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REVIEW

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

Jan Lerut[1], Vincent Karam[2], Valérie Cailliez[2], Henri Bismuth[2], Wojciech G. Polak[3], Bridget Gunson[4], Rene Adam[2] & for the European Liver, Intestine Transplantation Association (ELITA)

1 Institut de Recherche Expérimentale et Clinique (IREC), Université catholique de Louvain, Brussels, Belgium
2 European Liver Transplant Registry, INSERM U 935, APHP Hôpital Paul Brousse, Université Paris-Saclay, Villejuif, France
3 Division of Hepatopancreatobiliary and Transplant Surgery, Department of Surgery, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
4 Liver Unit and National Institute of Health Research Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust, University of Birmingham, Birmingham, UK

Correspondence
Prof. Em. Jan Lerut MD, PhD, FACS, Institut de Recherche Expérimentale et Clinique (IREC), Université Catholique Louvain (UCL), Avenue Hippocrates 10, 1200 Brussels, Belgium.
Tel.: +32 475 859504;
fax: +3216463436;
e-mail: jan.lerut@uclouvain.be

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.

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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.

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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), 'Organisacion 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.

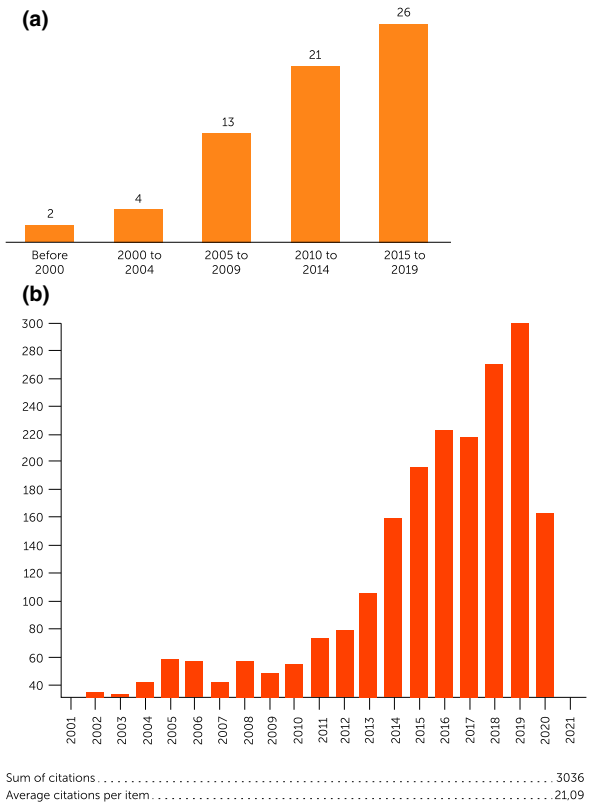

Figure 1 (a) Evolution of number of ELTR-ELITA publications, and (b) sum of yearly citations (web of science as of July 2020).

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

Table 1. Messages generated by the ELTR-ELITA studies.

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% 63%	57% 50%	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% 67% HBV-HCC 68% 61%	70% 63% HBV-HCC 65% 58%	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, long-life antiviral therapy is therefore warranted

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
Belli L	17	2018	HCV and direct antiviral agents (DAA)	12 452	65.1% interferon and ribaverine 76.9% DAA 3 years		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% 3 years	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							
Burra P	15	2010	Alcoholic cirrhosis (ALCI)	9880 ALCI 1478 ALCI and viral cirrhosis	73% 56%	73% 58%	1. Indication for LT significantly increased 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
Haldar D	19	2019	Nonalcoholic steatohepatitis (NASH)	2741	75% NASH HCC 68.6%		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
Autoimmune disease							
Harms MH	22	2019	Primary biliary cholangitis (PBC)	6026	NA	NA	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%)

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
Schramm C	23	2010	Autoimmune cirrhosis/hepatitis	828 1584 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							
Mentha G	29	2006	Budd-Chiari syndrome	248	71% 68%		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
Lerut J	30	2006	Hereditary haemorrhagic teleangiectasia	40	82.5% 82.5%	82.5% 52.5%	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%)

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
Biliary disease							
de Kerckhove L	34	2006	Caroli disease or syndrome	110	86% 76%	71% 68%	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
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							
Wahlin S	36	2011	Erythropoietic protoporphyria	31	66% 66%		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
Pfister ED	37	2018	Wilson disease in children	338 (<18 years; median 14 years)	84% 81%	76% 71%	1. LT results improve with time 2. Excellent indication if early diagnosis to avoid acute liver failure 3. Young age is risk factor
Liver tumour – benign							
Chiche L	39	2016	Adenomatosis	49	41/49 (83.7%) Median follow-up 108 months	Recurrent HCC (6%)	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
Van Keimpema L	40	2011	Isolated adult polycystic disease	58	92.3% 88%	87.5% 83%	1. LT is more difficult after previous liver surgery 2. Liver (cyst) surgery should be avoided at any price

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
Liver tumour – malignant							
Lai Q Lerut J	31 32	2007 2017	Haemangioendothe- lioma	149	79.5% 74.4% DFS 79.5% 72.8%	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
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
Mergental H	41 42	2012	Hepatocellular cancer and noncirrhotic, nonfibrotic liver	105 LT 62 primary 43 rescue	59% vs. 16% No Macro-VI and LN positivity Primary LT 43% Rescue LT 58% No risk factor 83%		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%)
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 transarterial 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% MC and Up-to-7 OUT: 64.9–43.8% Microvascular invasion MC and Up-to-7 IN/ OUT: 69.0% and 58.8% Macrovascular invasion MC and Up-to-7 OUT: 39.6%		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 28 Mayo criteria IN vs. 77 OUT patients	32% PS 59% vs. 21%	DFS 46% vs. 79%	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 47	2013	Neuroendocrine metastases	213	52% DFS 30% 2004–2009 No or one risk factor: 59% OS 57% DFS If 2 or 3 risk factors: 38% OS 19% DFS		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

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
Foss A	44	2008	Colorectal metastases	50	18%		1. LT allows to obtain good results in very well selected patients 2. Majority of patients were lost because of nononcologic reasons 3. Nine (18%) patients survived more than 5 years 4. Selection to be refined by inclusion of tumour markers, Kras; Braf, Ki67 etc.

DAA, direct antiviral agents; DFS, disease-free survival; HCC, hepatocellular cancer; LT, liver transplantation; MC, Milan criteria; OS, overall survival.

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 at 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

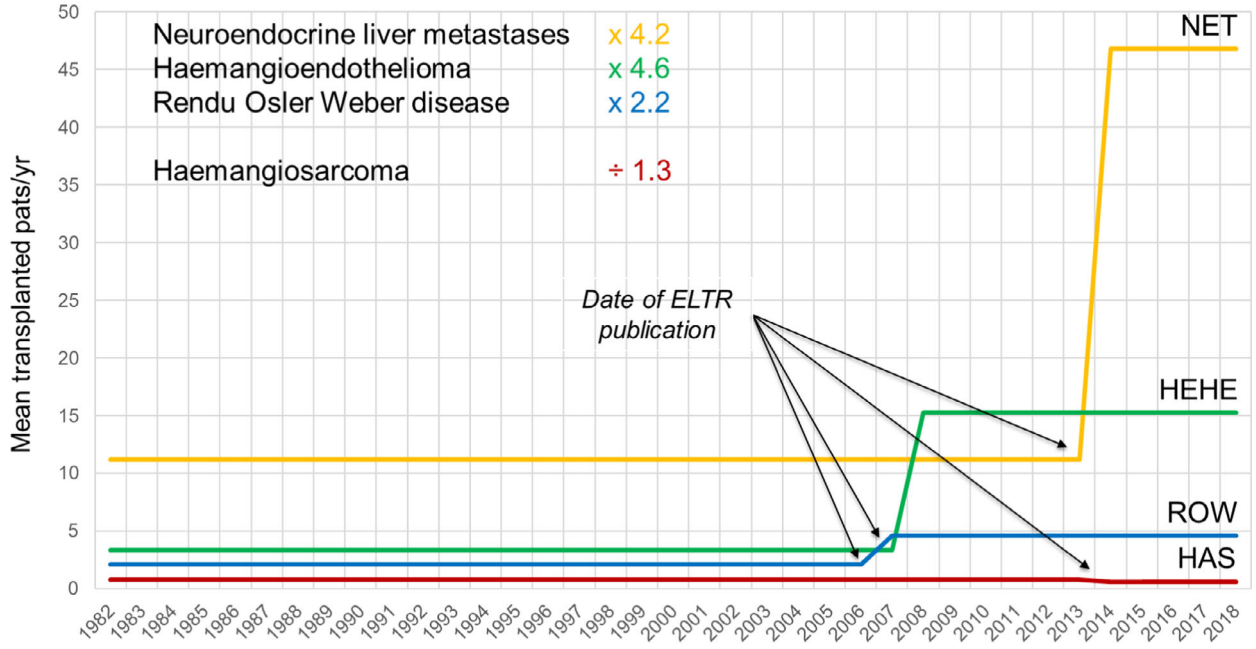

Figure 2 Impact of ELTR-ELITA studies of rare diseases on clinical practice. HAS, haemangiosarcoma; HEHE, haemangioendothelioma; NET, neuroendocrine liver metastases; ROW, Rendu–Osler–Weber disease.

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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!

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Conflicts of interest

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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]).

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