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ORIGINAL ARTICLE

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

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Abbreviations: BMI, body mass index; DBD, donors after brain death; DCD, donors after circulatory death; DRWR, donor weight/recipient weight ratio; ELTR, European Liver Transplant Registry; FS, full-size (liver); LD, living donor; LDLT, living donation LT; LT, liver transplantation; PLT, pediatric LT; RL, reduced liver; SG, split graft; SRTR, Scientific Registry of Transplant Recipients; UNOS, United Network for Organ Sharing.

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Abstract

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

Approach and Results: Over a 50-year 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 three successive periods (A, before 2000; B, 2000–2009; 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 versus 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 teenagers is higher than that in children aged <12 years and similar to that of young adults. No evidence for accelerated graft loss after age 18 years 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 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 revisit 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.

INTRODUCTION

Pediatric liver transplantation (PLT) started the whole history of liver transplantation (LT) 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, LT evolved from an experimental to an 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). The ELTR is a database that collects a defined set of clinical and surgical parameters on transplantations, patients, and outcomes: the registry is unique in that it has collected information on transplantation in Europe from 1968 until the present day.

MATERIALS AND METHODS

Data were extracted from the 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 are entered into the registry by European LT centers (currently 168 centers from 31 countries) on a voluntary basis (initially retrospectively but prospectively from 1985 onward). ELTR is compliant with RGPD rules (https://gdpr-info.eu) and centers are responsible for collecting informed consent from all patients before registration of any patient—waiving thereby the need for ELTR to collect the consents. 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 the ELTR for PLT performed between May 1968 and December 2017 were selected for this analysis, with no exclusions. Data were pseudoanonymized, and a prespecified limited set of data on donor, graft, transplant, and outcome was collected. To guarantee a minimum follow-up of 1 year, data were collected from patients transplanted up to December 31, 2017.

Study design and analysis plan

In order to analyze trends and changes, three successive periods of time were defined, as follows: (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 three groups were similar in the number of transplantations performed (A, *n* = 5518 transplants in 4482 children; B, *n* = 5688 transplants in 4972 children; C, *n* = 5435 transplants in 5061 children).

Finally, we compared graft survival of various age groups at LT, including adult age groups: for the latter group, data of patients registered at the ELTR between 1968 and December 31, 2017, for LT 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 transition, we have chosen to (arbitrarily) 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 (an external audit has been part of the quality-control procedures for ELTR data since 1998), censoring due to loss to follow-up documentation in the 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 data set confirmed a random distribution (this was observed with various data types). The loss-to-follow-up rate within 5 years was 10% (4% before 2000 and 14% between 2000 and 2009; the 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 (SAS Institute Inc., Cary, NC). Significance was accepted at $p < 0.05$ and 95% confidence.

RESULTS

During the study period, 16,641 PLTs were performed, consisting of 14,515 first PLTs and 2126 retransplantations (Figure S1). In the last decade (group C), PLTs were performed at a rate of around 650 per year in the ELTR area.

Of all PLTs, 25.4% were performed in children aged <1 year at the time of transplant, 37.1% were in children aged 6–12 years, 18.0% were in children aged 6–12 years, and 19.5% in children aged 12 and above (teenagers). In line with the epidemiology of liver disease in children, the indications for LT in teenagers were significantly different from those for children <12 years (Table 1).

Donor and graft characteristics

Overall, full-size (FS), reduced livers (RLs), split grafts (SGs), and grafts from living donors (LDs) 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 1A).

There was a definitive change of clinical practice over the three groups (Figure 1A), 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 SGs used for PLT increased from *n* = 450 (10%) before 2000 to *n* = 1666 (34%) between 2000 and 2009 but has slightly decreased to *n* = 1478 (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 2138 (59%) before 2000 to 1204 (24%) since

TABLE 1 Patient characteristics by age (at transplant) groups (< or ≥12 years)

Age at transplant (years)	<12 years	12–17 years	*p*
Type of graft			
FS liver	35%	**76%**	<0.0001
RL	**9%**	4%	
SG	**29%**	11%	
LD 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%	
Socially related	0,4%	2%	
De novo (oncological)	6%	8%	
De novo (viral)	0,05%	0%	
Not available	9%	11%	
Graft loss occurrence			
Early (<6 months after LT)	**53%**	39%	<0.0001
Late (>6 months after LT)	47%	61%	
Before recipient age 18 years	**84%**	49%	<0.0001
After recipient age 18 years	16%	51%	

2010 (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 (SG and LD; Figure S4). Although group C corresponds to a predominant use of grafts from LDs, a move toward using older donors was also observed in RL and SG (Figures S2–S4).

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

Using part of a liver instead of an FS liver graft is largely driven by the respective weights of the donor and recipient. According to a decline in the use of pediatric donors over time, most liver grafts in groups B and C were from large donors. While transplants in teenagers were mostly with FS through the whole series (76% of LTs in those > 12 years old) (Table 1; Figures S6 and S7), LT with LD and SG were the predominant graft types (75% of LTs) used in recipients under the age of 6. In the intermediate age group (6–12 years), the use of FS grafts has reduced with time, from 75% in group A to 35% in group C (Figure 1; Figures S6 and S7).

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 1A; Figures S4–S7). 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 PLTs 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 (Figures S6 and S7).

Sixty-seven centers (50% of ELTR centers) have performed at least one LDLT in the whole study period, but there was a large caseload variation between centers: 33 centers (49%) performed fewer than five LDLTs/year as an average, 11 centers performed 5–10 cases/year, and 23 centers performed >10 cases/year. Overall, >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 seven of 30 European countries (23%). Higher experience with technical variants (SG and LD) was associated with significantly better outcome (Figure 2).

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 1B). Comparing graft outcome since 2010 showed a similar 5-year graft survival for FS (79%), SG (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; Figure S8). Outcome of SG and LD was found to be significantly better in centers with a larger average case volume (performing more than five of these transplants per year) (Figure 2).

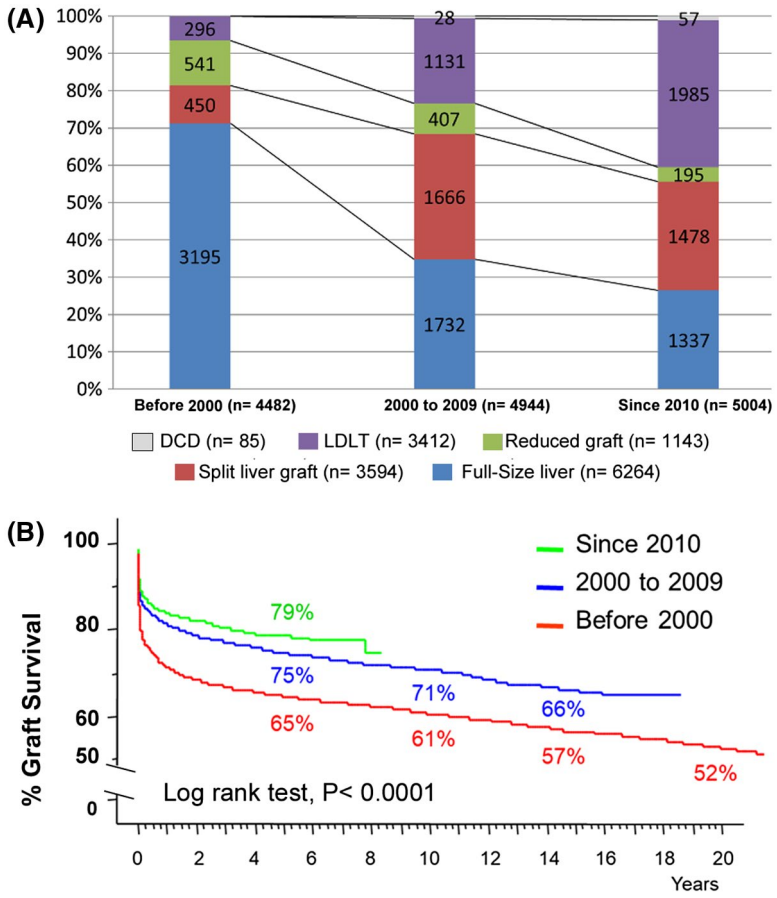

FIGURE 1 Evolution of type of graft (A) and overall graft survival (B) by group. Graft type use evolved over time, with FS liver grafts representing the major type before year 2000 and left liver lobe from living donors being the most common single type since 2010. Graft survival has significantly improved over time

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

Ischemia time (Table S1 and Figures 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 (Figure S10).

Transplantation of grafts after reduction of the liver size or procurement 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 1A; Figures S4, S5, and S7).

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) (Figures S4 and S7); of these 86 donors, 57 were children (66%) and 10 were >40 years of age (including 2 who were >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 1A). Most DCD livers were transplanted FS (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 LTs, this subgroup was not analyzed further, nor has it been compared to other subgroups (Figure 1; Figures S4, S6, and S7).

Donor to recipient match

Graft type varied between age groups; three quarters of grafts used in infants were RL, SG, or LD; these

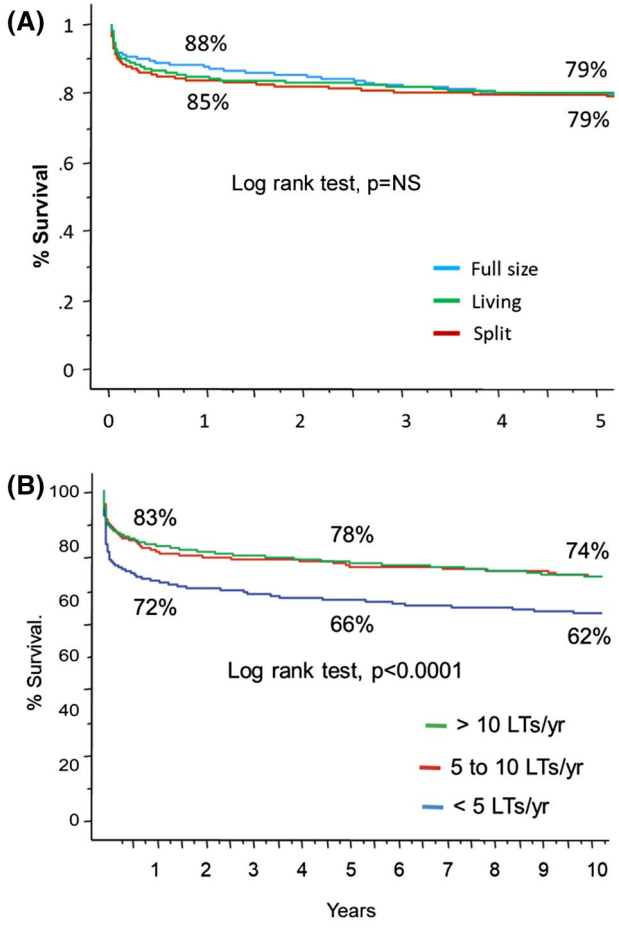

FIGURE 2 Graft survival according to graft type since 2010 (A) and according to center experience (number of SGs and LD grafts transplanted annually) (B). Abbreviation: NS, not significant

TABLE 2 Graft survival according to recipient age and graft type since 2010

Recipient age	Type	*n*	Graft survival 1 year	Graft survival 5 years	*p*
<1 year	SG	423	80%	74%	0.002
	LD	818	87%	80%	
1–6 years	SG	706	88%	83%	0.522
	LD	772	87%	81%	
6–12 years	SG	235	86%	77%	0.514
	LD	227	82%	76%	
12–18 years	SG	114	83%	78%	0.683
	LD	168	84%	73%	

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 FS livers (Table 1; Figures S4 and S7).

A younger donor age was associated with favorable results in general (Figures S8 and S12), particularly in the case of SGs 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 SGs—there was no significantly worse outcome when DBD grafts from older donors were used to prepare reduced-liver transplants or LDLTs.

The graft weight being not registered in the ELTR in <55% of LTs, a graft-to-recipient-weight ratio could not be analyzed to estimate the size (mis)match between donor and recipient. As high donor body mass index (BMI) is a negative selection criterion for many teams in Europe,[2] donor BMI was found to be within the "healthy weight range" (BMI 18–25) for most donors (Figure S11). Donor BMI was available for 75% of LDs and 92% of SGs, 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 SGs, RL, left SGs, and LDs (Table 3; Figure S13). Two interesting observations were made: (1) LDLT was associated with the largest ratio, larger even than left SGs, and (2) there was a trend for selecting better size-matched donors throughout the study period, resulting in significant differences between groups, for each graft type except those from LDs (Table 3; Figure S13). Overall, the number of donors with BMI > 30 kg/m^2 is small in this series and did not allow a satisfactory comparison. The analysis confirmed that grafts from donors with a BMI < 26 kg/m^2 were associated with long graft survival (Figure S11).

Retransplantation

Retransplantation was necessary in 2126 cases (Figures S17–S20): 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 years). 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 from what was observed in the group retransplanted within the pediatric age range, where the main indications were vascular problems and early graft dysfunction or nonfunction.

Overall, the need for retransplantation in children has reduced with time ($p < 0.0001$)—from 23.1% ($n = 1036$) in group A to 14.4% ($n = 716$) in group B to as low as 7.5% ($n = 374$) in group C (Figures S17–S20).

TABLE 3 DRWR according to graft types and groups

DRWR	Group A: before 2000	Group B: 2000–2009	Group C: since 2010	p^a
DBD FS	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 RL	4.3 ± 3.0	4.7 ± 3.0	5.5 ± 3.7	0.003
DBD left SG	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

Abbreviation: ns, not significant.
[a]Group A versus group C.

Graft loss due to primary nonfunction, rejection, and general causes reduced; but retransplantations for vascular problems slightly increased (n = 210 [4.7%], 240 [4.8%], and 370 [7.4%] in groups A, B, and C, respectively) (Figures S17–S20).

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 >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 (Figure S21A).

Interestingly, the half-life is shorter (21 years) for those transplanted as teenagers (age 12 and above) (Figure 3), while it is 32 years in children aged <12 at LT (Figure 3A). 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 3B). 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 teenagers (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 range, while, in contrast, the incidence of loss after transition increased sharply after 2010 (Figure 4A).

To study this phenomenon further, the same transplant and graft loss data were analyzed as cumulative longitudinal numbers and presented in a semilogarithmic fashion (Figure 4B); 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.

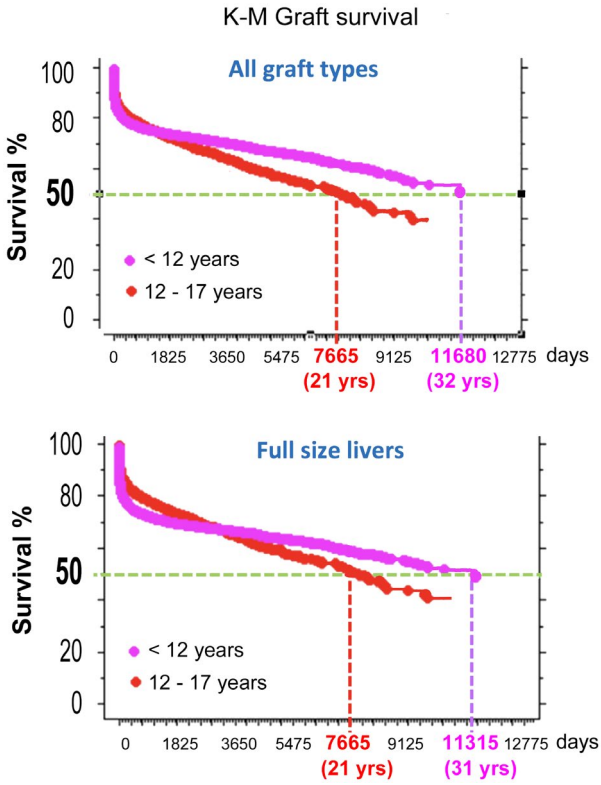

FIGURE 3 Graft half-life after transplantation in children according to age group (<12 or ≥ 12 years): all graft types (A) and FS liver grafts only (B). Abbreviation: K-M, Kaplan-Meier

Because teenagers 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). Long-term graft survival is very similar between children transplanted at age <6 years and those aged 6–12 years, but the survival in the group 12–18 years of age is more like that of adults 18–45 years of age at LT (Figure 5). Finally, becasue the slope of the survival curve is much steeper during the first year after LT compared to what it is later (Figure S21A), long-term graft survival with conditional 1-year survival was also calculated: the

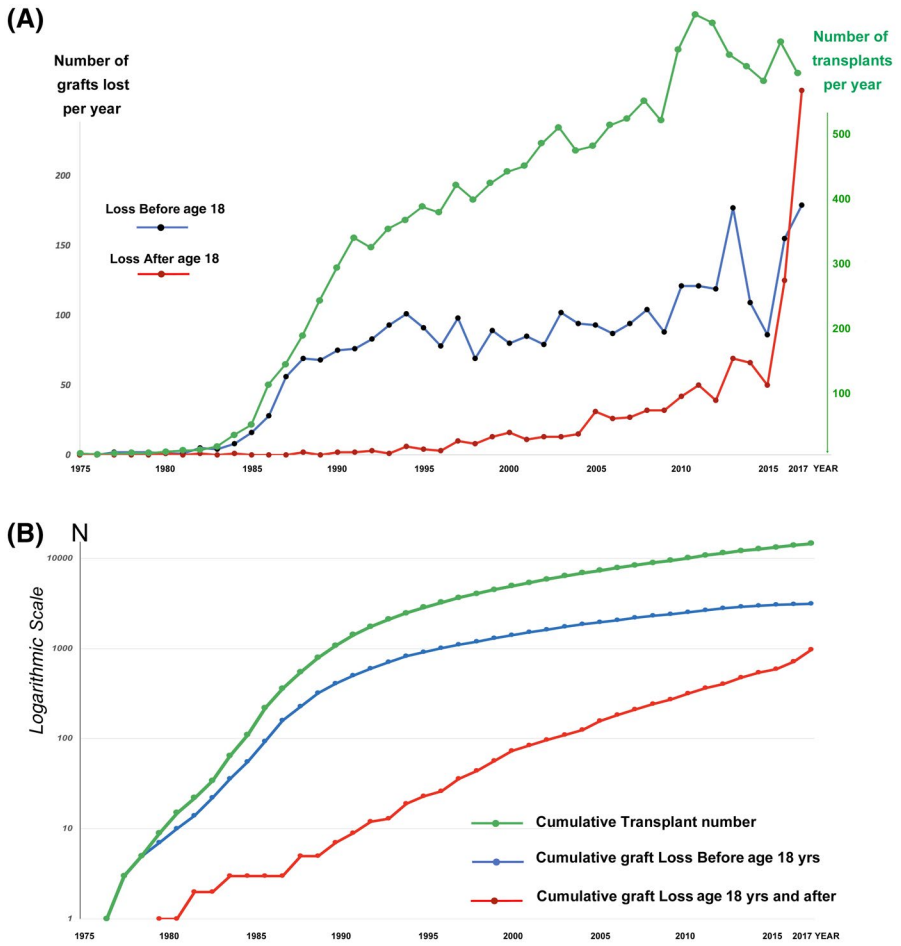

FIGURE 4 Graft loss over time (1975–2017) according to age at loss (<18 or ≥18 years of age)

graft half-life of the children who survived the first year (conditional 1-year survival) was then estimated to be 41 years (Figure 5, Figure S21B).

DISCUSSION

Over the last five decades, the ELTR has systematically collected data on virtually all LTs performed in most European countries: data acquisition quality has been monitored prospectively, which has made this data set so valuable and unique. This 50-year experience in PLT is really second to no other series in the literature in terms of total number of patients and time span: the largest surveys available in the literature are currently about 1911 PLTs in 2011–2018 (Society of Pediatric Liver Transplantation),[3] 8982 PLTs in 2000–2015 (United Network for Organ Sharing [UNOS]),[4] 2085 PLTs in 1989–2015 (Japanese Liver Transplantation Society registry),[5] and a 10-year review of activity (around 6000 PLTs) by the Scientific Registry of Transplant Recipients (SRTR).[6] The abundance of data confirms that the 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 LT over a 50-year 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 in further analyzing this extraordinary reservoir of data. The objectives were reached, and observations are brought forward in this paper.

As this registry data covers LTs 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 the UNOS and the SRTR,[4,6] but it is very similar to that reported by Bowring et al., who analyzed 13,442 pediatric LTs from the SRTR[7] and found that the observed 30-year graft survival was 45.5% for LTs performed between 1987 and 1996 and that the predicted 30 years graft survival was 56.7% for LTs performed 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

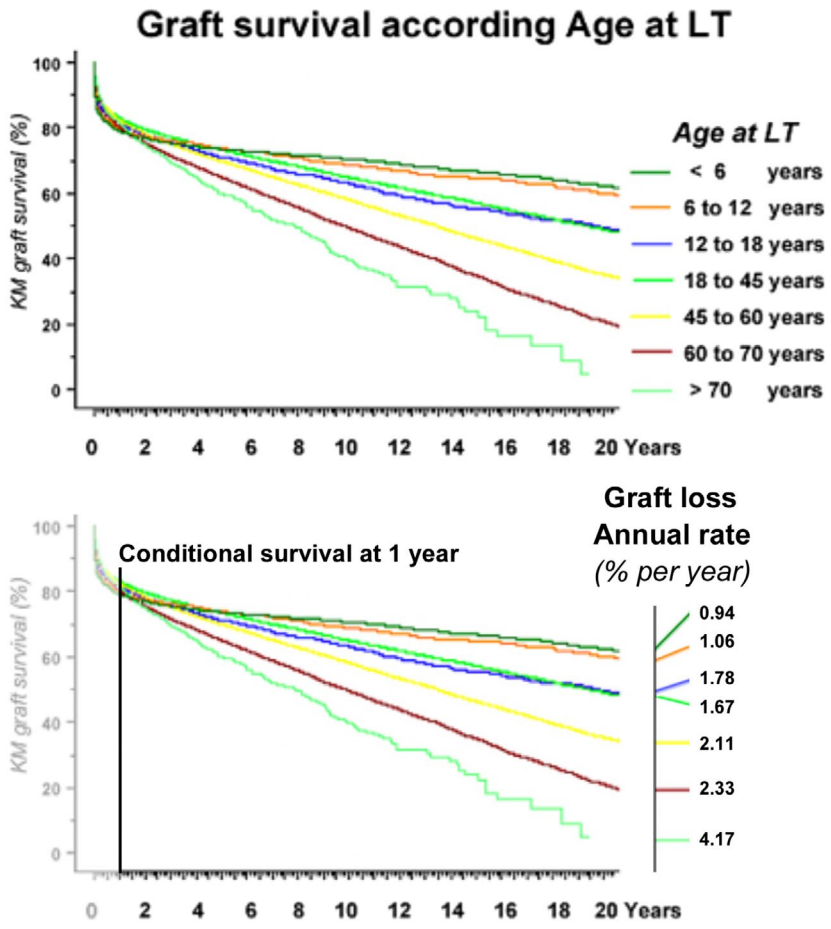

FIGURE 5 Graft survival according to age at transplantation and graft loss annual rate for conditional 1-year survival. Based on data of patients registered at ELTR between 1968 and December 31, 2017, for LT either as children (age < 18 years. *n* = 16,641) or as adults (age ≥ 18 years, *n* = 123,967). Abbreviation: KM, Kaplan-Meier

PLT as the liver is 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 terms of survival is even greater and that the graft half-life is >31 years. Although this is a mathematical calculation—with human factors of compliance, social integration, and psychosocial 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 teenagers. 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 two age groups (for patient, not graft, survival) in the SRTR database,[8] as did Ekong et al. in the UNOS 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 in the indications for LT and the causes of graft failure (Table 1). From an epidemiological point of view and compared to the younger ones, teenagers 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 comorbidities. Overall, the teenage group has a profile similar to that of 18- to 45-year-old patients,[10] and they share with the latter group a similar graft outcome and graft half-life (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 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 groups, from 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 at 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 teenagers (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, behavioral, 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 <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] The possible role of puberty in reshaping the immune system seems worth exploring, as well as further analyzing the mechanism(s) underlying the different long-term graft loss rates of those transplanted as teenagers or as 6- to 12-year-olds.

As stated above, the ELTR does not include specific data about the transition of care. To allow estimation of the effect of transfer of care, we arbitrarily set the transition age at precisely 18 years, acknowledging that this does not reflect exactly the real world. Nevertheless, the large size of the cohort may still allow us to regard 18 years as an approximation. Based on the choice of 18 years as the time of transition, transition of care toward adult services *per se* (specifically, treatment before or after the 18th birthday) did not seem directly associated with higher graft loss. Contradictions remain in the literature,[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 (Figure 22A). As this cohort became adult in the period 2000–2010 (Figure 22B), 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 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 the last decade: though the absolute numbers remained low (Figure 22**)**. A continuous (and steadily steeper) increase of the annual number of graft losses is, however, what can be expected in this age group (>18 years) because this is an open-ended category, with increasing numbers of patients who 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 semilogarithmic scale, a straight line of grafts lost after the age of 18 years, which is a proportionally stable rate.

Overall, graft survival has significantly improved in the 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 recent reports based on SRTR data.[6,7] SRTR series are remarkable for a high proportion of PLTs using FS grafts 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 grafts from pediatric donors for decades. The latter grafts are technically more demanding and carry a slightly higher graft loss rate, but their large use has allowed us to meet the pediatric organ demand—resulting in a drop in pretransplant mortality rates to very low figures (1–3 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 out by many authors in the literature.[16–18] Though it is difficult to compare the two cohorts, it is likely that in terms of an "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 Europe and USA. 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 in both the short and the long term in each of the 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 room for improvement. Most graft losses during the first year are directly related to the operation, from primary technical problems to related secondary issues including sepsis and liver dysfunction. It has been clearly pointed out by many authors that posttransplant 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 the case volume size of a center and its performance, with a significantly lower graft survival in centers performing fewer than five 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 perioperatively and in the long term. Centralization of care toward 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 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, which is half of a healthy human life span.

In comparison to children <12 years of age, the risk of graft loss is higher for those transplanted as teenagers. In many aspects, the outcome for transplanted teenagers is more like that of young adults transplanted between 18 and 45 years than it is like that of 0- to 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 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 data set.

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CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

Jean de Ville de Goyet was responsible for research design, data analysis and interpretation, writing, editing and review of manuscript, and coediting figures. Ulrich Baumann and Henkjan J. Verkade were responsible for concept generation, research design, and editing and review of manuscript. Vincent Karam was responsible for data gathering, data analysis, statistical analysis, editing figures, writing, and editing and review of manuscript. All other authors participated in data acquisition.

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SUPPORTING INFORMATION

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