT

	Univariable			Multivariable		
Variables	**HR[1]**	**95% CI[1]**	**p-value**	**HR[1]**	**95% CI[1]**	**p-value**
MELD	1.04	0.99, 1.08	0.11			
Pt. location						
Hospital	0.38	0.05, 2.94	0.4			
ICU	1.48	0.70, 3.11	0.3			
Clavien >= 3b	6.53	1.98, 21.5	0.002	5.12	1.12, 23.5	0.036
LOS (d)	0.99	0.98, 1.00	0.2			
ICU stay (d)	1.02	0.99, 1.04	0.15			
PNF	18.7	4.38, 79.5	<0.001	7.74	1.58, 37.8	0.011
EAD	1.67	0.82, 3.40	0.2	1.89	0.72, 4.93	0.2
Bil. stenosis	0.45	0.11, 1.90	0.3			
ITBL	1.25	0.17, 9.17	0.8	226	4.62, 11,030	0.006
Biliary leak	0.39	0.05, 2.89	0.4			

Table XII. Simple and Multivariable logistic regression on determinants of graft survival after Re-LT

	Univariable			Multivariable		
Variables	**HR[1]**	**95% CI[1]**	**p-value**	**HR[1]**	**95% CI[1]**	**p-value**
PVT	0.00	0.00, Inf	>0.9			
HAT	0.50	0.12, 2.10	0.3	0.29	0.04, 2.35	0.2
HA Stenosis	1.51	0.21, 11.1	0.7			
Acute reject.	0.23	0.06, 0.97	0.045	0.15	0.02, 1.16	0.069
Donor age	1.01	0.99, 1.02	0.6			
CIT	1.00	1.00, 1.01	0.2			
pRBC	1.06	1.01, 1.13	0.030	1.10	1.01, 1.19	0.028
SMLR > 9.5	1.17	0.38, 3.60	0.8			
LRRS >= 6	1.49	0.94, 2.38	0.092	2.08	1.08, 4.01	0.029

[1] HR = Hazard Ratio, CI = Confidence Interval

Table XIII. Multivariable logistic regression on determinants of 1-year graft survival after Re-LT

Variable	HR[1]	95% CI[1]	p-value
Clavien >= 3b	4.57	1.00, 20.9	0.050
PNF	8.09	1.66, 39.6	0.010
EAD	1.99	0.77, 5.15	0.2
Acute reject.	0.15	0.02, 1.20	0.074
pRBC	1.11	1.02, 1.20	0.013
LRRS >= 6	1.99	1.01, 3.91	0.046

[1] HR = Hazard Ratio, CI = Confidence Interval

5. DISCUSSION

Liver transplantation (LT) is the standard treatment modality for patients with end-stage liver disease and acute liver failure. Today, more than 50% of grafts survive 10 years or more after LT, but when the transplanted organ fails (which occurs in 5-22% of all LTs according to the published literature (36)), liver retransplantation (re-LT) is the only option for survival. In an era of severe organ shortage, the decision to provide re-LT to patients with a failed graft is challenging considering that the outcomes of re-LT are inferior compared to first LT. Currently, there are no universally accepted guidelines to help clinical decisions for patients who require re-LT.

Despite being based on a monocentric experience, our study has analyzed almost 700 transplanted patients, and our LT program is one of the largest in Italy.

Our study showed a 5 years graft survival as high as 70% after LT with a re-LT rate of 7%, consistent with the previous literature report (36,40,55)

Leading indications to re-LT were primary non function (PNF) (43%) and vascular complications (22.2%), which is in agreement with previous literature (40,42,43).

HCV recurrence was observed in 57 / 262 (22%) LT, however only 4 / 63 (6.3%) patients underwent re-LT for HCV recurrence. Notably, the latter were patients primarily transplanted before 2010, and no patients who underwent LT from 2010 needed re-LT due to HCV recurrence. On the contrary, in recent studies HCV recurrence accounts for up to 30% of re-LTs (72). It is not negligible that the introduction of DAAs played a major role for the achievement of those results.

ELTR reported a graft survival after re-LT of 61% and 49% at 1 and 5 years respectively (40). Our study cohort showed a graft survival of 49.2% and 44.2% at 1 and 5 years respectively. Such results support re-LT as an effective rescue procedure, despite its greater complexity.

The definition of EAD applies to 19% of our LT patients whereas PNF occurred in 4.6% of primarily transplanted patients, compared to a mean reported incidence of 2.2% (26), which is probably related to a more extensive availability of ECD grafts at our center.

Our study confirms that biliary and vascular complications (in particular PVT) are major determinants of poor graft survival. If PVT and major complications (i.e. Clavien >= 3b) can be controlled more easily by technical refinements, PNF and ischemic cholangiopathy are more often associated to IRI and depend more on graft quality (e.g. DCD, CIT ect.) and donor-recipient matching.

We used four of the prognostic scoring systems for risk stratification of graft failure after LT, that are Donor Risk Index (DRI) (77), D-MELD (78), Eurotransplant Donor Risk Index (ET-DRI) (79) and Model for Early Allograft Function (MEAF) (80) scores.

Despite its large diffusion among LT clinicians, our study fails to find a statistically significant difference in terms of graft survival between LT patients with low DRI compared to high. This is probably due to the too short prevalence of low DRI LT in our cohort (15%), indirectly confirming the drop of ideal graft in the last decade in favor of ECD graft. However, a model as simple as D-MELD was able to show a statistically significant reduction of graft survival for LT patients scored >= 1600 ($p = 0.014$). Moreover, D-MELD >= 1600 was an independent predictor of graft survival (HR, 1.45; 95% CI, 1.05, 2.01; $p = 0.025$). Even though elderly donors can be safely used for LT, our study confirms previous findings that matching such graft with patients with high MELD scores should be avoided.

The early prediction of graft failure after LT through the kinetic of laboratory tests is an open field of investigation, with many scores recently published (e.g. MEAF, L-GrAFT, EASE) and more to come. The utility of such models would be to help clinicians to make a prompt decision for re-LT as long as the patient is still in the clinical condition to face the procedure, and avoid futile re-LT. Our finding, that patients with MEAF < 8 showed statistically significant higher graft survival ($p = 0.0021$), reinforce those concepts. However, the short number of patients for whom MEAF was calculated, and the retrospective nature of the study, limited our analysis and possibility to draw conclusions.

Determinants of graft failure after re-LT do not differ from primary LT, being Clavien >= 3b, PNF and ITBL independently associated with poor graft survival after re-LT. Notably, our study showed that, when it comes to re-LT, even

transfused pRBC during procedure were an independent variable associated with graft survival (HR, 1.10; 95% CI, 1.01, 1.19; p = 0.028). Re-LT is an extremely demanding surgical procedure, at high risk for major bleeding due to coagulopathy (that's the case of early re-LT) and strong intra-abdominal adhesions in a contest of portal hypertension (that's the case of late re-LT). The need for more blood transfusions relate to the complexity of surgical procedure and greater morbidity for the patient.

Graft survival risk scores in the setting of re-LT have been implemented by Rosen et al. (83) and Brüggenwirth et al. (87) as tools that may serve as a guidance for clinical decision-making on liver acceptance for re-LT. SMLR uses bilirubin, creatinine and time from primary LT to predict the survival probability after re-LT, whereas LRRS assigns points to recipient- and donor-related variables. According to both SMLR and LRRS, patients with high risk scores showed 5-years graft survival largely below 50%. Unfortunately, our study failed to find a statistically significant graft survival between patients in the different risk strata and this is probably related to the small sample size. However, LRRS >= 6 resulted in an independent predictor of graft survival after re-LT (HR, 2.08; 95% CI, 1.08, 4.01; p = 0.029), further reinforcing the concept that correct matching between donor and recipient is essential to achieve good survival.

The current study has several limitations: the retrospective nature of our analysis, the broad timeframe (in 10 years many technical and clinical refinements have been made in LT field), the limited sample size; moreover, several variables were missing which has made it difficult to calculate every risk score on each patient.

Therefore, besides dividing the analysis into different time periods to account for the refinement of transplantation techniques, further studies should gather more data in order to calculate and validate each prognostic score as well as involve other centers. The value of these predictive models must be stressed, as they can help to improve donor-recipient match selection and optimize the outcomes of primary LT and re-LT.

6. CONCLUSIONS

The present study has assessed the outcomes of primary LT and re-LT in our cohort of patients and determined which of the current predictive models of survival have the capacity to stratify patients according to their risk of poor overall and graft survival. D-MELD and MEAF risk scores have been shown to significantly predict reduced survivals in high-risk categories of patients.

This preliminary study may be corroborated by further multicentric analyses.

Future improvements of outcomes after LT may be achieved by implementing donor-recipient match selection criteria based on proven and validated predictive models of survival. Risk scores of poor outcome after re-LT may provide a practical guide for selection of optimal candidates to retransplant, that is patients with the best probability of survival, in order to minimize the issues caused by subtracting a donor liver from an increasingly scarce organ pool.

BIBLIOGRAPHY

1. Sabiston DC, Townsend CM, Beauchamp RD, Evers BM, Mattox KL, editors. Sabiston textbook of surgery: the biological basis of modern surgical practic. 20th edition. Philadelphia, PA: Elsevier; 2017. 2146 p.

2. McKenna G., Klintmalm G. The history of liver transplantation In: Busuttil R., Klintmalm G. Transplantation of the liver. Third edition Philadelphia, PA: Elsevier Saunders; 2015. 2-20.

3. Marzano A, Gaia S, Ghisetti V, Carenzi S, Premoli A, Debernardi-Venon W, et al. Viral load at the time of liver transplantation and risk of hepatitis B virus recurrence. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2005 Apr;11(4):402–9.

4. Terrault N, Roche B, Samuel D. Management of the hepatitis B virus in the liver transplantation setting: a European and an American perspective. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2005 Jul;11(7):716–32.

5. Roche B, Samuel D. Risk factors for hepatitis C recurrence after liver transplantation. J Viral Hepat. 2007 Nov;14 Suppl 1:89–96.

6. Wiesner RH. Liver transplantation for primary biliary cirrhosis and primary sclerosing cholangitis: predicting outcomes with natural history models. Mayo Clin Proc. 1998 Jun;73(6):575–88.

7. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001 Sep;35(3):421–30.

8. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996 Mar 14;334(11):693–9.

9. EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol. 2016 Feb;64(2):433–85.

10. Khungar V., Fox A., Brown R. Current indications, contraindications, delisting criteria, and timing for transplantation In: Transplantation of the liver. Third edition Philadelphia, PA: Elsevier Saunders; 2015. 94-103.

11. Farkas S, Hackl C, Schlitt HJ. Overview of the Indications and Contraindications for Liver Transplantation. Cold Spring Harb Perspect Med. 2014 May;4(5):a015602.

12. Mazzaferro V, Citterio D, Bhoori S, Bongini M, Miceli R, De Carlis L, et al. Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial. Lancet Oncol. 2020 Jul;21(7):947–56.

13. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology. 2003 Jan 1;124(1):91–6.

14. Freeman RB, Edwards EB. Liver transplant waiting time does not correlate with waiting list mortality: implications for liver allocation policy. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2000 Sep;6(5):543–52.

15. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, Ter Borg PCJ. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology. 2000;31(4):864–71.

16. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33(2):464–70.

17. Freeman RB. MELD: the holy grail of organ allocation? J Hepatol. 2005 Jan 1;42(1):16–20.

18. Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology. 2007 Mar;45(3):797–805.

19. Habib S, Berk B, Chang CCH, Demetris AJ, Fontes P, Dvorchik I, et al. MELD and prediction of post–liver transplantation survival. Liver Transpl. 2006;12(3):440–7.

20. Freeman Jr. RB, Gish RG, Harper A, Davis GL, Vierling J, Lieblein L, et al. Model for end-stage liver disease (MELD) exception guidelines: Results and recommendations from the MELD exception study group and conference (MESSAGE) for the approval of patients who need liver transplantation with diseases not considered by the standard MELD formula. Liver Transpl. 2006;12(S3):S128–36.

21. Busuttil RW, Tanaka K. The utility of marginal donors in liver transplantation. Liver Transpl. 2003;9(7):651–63.

22. Alkofer B, Samstein B, Guarrera JV, Kin C, Jan D, Bellemare S, et al. Extended-Donor Criteria Liver Allografts. Semin Liver Dis. 2006 Aug;26(03):221–33.

23. Kulik U, Lehner F, Klempnauer J, Borlak J. Primary non-function is frequently associated with fatty liver allografts and high mortality after re-transplantation. Liver Int. 2017 Aug;37(8):1219–28.

24. Jadlowiec CC, Taner T. Liver transplantation: Current status and challenges. World J Gastroenterol. 2016 May 14;22(18):4438–45.

25. van Reeven M, van Leeuwen OB, van der Helm D, Darwish Murad S, van den Berg AP, van Hoek B, et al. Selected liver grafts from donation after circulatory death can be safely used for retransplantation - a multicenter retrospective study. Transpl Int Off J Eur Soc Organ Transplant. 2020 Jun;33(6):667–74.

26. Hartog H, Hann A, Perera MTPR. Primary Nonfunction of the Liver Allograft. Transplantation. 2022 Jan 1;106(1):117–28.

27. Tector AJ, Mangus RS, Chestovich P, Vianna R, Fridell JA, Milgrom ML, et al. Use of extended criteria livers decreases wait time for liver transplantation without adversely impacting posttransplant survival. Ann Surg. 2006 Sep;244(3):439–50.

28. Tanaka K, Ogura Y, Kiuchi T, Inomata Y, Uemoto S, Furukawa H. Living donor liver transplantation: Eastern experiences. HPB. 2004 May 1;6(2):88–94.

29. González FX, Garcia-Valdecasas JC, Grande L, Pacheco JL, Cugat E, Fuster J, et al. Vena cava vascular reconstruction during orthotopic liver transplantation: A comparative study. Liver Transpl Surg. 1998;4(2):133–40.

30. Figueras J, Llado L, Ramos E, Jaurrieta E, Rafecas A, Fabregat J, et al. Temporary portocaval shunt during liver transplantation with vena cava preservation. Results of a prospective randomized study. Liver Transpl. 2001;7(10):904–11.

31. Busuttil RW, Goss JA. Split liver transplantation. Ann Surg. 1999 Mar;229(3):313–21.

32. Pichlmayr R, Ringe B, Gubernatis G, Hauss J, Bunzendahl H. Transplantation of one donor liver to two recipients (splitting transplantation) -a new method for further development of segmental liver transplantation. Langenbecks Arch Für Chir. 1988;373(2):127–30.

33. Lee WC, Chan KM, Chou HS, Wu TJ, Lee CF, Soong RS, et al. Feasibility of Split Liver Transplantation for 2 Adults in the Model of End-Stage Liver Disease Era. Ann Surg. 2013 Aug;258(2):306–11.

34. Hwang S, Lee SG, Lee YJ, Sung KB, Park KM, Kim KH, et al. Lessons learned from 1,000 living donor liver transplantations in a single center: How to make living donations safe. Liver Transpl. 2006;12(6):920–7.

35. Craig EV, Heller MT. Complications of liver transplant. Abdom Radiol. 2021 Jan;46(1):43–67.

36. Pfitzmann R, Benscheidt B, Langrehr JM, Schumacher G, Neuhaus R, Neuhaus P. Trends and experiences in liver retransplantation over 15 years. Liver Transpl. 2007;13(2):248–57.

37. Takagi K, Domagala P, Porte RJ, Alwayn I, Metselaar HJ, van den Berg AP, et al. Liver retransplantation in adult recipients: analysis of a 38-year experience in the Netherlands. J Hepato-Biliary-Pancreat Sci. 2020 Jan;27(1):26–33.

38. Eguchi S, Soyama A, Mergental H, van den Berg AP, Scheenstra R, Porte RJ, et al. Honoring the contract with our patients: outcome after repeated re-transplantation of the liver. Clin Transplant. 2011 Apr;25(2):E211-218.

39. Azoulay D, Linhares MM, Huguet E, Delvart V, Castaing D, Adam R, et al. Decision for retransplantation of the liver: an experience- and cost-based analysis. Ann Surg. 2002 Dec;236(6):713–21; discussion 721.

40. Adam R, Karam V, Cailliez V, O Grady JG, Mirza D, Cherqui D, et al. 2018 Annual Report of the European Liver Transplant Registry (ELTR) - 50-year evolution of liver transplantation. Transpl Int Off J Eur Soc Organ Transplant. 2018 Dec;31(12):1293–317.

41. Yoo PS, Umman V, Rodriguez-Davalos MI, Emre SH. Retransplantation of the Liver: Review of Current Literature for Decision Making and Technical Considerations. Transplant Proc. 2013 Apr 1;45(3):854–9.

42. Jain A, Reyes J, Kashyap R, Dodson SF, Demetris AJ, Ruppert K, et al. Long-Term Survival After Liver Transplantation in 4,000 Consecutive Patients at a Single Center. Ann Surg. 2000 Oct;232(4):490–500.

43. Chen GH, Fu BS, Cai CJ, Lu MQ, Yang Y, Yi SH, et al. A single-center experience of retransplantation for liver transplant recipients with a failing graft. Transplant Proc. 2008 Jun;40(5):1485–7.

44. Ploeg RJ, D'Alessandro AM, Knechtle SJ, Stegall MD, Pirsch JD, Hoffmann RM, et al. Risk factors for primary dysfunction after liver transplantation--a multivariate analysis. Transplantation. 1993 Apr;55(4):807–13.

45. Escorsell À, Mas A, Fernández J, García-Valdecasas JC. Limitations of Use of the Noninvasive Clearance of Indocyanine Green as a Prognostic Indicator of Graft Function in Liver Transplantation. Transplant Proc. 2012 Jul 1;44(6):1539–41.

46. Takaya S, Doyle H, Todo S, Irish W, Fung JJ, Starzl TE. Reduction of Primary Nonfunction With Prostaglandin E1 After Clinical Liver Transplantation. Transplant Proc. 1995 Apr;27(2):1862–7.

47. Al-Freah M a. B, McPhail MJW, Dionigi E, Foxton MR, Auzinger G, Rela M, et al. Improving the Diagnostic Criteria for Primary Liver Graft Nonfunction in Adults Utilizing Standard and Transportable Laboratory Parameters: An Outcome-Based Analysis. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg. 2017 May;17(5):1255–66.

48. Biggins SW, Beldecos A, Rabkin JM, Rosen HR. Retransplantation for hepatic allograft failure: prognostic modeling and ethical considerations. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2002 Apr;8(4):313–22.

49. Hwang S, Ahn CS, Kim KH, Moon DB, Ha TY, Song GW, et al. Liver retransplantation for adult recipients. Korean J Hepato-Biliary-Pancreat Surg. 2013;17(1):1.

50. Varotti G, Grazi GL, Vetrone G, Ercolani G, Cescon M, Gaudio MD, et al. Causes of early acute graft failure after liver transplantation: analysis of a 17-year single-centre experience. Clin Transplant. 2005;19(4):492–500.

51. Rosen HR. DISEASE RECURRENCE FOLLOWING LIVER TRANSPLANTATION. Clin Liver Dis. 2000 Aug 1;4(3):675–89.

52. Ravaioli M, Grazi GL, Ercolani G, Cescon M, Varotti G, Del Gaudio M, et al. Efficacy of MELD score in predicting survival after liver retransplantation. Transplant Proc. 2004 Nov;36(9):2748–9.

53. Immordino G, Bottino G, De Negri A, Diviacco P, Moraglia E, Ferrari C, et al. Predictability and Survival in Liver Replantransplantation: Monocentric Experience. Transplant Proc. 2014 Sep 1;46(7):2290–2.

54. Pérez-Saborido B, Menéu-Díaz JC, de los Galanes SJ, Barra V, Fundora Y, Abradelo M, et al. Short- and Long-Term Overall Results of Liver Retransplantation: "Doce de Octubre" Hospital Experience. Transplant Proc. 2009 Jul;41(6):2441–3.

55. Marudanayagam R, Shanmugam V, Sandhu B, Gunson BK, Mirza DF, Mayer D, et al. Liver retransplantation in adults: a single-centre, 25-year experience. HPB. 2010 Apr;12(3):217–24.

56. Markmann JF, Markowitz JS, Yersiz H, Morrisey M, Farmer DG, Farmer DA, et al. Long-Term Survival After Retransplantation of the Liver. Ann Surg. 1997 Oct;226(4):408–20.

57. Bellido CB, Martínez JMÁ, Artacho GS, Gómez LMM, Diez-Canedo JS, Pulido LB, et al. Have We Changed the Liver Retransplantation Survival? Transplant Proc. 2012 Jul;44(6):1526–9.

58. Moon HH, Kim TS, Song S, Shin M, Chung YJ, Lee S, et al. Early Vs Late Liver Retransplantation: Different Characteristics and Prognostic Factors. Transplant Proc. 2018 Nov;50(9):2668–74.

59. Bellido CB, Martínez JMA, Gómez LMM, Artacho GS, Diez-Canedo JS, Pulido LB, et al. Indications for and survival after liver retransplantation. Transplant Proc. 2010 Mar;42(2):637–40.

60. Sun CK, Chen CL, Concejero AM, Wang CC, Wang SH, Liu YW, et al. Retransplantation for End-Stage Liver Disease: A Single-Center Asian Experience. Transplant Proc. 2008 Oct;40(8):2503–6.

61. Yoo H. Retransplantation of liver: Primary graft nonfunction and hepatitis C virus are associated with worse outcome. Liver Transpl. 2003 Sep;9(9):897–904.

62. Montenovo MI, Hansen RN, Dick AAS. Outcomes of adult liver re-transplant patients in the model for end-stage liver disease era: is it time to reconsider its indications? Clin Transplant. 2014 Oct;28(10):1099–104.

63. López MJC, Franco CC, Artacho GS, Gómez LMM, Bellido CB, Martínez JMÁ, et al. Results of Early Liver Retransplantation. Transplant Proc. 2020 Jun;52(5):1486–8.

64. Bittermann T, Shaked A, Goldberg DS. When Living Donor Liver Allografts Fail: Exploring the Outcomes of Retransplantation Using Deceased Donors. Am J Transplant. 2017;17(4):1097–102.

65. Al-Freah MAB, Moran C, Foxton MR, Agarwal K, Wendon JA, Heaton ND, et al. Impact of comorbidity on waiting list and post-transplant outcomes in patients undergoing liver retransplantation. World J Hepatol. 2017 Jul 18;9(20):884–95.

66. Pastacaldi S, Teixeira R, Montalto P, Rolles K, Burroughs AK. Hepatic artery thrombosis after orthotopic liver transplantation: A review of nonsurgical causes. Liver Transpl. 2001;7(2):75–81.

67. Lui SK, Garcia CR, Mei X, Gedaly R. Re-transplantation for Hepatic Artery Thrombosis: A National Perspective. World J Surg. 2018 Oct;42(10):3357–63.

68. Laroche S, Maulat C, Kitano Y, Golse N, Azoulay D, Sa Cunha A, et al. Initial piggyback technique facilitates late liver retransplantation – a retrospective monocentric study. Transpl Int. 2021 May;34(5):835–43.

69. Schielke A, Scatton O, Boelle PY, Perdigao F, Bernard D, Soubrane O, et al. Ischemic-type biliary lesions: A leading indication of liver retransplantation with excellent results. Clin Res Hepatol Gastroenterol. 2019 Apr;43(2):131–9.

70. Chen C, Ke R, Yang F, Cai Q, Liu J, Huang X, et al. Risk factors for recurrent autoimmune liver diseases after liver transplantation: A meta-analysis. Medicine (Baltimore). 2020 May;99(20):e20205.

71. Choe J, Mulligan DC. Liver retransplantation: Recurrent primary sclerosing cholangitis may provide better outcomes. Liver Transpl. 2017 Jun;23(6):730–2.

72. Cholankeril G, Yoo ER, Hu M, Gadiparthi C, Khan MA, Perumpail RB, et al. Rates of liver retransplantation in the United States are declining in the era of direct-acting antiviral agents. J Viral Hepat. 2017 Dec;24(12):1194–5.

73. Belli LS, Perricone G, Adam R, Cortesi PA, Strazzabosco M, Facchetti R, et al. Impact of DAAs on liver transplantation: Major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. J Hepatol. 2018 Oct;69(4):810–7.

74. Young K, Liu B, Bhuket T, Wong RJ. Lower Likelihood of Post-transplant Graft Failure, Death, and Retransplantation in the Era of Direct-Acting Antivirals. J Clin Exp Hepatol. 2020 Dec;10(6):581–9.

75. Ivanics T, Rizzari M, Moonka D, Al-Kurd A, Delvecchio K, Kitajima T, et al. Retransplantation outcomes for hepatitis C in the United States before and after direct-acting antiviral introduction. Am J Transplant. 2021;21(3):1100–12.

76. Croome KP, Mathur AK, Pungpapong S, Lee DD, Moss AA, Rosen CB, et al. Equivalent Outcomes With Retransplantation and Primary Liver Transplantation in the Direct-acting Antiviral Era. Transplantation. 2019 Jun;103(6):1168–74.

77. Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, et al. Characteristics Associated with Liver Graft Failure: The Concept of a Donor Risk Index: Characteristics Associated with Liver Graft Failure. Am J Transplant. 2006 Apr;6(4):783–90.

78. Halldorson JB, Bakthavatsalam R, Fix O, Reyes JD, Perkins JD. D-MELD, a Simple Predictor of Post Liver Transplant Mortality for Optimization of Donor/Recipient Matching. Am J Transplant. 2009 Feb;9(2):318–26.

79. Braat AE, Blok JJ, Putter H, Adam R, Burroughs AK, Rahmel AO, et al. The Eurotransplant Donor Risk Index in Liver Transplantation: ET-DRI: Donor Risk Factors in Liver Transplantation within Eurotransplant. Am J Transplant. 2012 Oct;12(10):2789–96.

80. Pareja E, Cortes M, Hervás D, Mir J, Valdivieso A, Castell JV, et al. A score model for the continuous grading of early allograft dysfunction severity: GRADING EARLY ALLOGRAFT DYSFUNCTION. Liver Transpl. 2015 Jan;21(1):38–46.

81. Agopian VG, Harlander-Locke MP, Markovic D, Dumronggittigule W, Xia V, Kaldas FM, et al. Evaluation of Early Allograft Function Using the Liver Graft Assessment Following Transplantation Risk Score Model. JAMA Surg. 2018 May 1;153(5):436.

82. Avolio AW, Franco A, Schlegel A, Lai Q, Meli S, Burra P, et al. Development and Validation of a Comprehensive Model to Estimate Early Allograft Failure Among Patients Requiring Early Liver Retransplant. JAMA Surg. 2020 Dec 16;155(12):e204095.

83. Rosen H. Validation and refinement of survival models for liver retransplantation. Hepatology. 2003 Aug;38(2):460–9.

84. Linhares MM, Azoulay D, Matos D, Castelo-Filho A, Trivi??o T, Goldenberg A, et al. Liver Retransplantation: A Model for Determining Long-Term Survival: Transplantation. 2006 Apr;81(7):1016–21.

85. Northup PG, Pruett TL, Kashmer DM, Argo CK, Berg CL, Schmitt TM. Donor Factors Predicting Recipient Survival After Liver Retransplantation: The Retransplant Donor Risk Index. Am J Transplant. 2007 Aug;7(8):1984–8.

86. Hong JC, Kaldas FM, Kositamongkol P, Petrowsky H, Farmer DG, Markovic D, et al. Predictive Index for Long-Term Survival After Retransplantation of the Liver in Adult Recipients: Analysis of a 26-Year Experience in a Single Center. Ann Surg. 2011 Sep;254(3):444–9.

87. Brüggenwirth IMA, Werner MJM, Adam R, Polak WG, Karam V, Heneghan MA, et al. The Liver Retransplantation Risk Score: a prognostic model for survival after adult liver retransplantation. Transpl Int. 2021 Oct;34(10):1928–37.