What did the European Liver Transplant Registry bring to liver transplantation?

Jan Lerut1, Vincent Karam2, Valérie Cailliez2, Henri Bismuth2, Wojciech G. Polak3, Bridget Gunson4, Rene Adam2 & for the European Liver, Intestine Transplantation Association (ELITA)

SUMMARY

Since its foundation in 1985, the European Liver Transplant Registry has evolved to become an important tool to monitor the liver transplantation activity in Europe. The vast amount of data collected on 169,473 liver transplantations performed in 153,238 recipients has also resulted in scientific publications. Without doubt, several of these have influenced the daily practice of liver transplantation. This paper gives an overview of the development, the functioning, and the scientific activity of the European Liver Transplant Registry during more than three decades. Indeed, it can be said that the registry helped to advance the practice of liver transplantation not only in Europe but also worldwide.

Transplant International 2020; 33: 1369–1383

Key words
liver transplantation, scientific registry, European Liver Intestine Transplant Association, European Liver Transplant Registry

Introduction

History and Aim

In 1985, the idea arose to collect all data about what was at that time a burgeoning, clinical activity, namely liver transplantation (LT). The idea to exchange knowledge between the pioneering centres in order to evaluate and improve this new treatment in Europe was developed in Paris by the early transplant surgeons, Professors Henri Bismuth (Paris), Roy Calne (Cambridge) and Rudolf Pichlmayr (Hannover); an official collaboration: the European Liver Transplant Registry (ELTR) was born!

The first paper related to LT activity in Europe was published in the September 1987 issue of The Lancet.
Rather superficial information, about demographics, numbers and graft and patient survival concerning 1269 LT performed in 1218 recipients in 32 centres was given [1]. This given information was based on ten simple items only. The 2-year survival reached 41% only. Since then, LT has developed exponentially, and today, 175 centres from 33 countries contribute actively to the registry, and the number of transplantations multiplied by more than 100 and that of centres by five. These numbers reveal that ELTR closely followed the evolution of liver transplantation [1–10]. In contrast to United Network for Organ Sharing (UNOS), ELTR is an international register that has brought many different countries with different linguistic, cultural, political and health care backgrounds and systems together in a common effort.

Thirty years after its foundation, a symposium was organized in Paris to commemorate the birth of this collaboration. One could argue that collecting data about LT in Europe has become unnecessary, and the numbers indeed becoming so large that efficient use of all gathered data could be superfluous and, yes, even useless.

This paper looks back at three decennia focusing on the real impact made by the contributions of and to the registry in the field of liver transplantation medicine.

Governance and sustainability

In 1993, the ELTR became a service of the European Liver and Intestine Transplant Association (ELITA; www.elita.org), a section of the European Society for Organ Transplantation (ESOT; www.esot.org). The governance is an essential part of ELTR needed to ensure appropriate conduct of operations, budget and coherence with ELITA policies. The management of ELTR was revised in 2019 and includes (i) a Governing Board (GB) consisting of five members (ELTR general manager, ELTR data manager, ELITA treasurer, two members of ELITA board and one ESOT executive member), and (ii) a Scientific Committee (SC) consisting of five ELITA board members and the ELTR data manager. The GB organizes 3-monthly teleconferences to discuss budget issues and other governance business issues such as liaising with company or institution hosting the registry and with centres or collectives providing the data; fundraising for the registry activity and provide an annual budget for registry activities. The SC recommends on and supervises study requests; updates the ELTR questionnaire and key-word catalogue; harmonizes data collection; initiates ELTR-ELITA studies; plans publication activity; provides regular ELTR reports; and promotes and develops guidelines to apply for the use of registry data by external bodies such as researchers, nonprofit organizations and pharmaceutical industry.

The ELTR governance model relies on principles and constraints based on its mandate, operating procedures, legal environment and funding sources. Effective collaboration between all parties is needed to ensure both adequacy and quality of collected data. The ELTR performs several activities to strengthen the use of data. Amongst them is the agreement on principles of data sharing between the centres and ELTR and between ELTR and Organ Sharing Organizations (OSOs) and principles of data quality assurance and data control. Principles of data ownership, informed consent and data security are applied in accordance with the General Data Protection Regulation (GDPR).

Sustainability is a common issue discussed in all scientific registry initiatives. Studies conducted with ELTR data may provide an additional source of funding from public or private sectors. Governance principles are therefore proposed by the GB and the SC to facilitate interactions between all parties concerned while preserving the ELTR participants’ scientific independence. For this aspect, quality management is the main activity to provide confidence in the quality of the data that can be generated by ELTR.

The evolution for three decades

The initial choice was to create a limited, easy to fill out and use, questionnaire to get an ‘impression’ about the clinical impact of LT. It became however clear that two major adaptations to the founding bylaws had to be made in order to raise the scientific value: credibility criteria required substantial upgrade of items per transplant to be validated by the scientific ELTR board including hepatologists, intensivists and surgeons and data needed to be audited to strengthen the value of the given messages, especially those focusing on particular aspects of LT.

These modifications were rapidly implemented as shown by the consecutive publications in the 1987 (The Lancet), 2003 (Liver Transplantation), 2012 (Journal of Hepatology) and 2018 (Transplant International) papers dealing with 10,45, 65 and finally more than 100 items per LT performed in 32, 124, 145 and 168 centres belonging to 11,21, 26 and 33 countries. The number of LT continuously rose from 1,269 to a spectacular 147,161 [1,4,5,8,10]!
Audit visits were set up to ensure the reliability of the data. The ELTR audit visits have been continuously conducted since 1998 with, initially 10 randomly selected centres per year up to the year 2010, and five centres per year since then. In total, the ELTR visited 128 centres with good coverage from contributing countries. The concordance between the ELTR questionnaires and patient charts was checked during random visits, led by very experienced persons in LT clinical data handling (Chantal de Reyck, Luis Grande, Olaf Guckelberger, Bridget Gunson, Vincent Karam, Francine Roggen, Baltasar Sobredo and Wolfgang Wannoff) [11,12]. The ELTR completeness rate was 95% and the consistency between charts and ELTR data was 98%. This audit tool enabled the following: (i) a ‘barometer function’, in order to compare the LT activity of Europe to that in other continents; (ii) a ‘benchmark function’, in order to compare activity and outcome between European countries and centres and finally (iii) a ‘scientific function’, in order to study specific diseases as well as donor and recipient related outcomes.

Besides the verification of the routine internal quality process, the audit visits also contributed as an external quality process for the improvement of data bases handling by the respective centres evolving thereby from paper to electronic data capture and the creation of a collaborative link and even ‘team spirit’ building. On top of this, ‘exchange and cross-check’ collaborations were set up with the major OSOs such as National Health Services Blood and Transplant (NHSBT), ‘Organizacion Nacional de Transplantes’ (ONT), ‘Nederlandse Transplantatie Stichting’ (NTS), ‘Agence de Biomédecine’ (ABM), Eurotransplant Foundation (ET), Scandiatransplant and it is ongoing with Centro Nazionale Trapianti (CNT). These close collaborations again aimed at obtaining the highest possible numbers and the highest possible quality of data related to LT activities within Europe. These collaborations also markedly reduced the workload encountered by centres when providing data to different national and international databanks and/or authorities.

All ELTR members have a password protected access to the website and every six months, the data are actualized and put at disposal of the centre in the member area. These data are bundled in six booklets: the ‘Overall, the last 10-years, the adult, the paediatric and the living donor LT (LDLT) booklet. These five booklets contain more than 750 figures that can be used for PowerPoint presentations. Moreover, every centre receives a six-monthly confidential report of its own data and results that can be compared with the whole results of the registry for quality control and to look at potential improvements in case of lower performance [13].

Limitations are a common issue in registry studies. Data quality, reliability, and representativeness have been an everyday concern for the ELTR since its creation in 1986. With this in mind, the ELTR has continuously implemented several procedures and adapted them all along the years to improve quality of data, from collection to statistical analysis. However, biases may persist as for all observational studies; therefore, the interpretation of registry studies must be done with caution. Lost-to-follow-up (LTFU), a real problem in the reported outcomes, is mainly related to the increasing number of transplanted patients and their mobility within and between countries. More than 72% of ELTR data are shared with OSOs who have setup an intensive tracking procedure to minimize the rate of LTFU. The centres entering the remaining 28% of data directly in our platform are regularly invited to consult the online dynamically updated list of queries to solve all discrepancies and to report a recent patient follow-up.

All these efforts resulted in several papers that allowed LT to be benchmarked worldwide in relation to transplant activity and quality. The scientific output was further fostered by the establishment of clear and fair authorship and editing rules developed by the ELTR and ELITA scientific boards. This initiative rapidly proved to be beneficial in terms of scientific activity as exemplified by 68 publications, most of them in high impact factor journals and by a high number of invited lectures, oral or poster communications, at the most important national and international meetings, symposia and workshops. To stimulate these efforts further, all study results are put at the disposal of every centre in form of the famous ‘black slide’ PowerPoint presentations bearing the ELTR and ELITA logos. The evolution of this scientific activity is illustrated by the steady increase of publications (Fig. 1a) and the growing number of citations averaging 21 citations per publication (Fig. 1b). The average impact factor of the 68 publications was 7.7, which places the ELTR between Annals of Surgery and American Journal of Transplantation. The most cited publications per year are presented in Table S1 at the end of the manuscript.

The large amount of collected data generated a unique opportunity to look at different aspects of LT in both adult and paediatric as well as postmortem (PMLT) and LDLT. The whole scientific ELTR-ELITA production can be divided into seven different categories.
Overview papers

These papers give a clear information about numbers, changing indications, evolution of techniques, including LDLT, and mortality and morbidity in all different age groups. This information is important for the transplant community. These different overview papers indicate not only the place of LT with time but also the results obtained in all different acute and chronic liver diseases. They also document a return to oncologic indications, nowadays including both primary and secondary hepatobiliary tumours. Progresses have been remarkable with a steady improvement of patient and graft survival rates by more than 50% [1–10].

Large disease-specific studies

The increasing number of recipients enabled study of the outcome and/or evolution of LT in large patient populations (Table 1). The place of LT in the treatment of acute liver failure, alcoholic cirrhosis, HBV/HDV/HCV related cirrhosis, HIV infected patients, NASH, primary biliary cholangitis, autoimmune hepatitis were examined [14–24]. A hepatocellular cancer study focused on the value of locoregional therapies and the impact of vascular invasion on outcome after transplantation [25,26]. All these papers revealed a clear shift in indications for LT from viral and cholestatic diseases to alcoholic cirrhosis, nonalcoholic steatohepatitis and hepatobiliary cancers. The outlook of patients harbouring HBV/HDV and HCV cirrhotic recipients dramatically improved with the introduction of efficacious direct-acting antiviral medications. The same evolution was seen in HIV positive recipients.

Two papers looked at the outcome in paediatric LT and the evolution of LT in children for malignant tumours [9,27,28].

Rare disease-specific studies

The significant amount of data in the registry gave the exceptional opportunity to study the place and value of LT in the treatment of rare and or orphan disease (defined as up to 6/100,000 p; Table 1). These studies concerned benign and malignant vascular liver diseases (Budd-Chiari syndrome, hereditary haemorrhagic teleangectasia, haemangioendothelioma, haemangiosarcoma, haemangiopericytoma), Caroli disease and syndrome, cystic fibrosis, erythropoietic protoporphyria and Wilson disease [29–37]. The place of LT in the treatment of major liver trauma, adenomatosis, solitary polycystic liver disease, hepatocellular cancer in normal liver, hilar cholangiocarcinoma, secondary colorectal and neuroendocrine metastases were also addressed [38–47]. Every study contained daily practice influencers important to guide clinical activity; these are displayed in Table 1. The influence of such unique studies is very well exemplified by the ELTR-ELITA vascular disease study. These publications were followed by a drastic change in the attitude of the transplant, hepatologic and oncologic communities as can been seen by the progressively rising number of transplanted patients. (e.g. for haemangioendothelioma from 3.4 to 15.3, and for hereditary haemorrhagic teleangectasia from 2.1 to 4.6 LT yearly).

These studies also revealed that a (merely curative) LT should not be withheld in these, frequently, young patients. The futility of LT for haemangiosarcoma had also been clearly demonstrated thereby preserving the scarce allografts for other indications [33].

All papers focusing on smaller and larger disease-specific studies had a major impact on the attitude of the transplant physicians who clearly changed their diagnostic and therapeutic algorithms. That these generated messages were adopted readily by transplant surgeons and by hepatologists is well demonstrated by the

Figure 1 (a) Evolution of number of ELTR-ELITA publications, and (b) sum of yearly citations (web of science as of July 2020).
| First author | Ref. | Year | Study theme | No. patients studied | 5- and 10-year patient survival | 5- and 10-year graft Survival | Messages |
|--------------|------|------|-------------|----------------------|-------------------------------|-------------------------------|----------|
| **Acute liver failure** | | | | | | | |
| Germani G | 14 | 2012 | Acute liver failure | 4903 | 68% | 57% | 1. Outcome markedly improved by period (best 2004–2009)  
2. Combination recipient >50 and donor >60 years has the worst outcome (57% one-year mortality)  
3. Less compliance in paracetamol related failure (more suicide and nonadherence)  
4. Less good results in nonviral aetiology, ABO-incompatible, reduced size graft LT and non-UW preservation solution |
| Krawczyk M | 38 | 2016 | Liver trauma | 73 | 50.7% | 44.9% | 1. Indication exceptional  
2. Grades I to IV and injury severity score <33 are prognostic factors  
3. Major 3-month mortality (42.5%) and graft loss (46.6%)  
4. Major 3-month mortality if grade V trauma (68.8%)  
5. LT with inferior vena cava-sparing has a markedly better outcome  
6. LT without veno-venous bypass is a significant risk factor |
| **Viral disease** | | | | | | | |
| Burra P | 16 | 2013 | HBV/HDV cirrhosis | 5912 | 74% | 70% | 1. Outcome markedly improved by time period  
2. Indication markedly reduced over time (from 24% to 16%)  
3. Indication HBV-HCC markedly increased (from 15.9% to 29.6%)  
4. Outcome markedly better than LT for HCV-cirrhosis  
5. Outcome in HBV-DNA negative and positive patients became similar  
6. Outcome markedly improved in case of HBV-HDV co-infection  
7. Recurrence as cause of death has been significantly reduced (<1%)  
8. HBV-DNA positivity increases risk for HCC development  
9. Long-life antiviral therapy is therefore warranted |
| First author | Ref. | Year | Study theme                        | No. patients studied | 5- and 10-year patient survival | 5- and 10-year graft survival | Messages |
|--------------|------|------|------------------------------------|----------------------|---------------------------------|-------------------------------|----------|
| Belli L      | 17   | 2018 | HCV and direct antiviral agents (DAA) | 12 452               | 65.1% interferon and ribaverine 76.9% DAA | 65% and 76.9% | DAA allow to obtain results similar to LT for HBV cirrhosis |
|              |      |      |                                    |                      |                                 |                               | 1. DAA allow to obtain results similar to LT for HBV cirrhosis |
|              |      |      |                                    |                      |                                 |                               | 2. DAA reduced the indication for LT by 60% (from 21.1% to 10.6%) |
|              |      |      |                                    |                      |                                 |                               | 3. DAA reduced the indication for HCV-HCC by 41% |
|              |      |      |                                    |                      |                                 |                               | 4. DAA significantly reduced the incidence of Deadly recurrence (from 6.3% to 1.2%) |
| Campos-Varela I | 18 | 2019 | HIV infection                      | 658 UNOS and ELTR cohorts | 64.4%                          | 64.4% 3 years | HIV infection only accounts for 0.9% of LT |
|              |      |      |                                    |                      |                                 |                               | 1. HIV infection only accounts for 0.9% of LT |
|              |      |      |                                    |                      |                                 |                               | 2. Patient and graft survival of HIV patients improved over time |
|              |      |      |                                    |                      |                                 |                               | 3. High MELD, HCV co-infection and BMI <21 are risk factors for graft loss |
| Parenchymal disease |      |      |                                    |                      |                                 |                               | 1. Indication for LT significantly increased |
| Burra P      | 15   | 2010 | Alcoholic cirrhosis (ALCI)         | 9880 ALCI 1478 ALCI and viral cirrhosis | 73% 56%                        | 73% 58%                      | 2. Outcome significantly better than for viral and cryptogenic cirrhosis |
|              |      |      |                                    |                      |                                 |                               | 3. HCV co-infection eliminates this advantage |
|              |      |      |                                    |                      |                                 |                               | 4. De novo tumours (13.7%) and cardiovascular events (8%) are the main causes of mortality |
|              |      |      |                                    |                      |                                 |                               | 5. Post-LT oropharyngeal and gastro-intestinal cancers are more frequent |
|              |      |      |                                    |                      |                                 |                               | 6. Death due to suicide (1.3%) more frequent |
|              |      |      |                                    |                      |                                 |                               | 1. Indication increased (from 1.2% to 8.4%) |
|              |      |      |                                    |                      |                                 |                               | 2. Marked raise in LT for NASH-HCC (39.1% of patients) |
|              |      |      |                                    |                      |                                 |                               | 3. Outcome comparable to other indications |
|              |      |      |                                    |                      |                                 |                               | 4. Increased mortality due to infectious (24%) and cardiovascular diseases (5.3%) |
|              |      |      |                                    |                      |                                 |                               | 5. Female recipients >60 years, high Meld and extreme high or low BMI are risk factors |
| Haldar D     | 19   | 2019 | Nonalcoholic steatohepatitis (NASH) | 2741                 | 75% NASH HCC 68.6%             | 75%                          | 1. Indication continuously decreased from 20% to 4% in 30 years |
|              |      |      |                                    |                      |                                 |                               | 2. More effective treatments, e.g. ursodeoxycholic acid |
|              |      |      |                                    |                      |                                 |                               | 3. LT done at higher age (56 years) and Meld score; also more frequent in males (15%) |
| First author | Ref. | Year | Study theme | No. patients | 5- and 10-year patient survival | 5- and 10-year graft Survival | Messages |
|--------------|------|------|-------------|--------------|-------------------------------|-------------------------------|----------|
| Schramm C    | 23   | 2010 | Autoimmune cirrhosis/hepatitis | 828 PBC     | 73% 83%                       | 66% 71%                       | 1. Patient and graft survival rates significantly lower than those obtained in PBC 2. Infection rate is high, especially in patients over 50 years. This incidence is also significantly higher than in PBC recipients 3. Due to the recurrence risk adaptation (reinforcement) of immunosuppressive schemes is advocated despite the higher risk for infections; (immunosuppression schemes were unfortunately not analysed) |
| Heinemann M  | 24   | 2020 | Autoimmune cirrhosis/hepatitis (AIH) | 2515        | 79.4% 70.8%                   | 73.2% 63.4%                   | 1. AIH patients have a significantly lower survival compared to PBC and primary sclerosing cholangitis patients 2. Mortality is related to early (<3 months) fatal infections, including fungal ones 3. Living donor LT does not improve results |
| Vascular disease |     |      |             |              |                               |                               | 1. Allograft recurrence is rare (0.2%) if effective anti-coagulation given 2. Venous thrombosis occurred in 11% of recipients despite anti-coagulation therapy; 41% of them died 3. Pre-LT renal failure and previous (surgical or radiological) shunt are bad prognostic factors |
| Mentha G     | 29   | 2006 | Budd-Chiari syndrome | 248         | 71% 68%                       |                               | 1. Excellent indication for life-threatening disease 2. Indications for LT are cardiac failure, biliary necrosis and portal hypertension 3. Early LT is recommended in symptomatic disease 4. Complete investigation is mandatory to exclude and treat arterio-venous malformations in lung, brain, gastro-intestinal tract 5. Hepatic arterial interventions to be avoided at any price due to high risk of (infected) biliary necrosis 6. Porto-pulmonary hypertension can be reversed by LT 7. Long-term follow-up is necessary because of possible disease recurrence (5%) |
| Lerut J      | 30   | 2006 | Hereditary haemorrhagic teleangiectasia | 40          | 82.5% 82.5%                   | 82.5% 52.5%                   |                                |
| First author       | Ref. | Year | Study theme                                         | No. patients studied | 5- and 10-year patient survival | 5- and 10-year graft Survival | Messages                                                                                                                                                                                                                                                                                                                                 |
|-------------------|------|------|-----------------------------------------------------|----------------------|-------------------------------|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Biliary disease   |      |      |                                                     |                      |                               |                            |                                                                                                                                                                                                                                                                                                                                                                                                          |
| de Kerckhove L    | 34   | 2006 | Caroli disease or syndrome                         | 110                  | 86%                           | 71%                        | 1. Indication in severe cholangitis, bi-lobar localization or suspicion of malignant transformation  
2. Combined liver-kidney transplantation (15%) recommended if associated congenital hepatic fibrosis and renal failure  
3. Renal transplantation is often necessary early in course of disease in case polycystic renal disease is present  
1. LT indicated before severe worsening of respiratory function  
2. Poor respiratory function is the main risk factor  
3. Respiratory function improves after LT due to improved muscular mass and function |
| Melzi ML          | 35   | 2006 | Cystic fibrosis                                     | 57                   | 81.4%                         | NA                         | 1. LT indicated before severe worsening of respiratory function  
2. Poor respiratory function is the main risk factor  
3. Respiratory function improves after LT due to improved muscular mass and function |
| Metabolic disease |      |      |                                                     |                      |                               |                            | 1. LT is lifesaving in a minority of patients with severe (cholestatic) acute or chronic liver failure  
2. Allograft recurrence in majority of grafts (69%; 44% within first year)  
3. Protective light filter necessary to avoid intra-operative burn injuries (25%)  
4. Prolonged ventilation frequently necessary because of motor neuropathy  
5. Stem cell transplantation will be(come) the better treatment |
| Wahlin S          | 36   | 2011 | Erythropoietic protoporphyia                        | 31                   | 66%                           | 66%                        | 1. LT results improve with time  
2. Excellent indication if early diagnosis to avoid acute liver failure  
3. Young age is risk factor |
| Pfister ED        | 37   | 2018 | Wilson disease in children                         | 338                  | 84%                           | 76%                        | 1. Indication for LT is extremely rare (0.03%)  
2. More frequent if underlying Glycogen storage disease IA and if vascular anomalies present  
3. Indication for LT if development of HCC or suspected degeneration  
4. Decision for LT needs to be based on patho-molecular tumour examination  
1. LT is more difficult after previous liver surgery  
2. Liver (cyst) surgery should be avoided at any price |
| Liver tumour – benign |      |      |                                                     |                      |                               |                            | 1. Indication for LT is extremely rare (0.03%)  
2. More frequent if underlying Glycogen storage disease IA and if vascular anomalies present  
3. Indication for LT if development of HCC or suspected degeneration  
4. Decision for LT needs to be based on patho-molecular tumour examination  
1. LT is more difficult after previous liver surgery  
2. Liver (cyst) surgery should be avoided at any price |
| Chiche L          | 39   | 2016 | Adenomatosis                                        | 49                   | 41/49 (83.7%)                 | 76%                        | 1. Indication for LT is extremely rare (0.03%)  
2. More frequent if underlying Glycogen storage disease IA and if vascular anomalies present  
3. Indication for LT if development of HCC or suspected degeneration  
4. Decision for LT needs to be based on patho-molecular tumour examination  
1. LT is more difficult after previous liver surgery  
2. Liver (cyst) surgery should be avoided at any price |
| Van Keimpema L    | 40   | 2011 | Isolated adult polycystic disease                  | 58                   | 92.3%                         | 87.5%                      | 1. LT is more difficult after previous liver surgery  
2. Liver (cyst) surgery should be avoided at any price |
| First author | Ref. | Year | Study theme | No. patients studied | 5- and 10-year patient survival | 5- and 10-year graft survival | Messages |
|--------------|------|------|-------------|----------------------|-------------------------------|-------------------------------|----------|
| **Liver tumour – malignant** | | | | | | | |
| Lai Q | 31 | 2007 | Haemangioendothelioma | 149 | 79.5% | NA | 1. LT offers excellent disease-free survival 2. Limited extrahepatic disease is not a contraindication to LT 3. Hilar lymph node and macrovascular invasion and waiting time (<4 months) are risk factors for recurrence 4. Outcome is related to these risk factors (low vs. high prognostic risk score: 93.9% vs. 38.5% 5-year disease-free survival) |
| Lerut J | 32 | 2017 | | 32 | 74.4% DFS 79.5% 72.8% | | |
| Orlando G | 33 | 2013 | Haemangiosarcoma | 22 | 7.2 ± 2.6 months | NA | 1. LT is an absolute contraindication due to universal rapid (within 6 months) and lethal (within 24 months) recurrence 2. Diagnosis and differential diagnosis with HEHE can be difficult; angiosarcoma patients are much sicker 1. LT generates excellent results in primary as well as recurrent cancer after partial liver resection 2. Milan criteria are not valid in this context; tumour size and differentiation are not associated with survival 3. Macrovascular invasion, hilar lymph node involvement and number of tumours are bad prognostic factors 4. Rescue LT for recurrence after liver resection has a better prognosis if performed after a delay of 12 months (71% vs. 24%) |
| Mergental H | 41 42 | 2012 | Hepatocellular cancer and noncirrhotic, nonfibrotic liver | 105 LT 62 primary rescue | 59% vs. 16% No Macro-VI and LN positivity Primary LT 43% Rescue LT 58% No risk factor 83% | | |
| Pommergaard HC | 25 | 2016 | Hepatocellular cancer and locoregional treatment (LRT) | 3572 LRT 1406 NON-LRT patients | 69.7% NO LRT 65.8% | P: 0.001 | 1. Radiofrequency is the best monotherapy (but selection bias) 2. Outcome improved if radiofrequency and transcatheter chemo-embolization are combined 3. Advantage of locoregional treatment is lost when 3 or more sessions needed |
Table 1. Continued.

| First author | Ref. | Year | Study theme | No. patients studied | 5- and 10-year patient survival | 5- and 10-year graft Survival | Messages |
|--------------|------|------|-------------|----------------------|-------------------------------|----------------------------|----------|
| Pommergaard HC | 26   | 2018 | Hepatocellular cancer and micro- and macrovascular invasion | 9324 | MC and Up-to-7 IN: 79.1–60% | 64.9–43.8% | 1. Vascular invasion is the strongest prognostic factor and is superior to tumour number and diameter  
2. Similar results are obtained in Milan criteria IN or OUT or Up-to-7 IN patients when presenting microvascular invasion  
3. Similar results are obtained in Milan criteria IN or OUT or Up-to-7 IN patients when presenting macrovascular invasions |
| Mantel HT | 43   | 2016 | Hilar cholangiocarcinoma | 105 | Mayo criteria IN vs. 77 OUT patients | MC and Up-to-7 IN: 69.0% and 58.8% | Microvascular invasion  
MC and Up-to-7 OUT: 69.0% and 58.8% | 1. Justification for LT requires a strict selection process  
2. If Mayo criteria (tumour longitudinal size <3 cm; no metastases; no lymph nodes) respected (present in 18% of included patients) outcome after LT is similar to combined neo-adjuvant chemo-radiotherapy and LT (63%)  
3. Selection process seems to be more important than chemo-radiotherapy |
| Le Treut P | 46   | 2013 | Neuroendocrine metastases | 213 | No or one risk factor: 59% OS  
57% DFS  
If 2 or 3 risk factors: 38% OS  
19% DFS | DFS 46% vs. 79% | | 1. LT is a good indication in well selected patients with unresectable NET LM because the only therapy allowing disease-free survival  
2. Simultaneous major abdominal resection, age ≥45 years, hepatomegaly, and poor differentiation (Ki67 >10–20%) are bad prognostic factors  
3. Good results also obtained in case of LT performed in the absence of primary tumour localization or in case of primary tumour resected after LT |
number of LT for some of these diseases (Fig. 2). The average annual number of LT for NET was multiplied by 4.2, that of HEHE by 4.6 and that of ROW by 2.2. In contrast, the average annual number of LT for HAS was reduced by 1.3 times.

**Donor factors in liver transplantation**

Seven papers dealt with specific donor-related factors. Advancing donor age was shown to have a significant adverse influence on graft and patient survival in 4736 HCV recipients; this negative impact starts from 40 years on and increases for each advancing decade of donor age [48].

European Liver Transplant Registry data contributed to the validation of donor risk index (DRI) and balance of risk score (BAR) scores. Two papers looked at the DRI within the Eurotransplant area [49,50] as well as the definition of extended criteria donor (ECD) [51]. The DRI was markedly higher in 5723 patients belonging to the ET-area compared to Organ Procurement and Transplantation Network (OPTN) indicating different donor populations. The ET-DRI, comprising the DRI criteria (donor age, cause of death, split and LT from donors after circulatory death), latest GGT and rescue allocation was the strongest (and better than DRI) predictor of outcome. This finding could be helpful in the allocation process, especially in the weighing of risks involved and to decide whether to or not to accept a specific liver allograft for a specific recipient [49,52].

The use of steatotic liver grafts combined with the BAR score has been analysed by comparing large ELTR and United Network for Organ Sharing cohorts (11.942 and 37.255 recipients respectively) [49]. Livers with less than 30% macro-steatosis can be used without risk adjustment up to a BAR score of 18, but more than 30% macro-steatosis should call for caution and should be accepted only with a BAR score of 9 or less [53].

Another study including 4701 donors did not enable a clear definition of ECD to be made [54].

A study including 42,869 primary LT looked at the long-term efficacy of different preservation solutions in LT [53]. Liver graft preservation with histidine-tryptophan-ketoglutarate (HTK) was shown to be an independent risk factor for graft loss. The 5-year graft survival was much higher with University of Wisconsin, Institute Georges Lopez preservation (IGL-1) and Celsior (70, 68% and 68%) compared to HTK (60%; \( P < 0.0001 \)). In cold ischaemia times over 12 h, these differences became even more pronounced. These results were confirmed after propensity score matching analysis [55–58].
Surgical techniques and liver transplantation

The outcome of left split LT (SLT) was analysed in a series of 15 paediatric recipients. Five-year survival reached 82.9%. Seventy % of grafts were lost within the first three months. Significant risk factors for graft failure included urgent SLT, recipient body weight ≤6 kg, donor age >50 years and increasing cold ischaemic time (CIT) per hour. If these risk factors are considered left split grafts generate particularly good results [59].

A web survey of 65 LT surgeons showed that within the ELTR community there is a large heterogeneity in bile duct handling during organ procurement, preservation and transplantation. Bile duct rinsing, gallbladder removal, the use of preservation solutions, back-table arterial pressure perfusion and use of donor protective interventions varied widely. This heterogeneity is an important part of the development of ischaemic cholangiopathy after liver transplantation [60].

Immunosuppression and liver transplantation

The impact of immediate or prolonged-release tacrolimus was studied using propensity score matching in a large ELTR-cohort including 4367 primary liver transplants performed between 2008 and 2016 [61,62]. The initial results were confirmed in the 2019 study. Prolonged-release tacrolimus confers a significant advantage in relation to long-term outcome compared to the immediate-release form with a 4-year graft survival of 83% (vs. 77%), and patient survival of 85% (vs. 80%). One graft loss in four years was avoided for every 14.3 patients treated with the prolonged form.

Ethical issues in LT

The ethical problems related to informed consent in the use of marginal liver allografts, LT in septuagenarians and LDLT were addressed in short papers [63–65]. Between 1989 and 2006, 19 donors died after a liver donation. LDLT registries such as the one kept by ELTR are and will be fundamental in the development of this technique. The information gathered about LDLT represents another particularly important task of the registry [66,67]. The data are currently edited in separate issues of the ELTR and they give a good picture about the actual status of LDLT in Europe. One dares to hope that this information will lead to a better organization of LDLT centres (not everyone can do!), a condition ‘sine qua non’ to foster this activity in the Western world.

Conclusion

The ELTR is a very valuable tool to monitor LT activities in Europe, and the audited ‘formula’ of the register
permits reliable scientific analysis which are divided into large surveys and patient series studies as well as large and small disease-specific studies. It has contributed to change clinical practice in liver preservation, in post-transplant immunosuppression and in indications of LT for malignant tumours leading, for example, to safe scarce allografts by avoiding futile transplantations and to allow others to have access to a potentially curative treatment.

European Liver Transplant Registry data are also a powerful tool to evaluate and, hopefully, foster living donor liver transplantation activity in Europe. The young generation of transplant doctors should be stimulated to analyse the registry data further generally and scientifically to allow progress in this field of medicine. Thirty years after the foundation of the ELTR, it can really be stated that the registry brought ‘more than something’ to the transplant community not only in Europe but also worldwide. Without the continuous and enthusiastic support of all European liver transplantation centres, collaborators and partners, this endeavour could never have succeeded!

Funding

The authors have declared no funding.

Conflicts of interest

The authors have declared no conflicts of interest.

Acknowledgements

The ELTR thanks all liver transplantation centres who contributed during more than three decades to the data collection and participated in the ELTR-ELITA studies. The ELTR is supported by a grant from Astellas, Novartis, Institut Georges Lopez, Sandoz and logistic support from the Paul Brousse Hospital (Assistance Publique – Hôpitaux de Paris). The Organ Sharing Organizations: the French ABM (Sami Djabbour), the Dutch NTS (Maaike de Wolf), the Eurotransplant Foundation (Marijeke Van Meel), the Spanish RETH (Gloria de la Rosa), the UK-Ireland NHSBT (Michael Daynes) and the Scandinavia-Transplant (Ilse Duus Weinreich) are acknowledged for the data cross-check and sharing with the ELTR.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. ELTR publications with annual number of citations greater than 5 (via Web of Science [WOS]).

REFERENCES

1. Bismuth H, Castaing D, Ericzon BG, et al. Hepatic transplantation in Europe: first report of the European Liver Transplant Registry. Lancet 1987; 330: 674.
2. Gordon RD, Bismuth H. Liver transplant registry report. Transplant Proc 1991; 23: 58.
3. Adam R, Cailliez V, Majno P, et al. Normalised intrinsic mortality risk in liver transplantation: European Liver Transplant Registry study. Lancet 2000; 356: 621. Erratum in: Lancet 2001; 367: 1296.
4. Adam R, McMaster P, O’Grady JG, et al. Evolution of liver transplantation in Europe: report of the European Liver Transplant Registry. Liver Transpl 2003; 9: 1231.
5. Adam R, Lucidi V, Karam V. Liver transplantation in Europe: is there a room for improvement? J Hepatol 2005; 42: 33.
6. Burroughs AK, Sabin CA, Rolles K, et al. 3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. Lancet 2006; 367: 225.
7. Adam R, Hoti E. Liver transplantation: the current situation. Semin Liver Dis 2009; 29: 3.
8. Adam R, Karam V, Delvart V, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry. J Hepatol 2012; 57: 675.
9. McLin VA, Allen U, Boyer O, et al. Early and late factors impacting patient and graft outcome in pediatric liver transplantation: summary of an ESPGHAN Monothematic Conference. J Pediatr Gastroenterol Nutr 2017; 65: e53.
10. Adam R, Karam V, Cailliez V, et al. 2018 Annual Report of the European Liver Transplant Registry (ELTR) – 50-year evolution of liver transplantation. Transpl Int 2018; 31: 1293.
11. Karam V, Gunson Bo, Roggen F, et al. Quality control of the European Liver Transplant Registry: results of audit visits to the contributing centers. Transplantation 2003; 75: 2167.
12. Van der Meulen JH, Jacob M, Copley L. Assessing the quality of data in a transplant registry: the European Liver Transplant Registry. Transplantation 2003; 75: 2164.
13. ELTR websites. public: and professional: www.eltr.orgwww.eltr.eu.
14. Germani G, Theocharidou E, Adam R, et al. Liver transplantation for acute liver failure in Europe: outcomes over 20 years from the ELTR database. J Hepatol 2012; 57: 288.
15. Burra P, Senzolo M, Adam R, et al. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). Am J Transplant 2010; 10: 138.
16. Burra P, Germani G, Adam R, et al. Liver transplantation for HBV-related cirrhosis in Europe: an ELTR study on evolution and outcomes. J Hepatol 2013; 58: 287.
17. Belli LS, Perricone G, Adam 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; 69: 810.

18. Campos-Varela I, Dodge JL, Berenguer M, et al. Temporal trends and outcomes in liver transplantation for recipients with human immunodeficiency virus infection in Europe and United States. Transplantation 2019 [Online ahead of print].

19. Haldar D, Kern B, Hodson J, et al. Outcomes of liver transplantation for non-alcoholic steatohepatitis: a European Liver Transplant Registry study. J Hepatol 2019; 71: 313.

20. Terrault NA, Pageaux GP. A changing landscape of liver transplantation: is HCV is dethroned, ALD and NAFLD take over? J Hepatol 2018; 69: 767.

21. Durand F, Pavesi M, Cheung R. Liver transplantation for non-alcoholic steatohepatitis in Europe: where do we stand? J Hepatol 2019; 71: 240.

22. Harms MH, Janssen QP, Adam R, et al. Trends in liver transplantation for primary biliary cholangitis in Europe over the past three decades. Aliment Pharmacol Ther 2019; 49: 285.

23. Schramm C, Babenhein M, Adam R, et al. Primary liver transplantation for autoimmune hepatitis: a comparative analysis of the European Liver Transplant Registry. Liver Transpl 2010; 16: 461.

24. Heinemann M, Adam R, Berenguer M, et al. Long-term survival after liver transplantation for autoimmune hepatitis – results from the European Liver Transplant Registry. Liver Transpl 2020; 26: 866.

25. Pommeggaard HC, Rostvedt AA, Adam R, et al. Locoregional treatments before liver transplantation for hepatocellular carcinoma: a study from the European Liver Transplant Registry. Transplantation 2018; 101: 531.

26. Pommeggaard HC, Rostvedt AA, Adam R, et al. Vascular invasion and survival after liver transplantation for hepatocellular carcinoma: a study from the European Liver Transplant Registry. HPB (Oxford) 2018; 20: 768.

27. De Ville de Goyet J, Morland B, Czauderna P. More is less: calling for joining forces for rare pediatric liver tumours research. Liver Transpl 2017; 23: 1501.

28. Baumann U, Adam R, Duuvoux C, et al. Survival of children after liver transplantation for hepatocellular carcinoma. Liver Transpl 2018; 24: 246.

29. Mentha G, Giostra E, Majno PE, et al. Liver transplantation for Budd-Chiari syndrome: a European study on 248 patients from 51 centres. J Hepatol 2006; 44: 520.

30. Lerut J, Orlando G, Adam R, et al. Hereditary hemorrhagic telangiectasia: report of the European liver transplant registry. Ann Surg 2006; 244: 854.

31. Lerut JP, Orlando G, Adam R, et al. The place of liver transplantation in the treatment of hepatic epithelioid hemangioendothelioma: report of the European liver transplant registry. Ann Surg 2007; 246: 949.

32. Lai Q, Feys E, Karam V, et al. Hepatic epithelioid hemangioendothelioma and adult liver transplantation: proposal for a prognostic score based on the analysis of the ELTR-ELITA Registry. Transplantation 2017; 101: 555.

33. Orlando G, Adam R, Mirza D, et al. Hepatic hemangiosarcoma: an absolute contraindication to liver transplantation – the European Liver Transplant Registry experience. Transplantation 2013; 95: 872.

34. De Kerckhove L, De Meyer M, Verbaandert C, et al. The place of liver transplantation in Caroli’s disease and syndrome. Transpl Int 2006; 19: 381.

35. Melzi ML, Kelly DA, Colombo C, et al. Liver transplant in cystic fibrosis: a poll among European centers. A study from the European Liver Transplant Registry. Transplant Int 2006; 19: 726.

36. Wahlin S, Stal P, Adam R, et al. Liver transplantation for erythropoietic protoporphyria in Europe. Liver Transpl 2011; 17: 1021.

37. Pfister ED, Karch A, Adam R, et al. Predictive factors for survival in children receiving liver transplants for Wilson’s disease: a cohort study using European Liver Transplant Registry Data. Liver Transpl 2018; 24: 1186.

38. Krawczyk M, Graeber C, Karam V, et al. Liver transplantation for haemochromatosis: a study from the European Liver Transplant Registry. Transplantation 2016; 100: 2372.

39. Chiche L, David A, Adam R, et al. Liver transplantation for adenomatosis: European experience. Liver Transpl 2016; 22: 516.

40. Van Keimpema L, Nevens F, Adam R, et al. Excellent survival after liver transplantation for isolated polycystic liver disease: a European Liver Transplant Registry study. Transpl Int 2011; 24: 1239.

41. Mergenthal H, Porte RJ. Liver transplantation for unresectable hepatocellular carcinoma in patients without liver cirrhosis. Transpl Int 2010; 23: 662.

42. Mergenthal H, Adam R, Ericzon BG, et al. Liver transplantation for unresectable hepatocellular carcinoma in normal livers. J Hepatol 2012; 57: 297.

43. Mantel HT, Westerkamp AC, Adam R, et al. Strict selection alone of patients undergoing liver transplantation for hilar cholangiocarcinoma is associated with improved survival. PLoS One 2016; 11: e0156127.

44. Foss A, Adam R, Daland S. Liver transplantation for colorectal liver metastases: revisiting the concept. Transpl Int 2010; 23: 679.

45. Hoti E, Adam R. Liver transplantation for primary and metastatic liver cancers. Transpl Int 2006; 21: 1107.

46. Le Treut YP, Gregoire E, Klemmner J, et al. Liver transplantation for neuroendocrine tumours in Europe-results and trends in patient selection: a 213-case European liver transplant registry study. Ann Surg 2013; 257: 807.

47. Bonacorsiti-Riani E, Lerut JP, Liver transplantation and vascular tumours. Transpl Int 2010; 23: 686.

48. Mutimer DJ, Gunson B, Chen J, et al. Impact of donor age and year of transplantation on graft and patient survival following liver transplantation for hepatitis C virus. Transplantation 2006; 81: 7.

49. Blok JJ, Braat AE, Adam R, et al. Validation of the donor risk index in orthotopic liver transplantation within the Eurotransplant region. Liver Transpl 2012; 18: 112.

50. Braat AE, Blok JJ, Putter H, et al. The Eurotransplant donor risk index in liver transplantation: ET-DRI. Am J Transplant 2012; 12: 2789.

51. Braat AE, Blok JJ, Rahmel AO, et al. Incorporation of donor risk into liver allocation algorithms. Am J Transplant 2013; 13: 524.

52. Burroughs AK, Marelli L, Cholangitas E, et al. Towards a better liver transplant allocation system. Liver Transpl 2007; 13: 935; author reply.

53. Dutkowski P, Schlegel A, Slankamenac K, et al. The use of fatty liver grafts in modern allocation systems: risk assessment by the balance of risk (BAR) score. Ann Surg 2012; 256: 861.

54. Silberhumer GR, Rahmel A, Karm V, et al. The difficulty in defining extended donor criteria for liver grafts: the Eurotransplant experience. Transpl Int 2013; 26: 990.

55. Adam R, Delvart V, Karam V, et al. Compared efficacy of preservation solutions in liver transplantation: a long-term graft outcome study from the European Liver Transplant Regist. Am J Transplant 2015; 15: 395.

56. Adam R, Cailliez V, Karam V. Evaluation of HTK preservation solutions in liver transplantation: a long-term propensity-based analysis of outcome from the European Liver Transplant Registry. Am J Transplant 2017; 17: 585.
57. Adam R, Delvart V, Karam V. Reply to letter regarding compared efficacy of preservation solutions in liver transplantation: a long-term graft outcome study from the European Liver Transplant Registry. *Am J Transplant* 2015; 15: 3274.

58. Adam R, Cailliez V, Segev D, Karam V. A Systematic review and meta-analysis of cold in situ perfusion and preservation of the hepatic allograft: working toward a unified approach. *Liver Transpl* 2018; 24: 1142.

59. Angelico R, Nardi A, Adam R, et al. Outcomes of left split graft transplantation in Europe: report from the European Liver Transplant Registry. *Transpl Int* 2018; 31: 739.

60. Meurisse N, Monbaliu D, Berlakovich G, et al. Heterogeneity of bile duct management in the development of ischemic cholangiopathy after liver transplantation: results of a European Liver and Intestine Transplant Association survey. *Transplant Proc* 2019; 51: 1926.

61. Adam R, Karam V, Delvart V, et al. Improved survival in liver transplant recipients receiving prolonged-release tacrolimus in the European Liver Transplant Registry. *Am J Transplant* 2015; 15: 1267.

62. Adam R, Karam V, Cailliez V, et al. Improved survival in liver transplant patients receiving prolonged-release tacrolimus-based immunosuppression in the European Liver Transplant Registry (ELTR): an extension study. *Transplantation* 2019; 103: 1844.

63. Bruzzone P, Giannarelli D, Adam R. A preliminary European Liver and Intestine Transplant Association-European Liver Transplant Registry study on informed recipient consent and extended criteria liver donation. *Transplant Proc* 2013; 45: 2613.

64. Karam V, Delvart V, Adam R. Is liver transplantation justified in septuagenarians? *Le Courrier de la Transplantation*, 2013; XIII - n° 3 - 2013: 88–95.

65. Bruzzone P, Balla A, Quaresima S, et al. Comparison of two questionnaires on informed consent in marginal donor liver. *Transplant Proc* 2016; 48: 359.

66. Bramstedt KA. Living liver donor mortality: where do we stand? *Am J Gastroenterol* 2006; 101: 755.

67. Trotter JF, Adam R, Lo CM, Kenison J. Documented deaths of hepatic lobe donors for living donor liver transplantation. *Liver Transpl* 2006; 12: 1485.