Dutch multidisciplinary guideline on Achilles tendinopathy

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TITLE:

European Liver Transplant Registry: donor and transplant surgery aspects of 16,641 liver transplantations in children.

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Additional Material File

A- Complementary analysis (2 Tables and 23 figures)

B- List of all European Centers who contributed to ELTR for the analyzed data.

Footnote 1

* All four authors contributed equally for first authorship.

† For the complete list of contributing centers, see Additional material B.

Keywords: Pediatric liver transplantation; Innovative techniques; Survival rate; Registries; Europe; Graft survival

List of abbreviations

ELTR:	European Liver Transplant Registry
PLT:	Pediatric liver transplantation
LT:	Liver Transplantation
FS:	full-size (liver)
RL	reduced liver
RSG	right split graft
LSG	left split graft
LD	living donor
LDLT	Living donation Liver Transplantation

DCD	Donors after circulatory death
DRWR	Donor weight/recipient weight ratio
D/R	Donor/recipient (ratio or match)
PMD	post-mortem donor
LLG	Left liver graft

Conflict of interest

The authors declare there is no conflict of interest concerning this manuscript.

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Author's contributions

- Jean de Ville de Goyet: first authorship, research design, data analysis and interpretation, principal co-investigator, writing, editing and review of manuscript, and co-editing figures.
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- All other authors participated in data acquisition.

ABSTRACT.

Background & Aims: The European Liver Transplant Registry (ELTR) has collected data on liver transplant procedures performed in Europe since 1968.

Approach & Results: Over a 50 years period (1968 – 2017), clinical and laboratory data were collected from 133 transplant centers and analyzed retrospectively (16,641 liver transplants in 14,515 children). Data were analyzed according to 3 successive periods (A: before 2000, B: 2000 to 2009, and C: since 2010), studying donor and graft characteristics, and graft outcome. The use of living donors steadily increased from A to C [A: n=296 (7%), B: n=1131 (23%) and C: n=1985 (39%); P=0.0001]. Overall, the 5-year graft survival rate has improved from 65% in group A to 75% in group B (p<0.0001), and to 79% in group C (B vs C, p<0.0001).

Graft half-life was 31 years, overall; it was 41 years for children who survived the first year after transplant. The late annual graft loss rate in teen-agers is higher than children aged < 12 years, and similar to that of young adults. No evidence for accelerated graft loss after age 18 year was found.

Conclusions: Pediatric liver transplantation has reached a high efficacy as a cure, or treatment, for severe liver disease in infants and children. Grafts that survived the first year had a half-life time similar to standard human half-life. Transplantation before or after puberty may be the pivot-point for lower long-term outcome in children. Further studies are necessary to re-visit some old concepts regarding transplant benefit (survival time) for small children, the role of recipient pathophysiology versus graft aging, and risk at transition to adult age.

TEXT

INTRODUCTION

Pediatric liver transplantation (PLT) started the whole history of liver transplantation with the first report, in 1968 (1), of a successful transplant in a child (i.e., the first patient discharged with a functioning liver, in fact). Within 50 years, liver transplantation (LT) has evolved from an experimental to a extraordinarily successful standard treatment, with numerous changes in the medical, anesthesiologic and surgical aspects of care. LT is nowadays proposed as a cure to a steadily increasing number of patients.

To analyze PLT as a therapeutic option with a focus on the clinical characteristics of the service, changes over time and outcomes, we retrospectively analyzed the collected data of the European Liver Transplant Registry (ELTR - www.eltr.org). ELTR is a database that collects a defined set of clinical and surgical parameters on transplantation, patient and outcome: the registry is unique in that it has collected information on transplantation in Europe from 1968 until the present day.

METHODS

Data were extracted from ELTR for retrospective analysis. The ELTR database collects a defined set of clinical and surgical parameters on transplantations, patients and their outcomes. This was done prospectively with the objective of supporting detailed analyses. The registry is unique in that it has collected information on transplantations in Europe from 1968 until now. Data is entered into the registry by European liver transplant centers (currently 168 centers from 31 countries), on a voluntary basis (initially retrospectively but prospectively from 1985 onwards). Follow-up information on each patient and each transplant is provided by the centers, and the accuracy of data is monitored retrospectively by ELTR staff at regular intervals for quality and reliability.

Study population

All children (< 18 years) registered in ELTR for PLT performed between May 1968 and December 2017 were selected for this analysis, with no exclusions. Data were pseudo-anonymized and a pre-specified limited set of data on donor, graft, transplant and outcome was collected. To guarantee a minimum follow-up of one year, data were collected from patients transplanted up to Dec. 31, 2017.

Study design and analysis plan

In order to analyze trends and changes, three successive periods of time were defined as follow: -1- November 11, 1968 to December 31, 1999 (group A), -2- January 1, 2000 to December 31, 2009 (group B), and -3-. January 1, 2010 to December 31, 2017 (group C). For analysis and discussion, we

considered the first group (A) to be the “historical group”, with group C describing the current clinical practice. Although group A covered a larger period (31 years), groups B and C roughly corresponded to the last two decades, and the 3 groups were similar in the number of transplantations performed (A: n=5,518 transplants in 4,482 children, B: n=5,688 transplants in 4,972 children, C: n=5,435 transplants in 5,061 children).

Finally, we compared graft survival of various age groups at LT, including adult age groups: for the latter group, ELTR data of patients registered at ELTR between 1968 and Dec. 31, 2017, for liver transplantation as adults (age ≥ 18 years - N=123,967) were used.

ELTR data collection does not include dedicated information about the transfer of care from pediatric to adult services or the actual transition process to adult care. To estimate the effect of tranbsition, we have chosen to (arbitrsrily) set the transition age at 18 years. The large size of the cohort may allow this approximation for estimating the effect of transition, but we do emphasize that we do not have individual transition ages of the patients.

Data management and statistical analyses

As ELTR staff conduct retrospective random checks at all centers at regular intervals (external audit is part of the quality control procedures for ELTR data since 1998), censoring due to lost follow-up documentation in ELTR was considered minimal. The last internal ELTR quality control analysis (January 2021) showed that, the percentage of missing values was 11 (0 - 55) when all variables were taken into account, while it was 4 (0 -18) when restricted to the 23 core variables. Checking missing data in the extracted dataset confirmed a random distribution (this was observed with various data types). Lost-to-follow-up rate within 5 years was 10% (4% before 2000 and 14% between 2000 and 2009)(period after 2010 was not taken into account as data were acquired in early 2018 and too many patients had not completed 5 years after LT.

Only completed data were used for statistical analysis with no data imputation. Categorical variables were summarized as frequencies and percentages, and groups were compared by chi-squared test, as appropriate, and Fisher’s exact tests. Kaplan–Meier analysis was used to estimate graft survival stratified by conditions; statistical analyses were performed using the log-rank test with StatView SAS Version 9.1.3 Enterprise Guide version 5.1 (Copyright© 2012 by SAS Institute Inc., Cary, NC, USA). Significance was accepted with a P value <0.05 and 95% confidence.

RESULTS

During the study period, 16,641 PLT were performed and consisted of 14,515 first PLT and 2,126 re-transplantations (Suppl. Figure S1). In the last decade (group C), PLT were performed at the rate of around 650 per year in the ELTR area.

Of all PLT, 25.4% were performed in children aged less than 1 year at the time of transplant, 37.1% in children aged 6 to 12 years, 18.0% in children aged 6 to 12 years, and 19.5% in children aged 12 and above (teen-agers). In line with the epidemiology of liver disease in children, the indications for LT in teen-agers were significantly different to that of children <12 years (Table 1).

1. Donor and graft characteristics

Overall, full-size (FS), reduced livers (RL), split grafts (SG), and grafts from living donors (LD) represented 43%, 8%, 25% and 24% of the whole series, respectively. In contrast to LT in adults, domino transplants and graft use from donors after circulatory arrest are rare in PLT, representing only 0.5 and 0.1% of the whole cohort, respectively (Figure 1-A).

There was a definitive change of clinical practice over the three groups (Figure 1-A), with FS livers being the predominant graft type before 2000 (70%) and LD grafts representing the single largest group in most recent years (40%). The number of split grafts used for PLT increased from n=450 (10%) before 2000 to n=1,666 (34%) between 2000 and 2009, but has slightly decreased to n=1,478 (29%) since 2010.

Overall, only 38% of grafts used for PLT were from pediatric donors (<18 years of age at procurement), with a clear reduction in graft use from pediatric donors over time – from 2,138 (59%) before 2000, to 1,204 (24%) since 2010 (Suppl. Figures S2 and S3). Thus overall, most grafts (62%) had been obtained from adult donors, which over time were increasingly used, from 41% in group A, to 65% in group B, and currently 76% in group C. Interestingly, the use of FS liver grafts procured from adult donors for PLT has decreased much over time (group A: 71%, group B: 35% and group C: 26**%**) and is currently replaced by other graft types (Split and LD - Suppl. Figure S4). Although group C corresponds to a predominant use of grafts from LD, a move towards using older donors was also observed in RL and SG (Suppl. Figures S2-4).

Ischemia time varied between graft types - as one would expect with different techniques and different logistical needs and technical limitations (Suppl. Figure S5). The proportion of grafts from brain death donors (DBD), with an ischemia time >12 hours reduced from 24.5% in group A, to 14.1% in group B and to 8.2% in group C (Suppl. Figure S5). In fact, ischemia time reduced for each graft type between group A and group C ($p<0.0001$; Suppl. Figure S5).

Using part of a liver instead of a FS liver graft is largely driven by the respective weights of donor and recipient. According to a decline in the use of pediatric donors over time, most liver grafts in group B and C were from large donors. While transplants in teen-agers were mostly with FS through the whole series (76% of LT in > 12 years old) (Table 1, Suppl. Figures S6-7), LT with LD and SG were the predominant graft types (75% of LT) used in recipients under the age of 6. In the intermediate age group (6 to 12 years old), the use of FS grafts has reduced with time, from 75% in group A, to 35% in group C (Figures 1, Suppl. Figures S6-7).

2. Developments in living donation

Living donation for PLT (LDLT) has increased significantly over time, providing 1.1%, 14.7% and 30.9% of all grafts in groups A, B and C, respectively (Figure 1-A) (Suppl. Figures S4-7). LDLT has expanded steadily in transplantation of infants and young children with biliary atresia (n=182, n=591 and n=867 in groups A, B, and C, respectively). Yet, LDLT also contributed to expanding the numbers of PLT in metabolic diseases (n=24, n=149 and n=316 in groups A, B, and C, respectively). Interestingly, over time LDLT has also more frequently been used in older and larger children (Suppl. Figures S6-7).

Sixty-seven centers (50% of ELTR centers) have performed at least 1 LDLT in the whole study period, but there was a large case-load variation between centers; 33 centers (49%) performed less than 5 LDLT/year as an average; 11 centers performed 5 to 10 cases/year, and 23 centers more than 10 cases/year. Overall, more than 50% of the LDLT experience has been concentrated in only 16 of the ELTR centers (12%), and 92% of all LDLT activity has been concentrated in 7 of 30 European countries (23%). Higher experience with technical variants (split and LD) was associated with significantly better outcome (Figure 2).

3. Graft outcome

Overall, 5-year graft survival has improved with time, from 65% in group A to 79% in group C (P<0.0001) (Figure 1–B). Comparing graft outcome since 2010 showed a similar 5-year graft survival for FS (79%), Split (79%) and LD (79%); only RL grafts were associated with a significantly lower 5-year graft survival (69%; data not shown; P<0.001) (Figure 2, Suppl. Fig S8). Outcome of split and LD was found to be significantly better in centers with a larger average case volume (performing more than 5 of these transplants per year) (Figure 2).

This analysis confirmed a worse outcome in the smallest transplant recipients; in the last group (C), infants (age <1year) had a 5-year graft survival of 76%, what is significantly lower than that of children aged 1 to 6 (who have the best outcome: 82% 5-year graft survival) (Suppl. Figure S9). A detailed analysis showed similar findings for each given graft type (Table 2).

Ischemia time (Suppl. Table S1, Suppl. Figure S5 and S10) was confirmed as an important correlate with graft outcome, with an overall graft survival rate of 73% at 5 years, when ischemia time was <6 hours, compared with 63% when ischemia time was >12 hours (Suppl. Figure S10).

4. Transplantation of grafts after reduction of the liver size or procured from donors after circulatory death.

Reduced livers have been used less frequently over time – from 541 to 407 and only 195 in groups A, B and C, respectively (9.8%, 7.2% and 3.6% of the transplantations in each era, respectively) (Figure 1-A, Suppl. Figures S4,5,7).

Grafts procured from donors after circulatory death (DCD) (previously known as non-heart-beating donors) were the rarest graft type (n=86 / 0.5% of all donors) (Suppl. Figures S4 and 7); of these 86 donors, 57 were children (66%) and 10 were > 40 years of age (including 2 > 60 years old). The use of RL decreased over time, but the use of DCD increased over time, although the actual percentage remained low (29 in group B and 57 in group C - 1% of all group C donors) (Figure 1-A). Most DCD livers were transplanted full-size (53/86 = 62%), and 14/86 (16%) DCD livers were used after reduction of parenchymal mass. The outcome of DCD grafts has been good (96% and 93% graft survival at 1 and 5 years, respectively); because DCD donors represent a very small fraction of all LT, this subgroup was not analyzed further, nor has it been compared to other subgroups (Figure 1, Suppl. Figures S4,6 and 7).

5. Donor to recipient match

Graft type varied between age groups; three quarters of grafts used in infants were reduced, split or LD; these graft types were also used in two thirds of children aged 1-6 years, - while three quarters of transplants in children >12 years of age used full-size livers (Table 1, Suppl. Figures S4 and S7).

A younger donor age was associated with favorable results in general (Suppl. Figures S8 and S12); particularly in the case of split or FS grafts where results were significantly better with pediatric donors and with those aged 18-40 years. Although the use of older donors was associated with poorer outcome - in particular for split liver grafts - there was no significantly worse outcome when DBD grafts from older donors were used to prepare reduced-liver or LDLT.

The graft weight being not registered in ELTR in more than 55% of LT, a graft-to-recipient-weight ratio could not be analyzed to estimate the size (mis)match between donor and recipient. As high donor BMI is a negative selection criterion for many teams in Europe (2), donor BMI was found to be within the “healthy weight range” (BMI 18 to 25) for most donors (Suppl. Figure S11). Donor BMI was available for 75% of LD and 92% of Split grafts, and mean BMI was <25 in 80% of these donors (BMI <30 in 98% of donors). For that reason, the ratio “donor weight/recipient weight” (DRWR) was considered appropriate as a substitute. Our analysis showed a progressive increase of the DRWR when comparing FS, right split grafts, RS, left split grafts and LD (Table 3, Suppl. Figure S13). Two interesting observations were made: 1- LDLT was associated with the largest ratio, larger even than left split grafts, and 2- there was a trend for selecting better size-matched donors throughout the whole study period, resulting in significant differences between groups, for each graft type except those from LD (Table 3, Suppl. Figure S13). Overall, the number of donors with BMI >30 kg/m2 is small in this

series and did not allow a satisfactory comparison. The analysis confirmed that grafts from donor with a BMI< 26 kg/m^2 were associated with long graft survival (Suppl. Figure S11).

6. Re-transplantation

Re-transplantation was necessary in 2126 cases (Suppl. Figures S17-20): of these 2126, 1813 (85%) were performed within the pediatric age range, and 304 (14%) when recipients were over 18 years of age (mean ± SD interval of time between transplants: 11.8 ± 7.1 yrs). In the latter group, chronic rejection was the leading indication (41%), while vascular or biliary problems and disease recurrence accounted for only 4%, 10% and 10% of the indications to retransplant, respectively. This distribution of indications was largely different to what was observed in the group retransplanted within pediatric age range, where the main indications were vascular problems and early graft dysfunction or non-function.

Overall, the need for re-transplantation in children has reduced with time (P <0.0001) – from 23.1% (N=1036) in group A, via 14.4% (N=716) in group B, to as low as 7.5% (N=374) in group C (Suppl. Figures S17-20). Graft loss due to primary non-function, rejection and general causes reduced, but re-transplantations for vascular problems slightly increased (N= 210 (4.7%), 240 (4.8%) and 370 (7.4%) in groups A, B and C, respectively (Suppl. Figures S17-20).

7. Liver graft half-life and graft loss according to recipient age

We calculated the half-life of liver grafts used for PLT using the whole ELTR pediatric cohort. The calculation was needed because of the 10-year graft survival above 70% since 2000, and the relatively short follow-up for those transplanted in groups B and C. Overall, the calculated graft half-life was 31 years (Suppl. Figures S21 A). However, the slope of the survival curve is much steeper during the first year after LT, compared to what it is later (Figure 5, Suppl. Figures S21 A). Indeed, the graft half-life of those who survived the first year (conditional 1-year survival) was estimated to be 41 years (Suppl. Figures S21 B).

Interestingly, the half-life is shorter (21 years) for those transplanted as teen-agers (age 12 and above) (Figure 3), while it is 32 years in children aged <12 at LT (Figure 3 A). Moreover, the latter difference is also present upon analysis of FS grafts only (half-life: 21 and 31 years, for >12 and <12 years at LT, respectively) (Figure 3 B). In patients >12 and <12 years at LT, indications for LT and causes of graft failure were significantly different (Table 1). The moment of graft loss was different with the majority of graft loss occurring beyond 6 months post-LT in teen-agers (61%) compared to children <12 years of age at transplantation (47%; P <0.0001) (Table 1).

Although most grafts were lost within the pediatric age range (half of these being lost during the first year after LT), 25% of graft loss occurred after transition to adult age (18 years and above). The dynamics of graft loss was however much different in that the annual incidence mirrored the LT

annual activity during the pediatric age, while in contrast, the incidence of loss after transition increased sharply after 2010 (Figure 4 A).

To study further this phenomenon further, same transplant and graft loss data were analyzed as cumulative longitudinal numbers and presented in a semi-logarithmic fashion (Figure 4 B); this analysis and presentation confirmed the difference in graft loss during pediatric or adult ages and showed that graft loss after transition proceeds at a regular, rather constant pace, while graft loss before age 18 years follows LT activity.

Since teen-agers had a rather different patient profile (epidemiology, causes of graft loss, timing of graft loss), and a shorter graft half-life, we finally compared their graft survival with that of various groups by age at LT, including the adult age range (Figure 5). The long-term graft survival is very similar between children transplanted at age <6 years and those aged 6 to 12 years, but the survival in the group 12 to 18 years of age is more alike to that of adults between 18 and 45 years of age at transplantation (Figure 5).

DISCUSSION

Over the last 5 decades, ELTR has systematically collected data on virtually all LT performed in most European countries: data acquisition quality has been monitored prospectively which has made its dataset so valuable and unique. This 50-year experience in pediatric liver transplants (PLT) is really second to no other series in the literature in term of total number of patients, and time-span: the largest surveys available in literature are currently about 1911 PLT/2011-2018 (Society of Pediatric Liver Transplantation (SPLIT))(3), 8,982 PLT/2000-2015 (United Network for Organ Sharing (UNOS))(4), 2,085 PLT/1989-2015 (Japanese Liver Transplantation Society registry)(5) and a ten year review of activity (around 6000 PLT) by the Scientific Registry of Transplant Recipients (SRTR)(6). The abundance of data confirms that ELTR is a unique source of data and offers quite formidable possibilities for researchers interested in more granular analysis in the future. Studying the evolution of liver transplantation over a 50-years span was the main objective of this analysis. A second objective was to present a 360-degree view of the ELTR content – to stimulate interest for further analyzing this extraordinary reservoir of data. Objectives were reached and novel observations are brought forward in this paper.

As this registry data covers LT over a significantly prolonged period, the calculated half-life of liver grafts transplanted in children was 31 years: this is 2 - 3 times longer than reported half-lives of livers in adults within UNOS and SRTR (4,6), but it is very similar to that reported by Bowring et al. who analyzed 13,442 pediatric LT from SRTR (7), and found that the observed 30 years graft survival was 45,5% for LT performed between 1987 and 1996, and predicted 30 years graft survival was 56,7% for LT between 1997 and 2006. Furthermore, extrapolating from the overall ELTR data, for children who survived the first year, graft half-life could be estimated to be as much as 41 years (half

the current life-expectancy of humans in the world - https://ourworldindata.org/grapher/life-expectancy)), emphasizing the uniqueness of pediatric liver transplantation as the solid organ most likely to survive after transplant potentially supporting a normal life-span for the recipient. For children who are transplanted today, given that the short-term survival of the graft has improved compared to previous decades, it is likely that the transplant-benefit in term of survival is even greater, and that the graft half-life is longer than 31 years. Although this is a mathematical calculation -with human factors of compliance, social integration or psycho-social issues not taken into account- it overall definitively supports the use of LT as a cure for children and infants.

The pediatric population that undergoes an LT, however, is not homogenous – with a clear division between younger children and teen-agers. The graft half-life is shorter for those transplanted at or above age 12 (half-life: 21 years), compared to younger patients (graft half-life: 32 years) (Figure 3). Dharnidharka et al. found similar figures in these 2 age-groups (for patient, not graft, survival) in SRTR database (8), as well as Ekong et al. in UNOSC database (9). Our present ELTR study confirms that late outcome after LT in teenagers is lower compared to younger children and provides evidence that the two groups differ significantly for the indications for LT and the causes of graft failure (Table 1). From an epidemiological point of view, and compared to the younger ones, teen-agers are transplanted more frequently for metabolic or immune-mediated liver disease, and for more aggressive types of malignancies; all these have in common a higher risk of recurrence and/or associated co-morbidities. Overall, the teen-ager group has a profile similar to that of 18-45 year old patients (10), and they share with the latter group a similar graft outcome and graft half-life time (Figure 5).

Overall, age at LT was the strongest determinant of long-term outcome. Nevertheless, independently of the age at LT, all graft survival curves show an important but equal early graft loss (first semester/year after LT); this represents around 20% of initial graft loss - in any age group. This early important loss is present in all age groups, while the graft loss then follows a different line that is a much shallower slope, with remarkable characteristics: after the first year, the annual loss is not a curve flattening with time, but it is a straight line (i.e. a constant decrease rate), with a steeper slope with increasing age at LT, over the whole range of ages at LT. (Figure 5). The slope of the graft loss increases over the age groupsfrom an annual 0.94% (children < 6 years) to 4.17% for patients > 70 years at LT (Figure 5). This observation suggests that the recipient characteristics a the time of LT (such as age, disease, condition and other issues) are very important as determinants for the long-term outcome.

Another interesting aspect is that the slope is equal for children < 6 years of age, and those aged 6 - 12 years, while it is also equal for teen-agers (12-18 years) and young adults (18 – 45 years old). Based on clinical indications (Table 1) and on previous observations, it can be hypothesized that for biological, pathophysiological, behavioural and possibly immunological reasons, the long-term graft

prognosis of teenagers is similar to that of young adults and more different than that of children below 12 years. Puberty or differences in indications for transplantation may contribute to a different graft outcome and this could be true for all organ types (8). It seems worth exploring to address the possible role of puberty re-shaping the immune system as well to further analyze the mechanism(s) underlying the differentlong-term graft loss rates of those transplanted as a teen-agers or as a 6-12 year old.

As stated above, ELTR does not include specific data about the transition of care. To allow estimation of the the effect of transfer of care, we arbitrarily set the transition age was set at precisely 18 years, acknowledging that this does not reflect exactly the real world, Nevertheless, the large size of the cohort may still allow to regard 18 years as an approximation Based on the chosen 18 years as time of transition, transition of care towards adult services -*per se*- (specifically, the treatment before or after 18th birthday) did not seem directly associated with higher graft loss. Contradiction remains in litterature (11,12) and this needs further dedicated studies. As the initial development of LT was exponential, a huge cohort (around 6000) of children (mostly aged < 6 years) had been transplanted in a short period, between 1985 and 1992 (Suppl. Figure 22: A). As this cohort became adult in the period 2000-2010 (Suppl. Figure 22: B), one would have expected (if transition is associated with higher graft loss) a rapid increase in graft loss in the group of patients 18 years of age and above (red line in Suppl. Figure 22**)**. However, no such rapid increase is observed around that period of time. We believe this might suggest that the transfer of care is not *per se* associated with a higher rate of complications.

We observed that the number of grafts lost annually in those children turned adults started rising rapidly in last decade: though the absolute numbers remained low (Suppl. Figure 22**)**. An continuous (and steadily steeper) increase of the annual number of graft loss is however what can be expected in this age group (> 18 years),because this is an open-end category, with increasing number of patients that have been transplanted at pediatric ages. It should nevertheless be realized that a constant rate of graft loss applies to each patient entering this adult cohort. Figure 4 clearly shows,using a semi-logarithmic scale, a straight line of grafts lost after the age of 18 years, which a procentually stable rate.

Overall, graft survival has significantly improved in ELTR, with 5-year graft survival improving from 65% to 79% over the years. The latter result is slightly below the 82% 5-year overall graft survival published in the recent reports based on SRTR data (Scientific Registry of Transplant Recipients) (6,7). SRTR series are remarkable by a high proportion of PLT using FS from pediatric donors (82,1% in 1987-1996 (7), 62.4% in 2016-2018 (6)). Using FS grafts offers some advantages (logistically, technically, and possibly functionally) compared to technical variants (13), but technical variants have been a necessity in Europe to face a severe shortage of FS from pediatric donors already for decades. The latter grafts are technically more demanding and carry a slightly higher graft loss rate,

but their large use has allowed to meet the pediatric organ demand - resulting in dropping pre-transplant mortality rates to very low figures (1 to 3 children/year in Eurotransplant, France-Transplant or Italy) (14,15). This was a major advantage compared to other allocation systems, in that it offered a chance of LT to most candidates – though at the price of a slightly higher graft loss. On the contrary, the SRTR cohort (6) is also remarkable in its long waiting times, the intense use of exception scores (peaking at 74.2% in 2018), and the high pretransplant death rates (overall, 6.5 deaths per 100 waitlist-years in 2017-2018 - peaking at 17.1 deaths per 100 waitlist-years in 2017-2018 for candidates < 1 year of age). This real problem has been pointed by many authors in literature (16-18).Though it is difficult to compare the two cohorts, it is likely that in term of “intent-to treat option” for children who are listed as candidates for LT, the European strategy is preferable and that real overall outcome is similar in both continents. This might deserve complementary in-depth analysis in the future (16-20).

Although a better outcome has been reached over the 50-year period, there has been little gain at both short and long term in each of last two decades. This observation suggests that the transplant community is approaching the intrinsic limit of transplantation as a cure, and that PLT has come of age. As analysis still points at the first 12 months after LT, as the time for the highest graft loss annual rate, there may remain a space for improvement. Most grafts losses during the first year are directly related to the operation, from primary tecnical problems and to related secondaries including sepsis and liver dysfunction. It has been clearly pointed out by many authors that the post-transplant surgical complications and/or the need for a reoperation in children are the most significant factors predicting patient and graft loss within 6 months after PLT (18-22). We present a significant association between case volume size of a center and its performance, with a significantly lower graft survival in centers performing less than 5 transplants per year (Figure 2): although it is not applicable strictly to every reality and clinical context, large transplant centers have the advantage of volume and experience, combined with well-developed and expert multidisciplinary teams. Surgical expertise and technical refinements are likely to have a direct impact on improving early outcome, and strong multidisciplinary teams are essential to adequately support the patient both peri-operatively, and at the long-term. Centralisation of care towards strong multidisciplinary teams may be the way forward in order to reach a new level; this would be a societal and medical choice for the future.

In conclusion,
the present analysis of the ELTR database details the world's largest collected experience in PLT and provides novel information on current trends in Europe. The most striking aspects are the increasing use of living donors as a source of grafts and the consolidation of the satisfactory outcomes observed since the year 2000 and the continuing improvement of PLT as a cure. Graft half-life in transplanted

patients reaching 1 year survival with the transplanted liver is now estimated to be 41 years, being half of a healthy human lifespan.

In comparison to children <12 years of age, the risk of graft loss is higher for those transplanted as teen-agers. A novel observation is that in many aspects, transplanted teen-agers outcome is more alike to that of young adults transplanted between 18 and 45 years than to that of 0-12 year-olds.

Overall, the analysis provided important insights into understanding transplant care in Europe, but it also brought to light many interesting observations to guide the clinicians globally, though it does not necessarily provide all the answers yet. The presented data and analyses are therefore also a call for further studies and possible expansion of the ELTR dataset.

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LEGENDS

Table 1

Title *Patients characteristics by age (at transplant) groups (below or above age 12 years).*

Table 2

Title *Graft survival according to recipient age and graft type since 2010*.

Table 3

Title *Donor/Recipient Weight ratio according to graft types and groups*

Legend * group A vs group C (DBD: Brain dead donor, LDLT: Living donor liver transplantation)

Figure 1

Title *Evolution of type of graft (A) and overall graft survival (B) by group*.

Legend Graft type use evolved over time, with full-size liver grafts representing the major type before year 2000, and left liver lobe from living donors being the most common single type since 2010. Graft survival has significantly improved over time.

Figure 2

Title *Graft survival according to graft type since 2010 (A) and according center experience (number of split and living donor graft transplanted annually) (B)*.

Figure 3

Title *Graft Half-life after transplantation in children according age group (below or above (included) age 12 years): all graft types (A) and full-size liver grafts only (B)*

Figure 4

Title *Graft loss along time (1975 – 2017) according age at loss (before or after (included) age 18 years.*

Figure 5

Title *Graft survival according age at transplantation, and Graft loss annual rate for conditional one-year survival. Based on ELTR data of patients registered at ELTR between 1968 and Dec. 31, 2017, for liver transplantation, either as children (age ≥ 18 years - N=*16,641*), or as adults (age ≥ 18 years - N=123,967).*

Table 1

Patients characteristics by age (at transplant) groups (below or above age 12 years).

Age at Transplant (years)	***< 12 yrs***	***12 - 17 yrs***	***p***
Type of graft			
Full-size liver	35%	**76%**	<0.0001
Reduced Liver	**9%**	4%	
Split liver graft	**29%**	11%	
Living Donor liver graft	**27%**	9%	
Indication			
Acute liver failure	10%	**19%**	<0.0001
Congenital biliary disease	**53,4%**	12,4%	
Cholestatic diseases other	6%	**10%**	
Cirrhosis	6%	**18%**	
Malignancies	6%	6%	
Metabolic disease	13%	**25%**	
Other liver diseases	4%	9%	
Cause of failure			
Sepsis	23%	21%	<0.0001
Other liver disease	7%	4%	
Other organ system cause	32%	33%	
Technical (transplant)	18%	10%	
Disease recurrence	1%	3%	
Rejection	5%	8%	
Social-related	0,4%	2%	
De-novo (oncological)	6%	8%	
De-novo (viral)	0,05%	0%	
Not available	9%	11%	
Graft loss occurrence			
Early (Before 6 months after LT)	**53%**	39%	<0.0001
Late (After 6 months after LT)	47%	61%	
Before recipient aged 18 years	**84%**	49%	<0.0001
After recipient aged 18 years	16%	51%	

Table 2 - Donor weight /Recipient weight ratio according to graft types and groups

Donor weight /Recipient weight Ratio	group A: Before 2000	group B: 2000 to 2009	group C: Since 2010	P*
DBD Full size	2.2 ± 2.2	1.7 ± 1.5	1.5 ± 1.3	<0.0001
DBD right split liver	2.6 ± 2.6	1.6 ± 0.9	1.5 ± 0.9	0.002
DBD reduced graft	4.3 ± 3.0	4.7 ± 3.0	5.5 ± 3.7	0.003
DBD left split liver	6.0 ± 3.6	7.0 ± 3.7	6.7 ± 3.4	0.005
LDLT	7.8 ± 3.9	7.4 ± 4.3	7.2 ± 4.7	ns

* group A vs group C (DBD: Brain dead donor, LDLT: Living donor liver transplantation)

Table 3 - Graft survival according to recipient age and graft type since 2010.

Recipient age	Type	N	Graft survival		P
			1 year	5 years	
Less 1 yr	Split	423	80%	74%	0.002
	Living	818	87%	80%	
1-6 yrs	Split	706	88%	83%	0.522
	Living	772	87%	81%	
6-12 yrs	Split	235	86%	77%	0.514
	Living	227	82%	76%	
12-18 yrs	Split	114	83%	78%	0.683

Figure 1

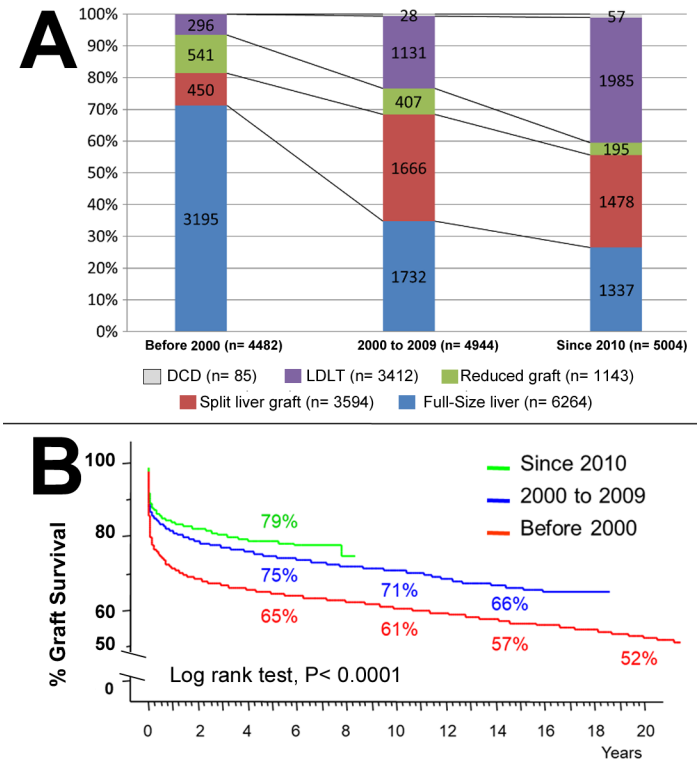

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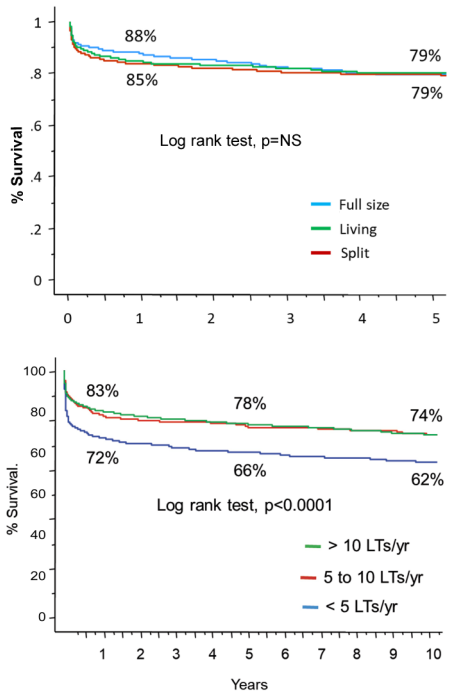
Figure 2



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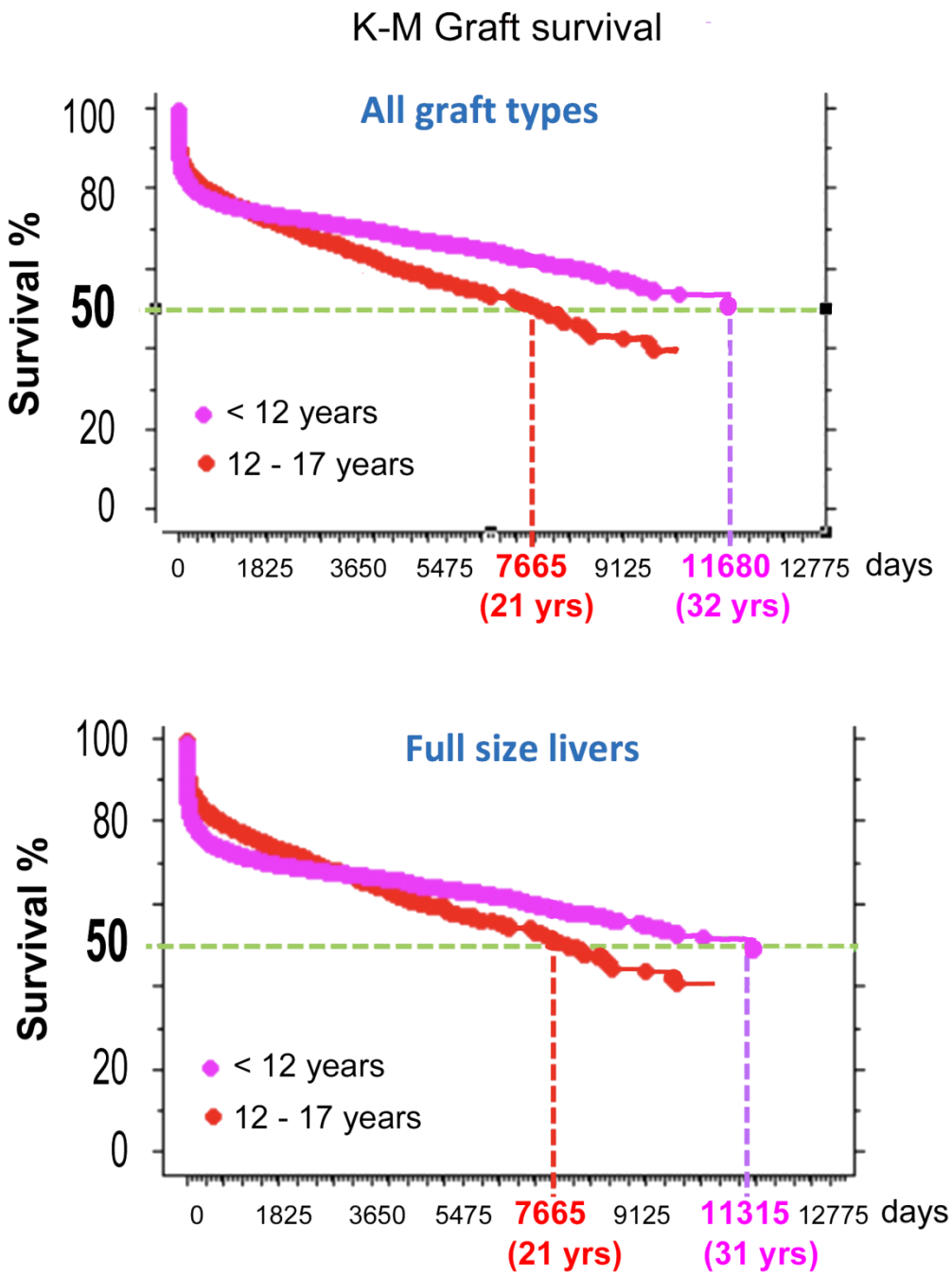

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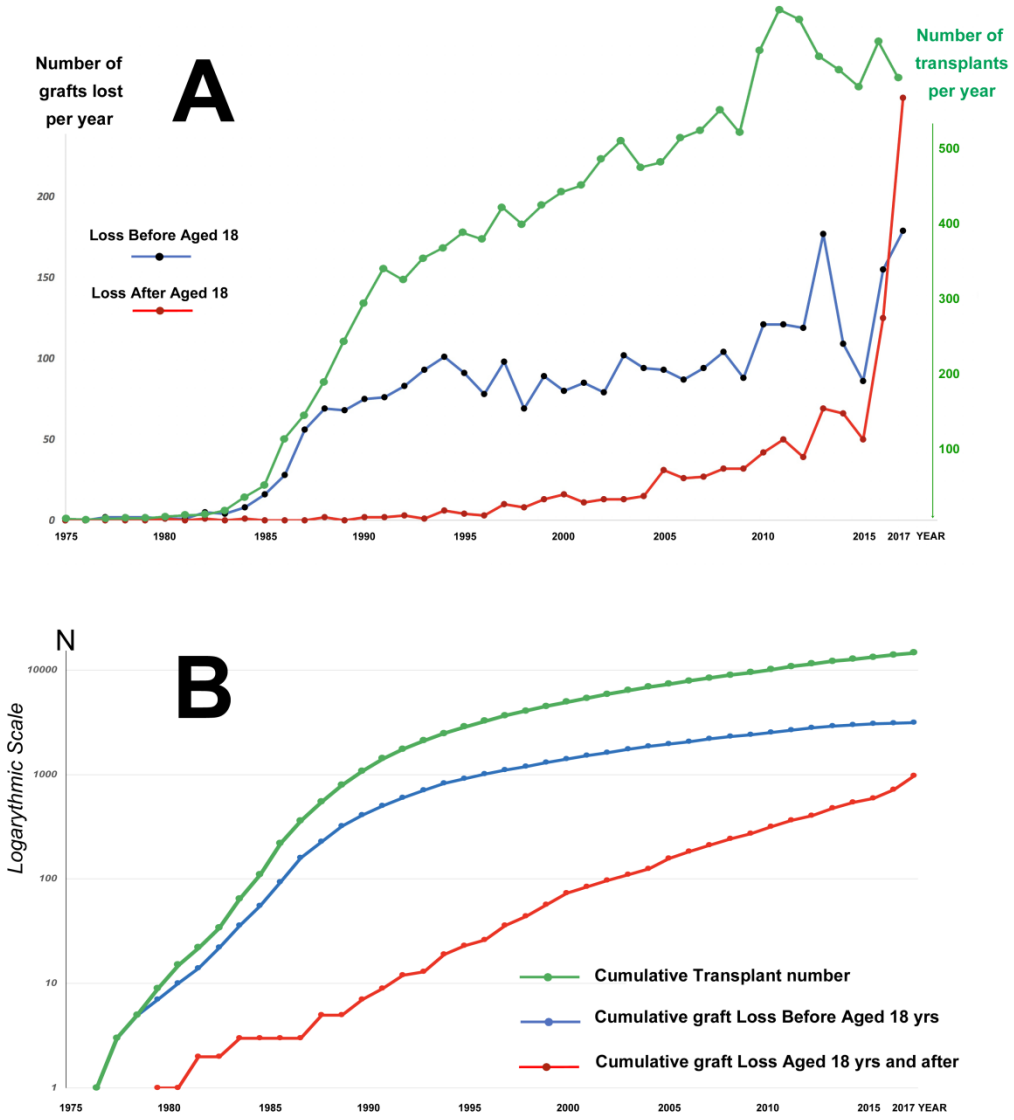

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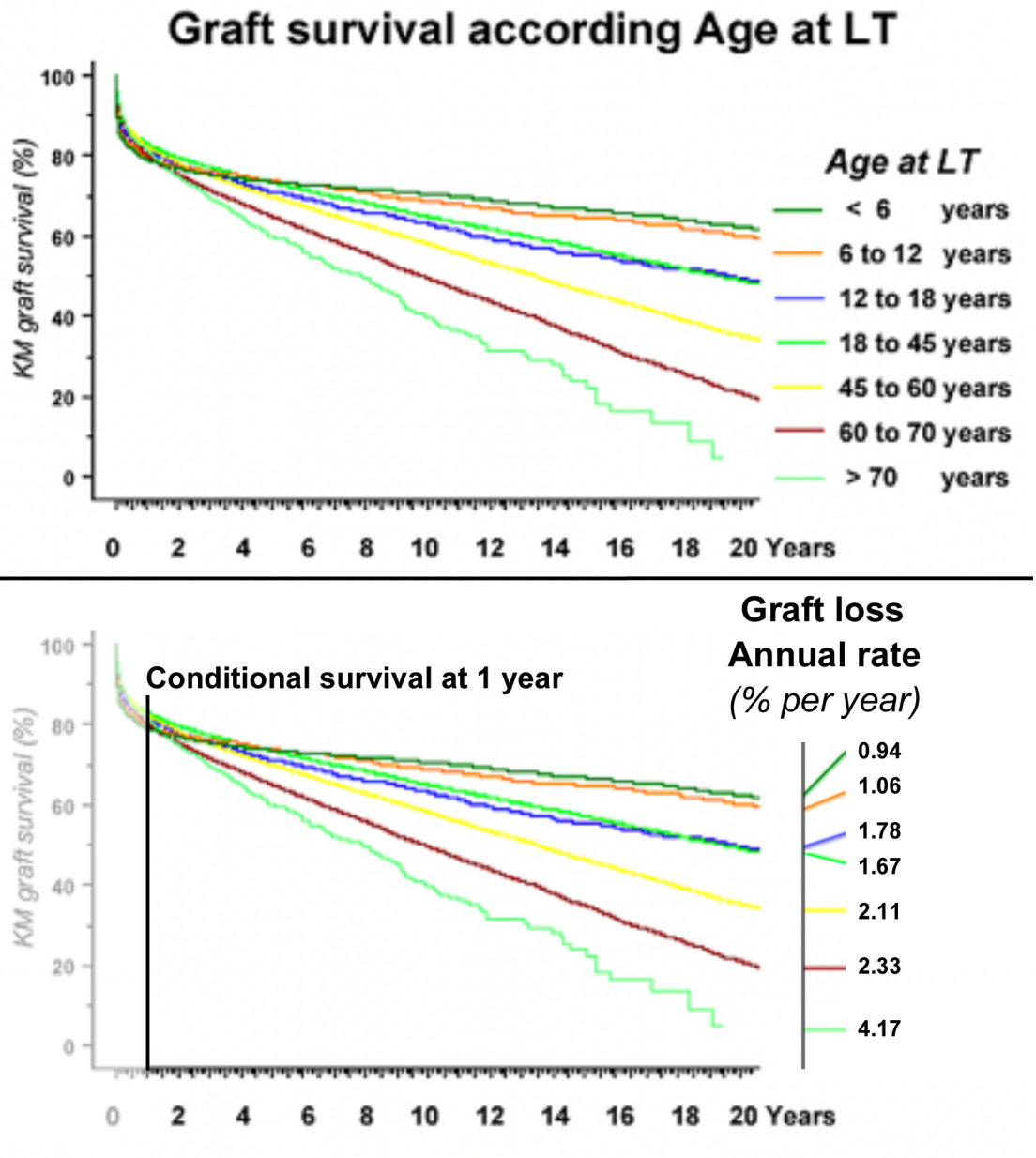
Figure 5



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