Outcomes of left split graft transplantation in Europe: report from the European Liver Transplant Registry

ORIGINAL ARTICLE

Outcomes of left split graft transplantation in Europe: report from the European Liver Transplant Registry

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SUMMARY

Split liver transplantation (SLT) has been widely adopted across Europe, resulting in remarkable reduction in the paediatric waiting-list mortality. Left split graft (LSG) is commonly used for paediatric recipients; however, deceased donor criteria selection are not universal. The aim of this study was to analyse the LSG outcome from the European Liver Transplant Registry and to identify risk factors for graft failure. Data from 1500 children transplanted in 2006–2014 with LSG from deceased donors were retrospectively analysed. Overall, graft losses were 343(22.9%) after 5 years from transplantation, 240(70.0%) occurred within the first 3 months. Estimated patient survival was 89.1% at 3 months and 82.9% at 5 years from SLT. Re-transplantation rate was 11.5%. At multivariable analysis, significant risk factors for graft failure at 3 months included the following: urgent SLT (HR = 1.73, $P = 0.0012$), recipient body weight ≤6 kg (HR = 1.91, $P = 0.0029$), donor age >50 years (HR = 1.87, $P = 0.0039$), and cold ischaemic time (CIT) [HR = 1.07 per hour, $P = 0.0227$]. LSG has good outcomes and SLT is excellent option for paediatric recipients in the current organ shortage era. We identified practical guidelines for LSG donor and recipient selection criteria: donor age may be safely extended up to 50 years in the absence of additional risk factors; thus, children <6 kg and urgent transplantation need CIT <6 h and appropriate graft/recipient size-matching to achieve good outcomes.

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donor and recipient risk factors, European Liver Transplant Registry, left split graft, outcomes, paediatric transplantation, split liver transplantation

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Introduction

Liver transplantation (LT) is the treatment of choice for end-stage liver disease in adult and paediatric population [1]. However, the number of deceased donor organs available worldwide has progressively became insufficient for the needs of both adults and children candidates. Paediatric recipients are also disadvantaged due to the lack of size-matched donors. In late 1980s, split liver transplantation (SLT) was introduced primarily to increase the limited donor organ pool by dividing a whole liver into two portions [2]. After the initial difficult splitting experiences and the steep learning curve, satisfactory outcomes were later achieved due to advances in surgical techniques and in donor/recipients matching strategies [3,4].

In the last decade, SLT has shown similar results to those obtained in transplantation of whole organs [5–7], allowing to reduce mortality in the paediatric waiting list without harming adult recipients outcomes [8,9]. Recently, a systematic meta-analysis reported similar outcomes in right lobe SLT compared to whole-liver transplantation in adult recipients [10]. In Europe, each country developed their own 'splitting policy', differing in logistical needs and donor criteria. The selection criteria commonly used for splitting liver donor include maximum age between 40 and 50 years (variable in different countries), stable haemodynamics, nonsteatotic liver, intensive care stay <5 days, Na <160 mmol/l and liver function test less than fivefold of normal, suitable vascular anatomy for reconstruction in the recipient. The scarcity of 'optimal' young deceased donors suitable for SLT and the progressive growth of the transplant waiting list inspired a renewed interest in a possible expansion of donor selection criteria to maximize the liver donor pool for splitting. However, to date, there is no universal agreement defining the deceased liver donors who are candidate for splitting.

The aim of this study was to report the outcome of the left split graft (LSG) in Europe and to identify the factors associated with a negative impact on patient and graft survival in paediatric LSG recipients from the European Liver Transplant Registry (ELTR).

Patients and methods

Basis for selection

The ELTR database contains information about all LTs performed in 28 Europe countries since 1968 [8]. We have first considered all data (n = 8048 SLT) from the first SLT performed in Europe from 1976 to show the evolution of results of splitting since its initial development (Figs 1 and 2). Transplant centres with percentage of data missing >50% at baseline or at last follow-up were excluded from the analysis (move to basis for selection). Then, we extensively analysed all SLTs performed from January 2006 to December 2014 (n = 3291 SLTs) aiming to provide a more recent evaluation of SLT results. The date from January 2006 was chosen as it corresponds to the introduction of the model of end-stage liver disease (MELD) in Europe [11].

All patients who received a left lateral segment (segments II and III ± IV) as first LT from a deceased donor in the observational period were considered in the analysis. Exclusion criteria included the following: living donor liver transplantation (LDLT), domino donors and donors after circulatory death, redo transplants, multiorgan transplants (with exception of combined liver–kidney transplant), right split graft and variants of splitting procedure such as full right/full left grafts and hyper-reduced grafts (Fig. 3).

Data collection

All the ELTR continuous and discrete variables of the enrolled SLT related to the recipient, donor and graft were analysed. Variables for the recipients were age, weight, height, body mass index (BMI), creatinine, bilirubin, INR, paediatric end-stage liver disease (PELD) score, United Network of Organ Sharing (UNOS) status at SLT, gender and combined transplantation of kidney. Indications for transplantation were classified as acute, chronic, tumours and metabolic diseases. The variable urgency indicates prioritization of a patient according to clinical condition.

Donors' variables included age, gender, height, weight, BMI and cause of death. Graft details were cold ischaemia time (CIT), fluid preservation and surgical techniques (*in situ*/*ex situ* splitting). Histological micro- and macrosteatosis of the graft were defined as absent, mild (<30%), moderate (30–60%) or severe (>60%) at the postreperfusion liver biopsy, when performed as for local practice.

Statistical analysis

Descriptive statistics were given as total number and percentage for categorical variables. As several continuous covariates showed a skewed distribution, median and interquartile range (IQR) were used as summary

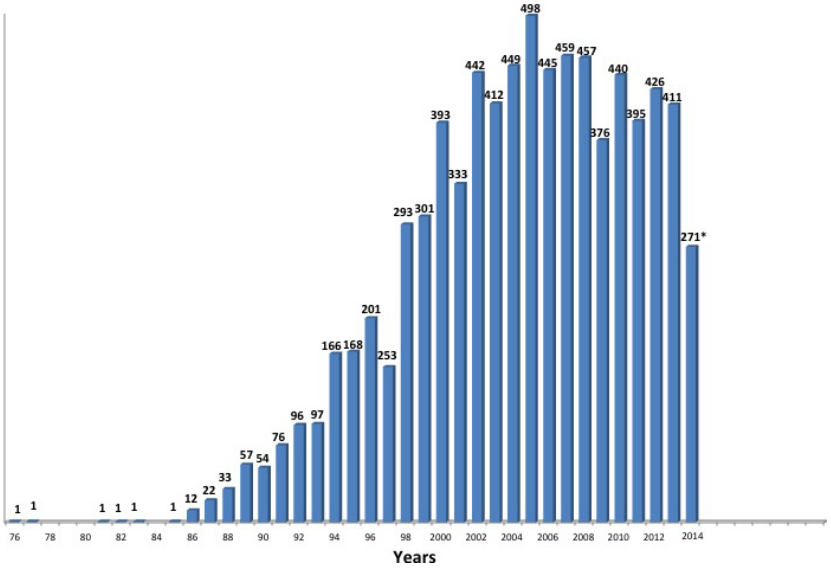

Figure 1 Evolution of split liver transplantation in Europe since 1976. *This decrease is owed to the fact that some centres did not update the registry before data have been analysed.

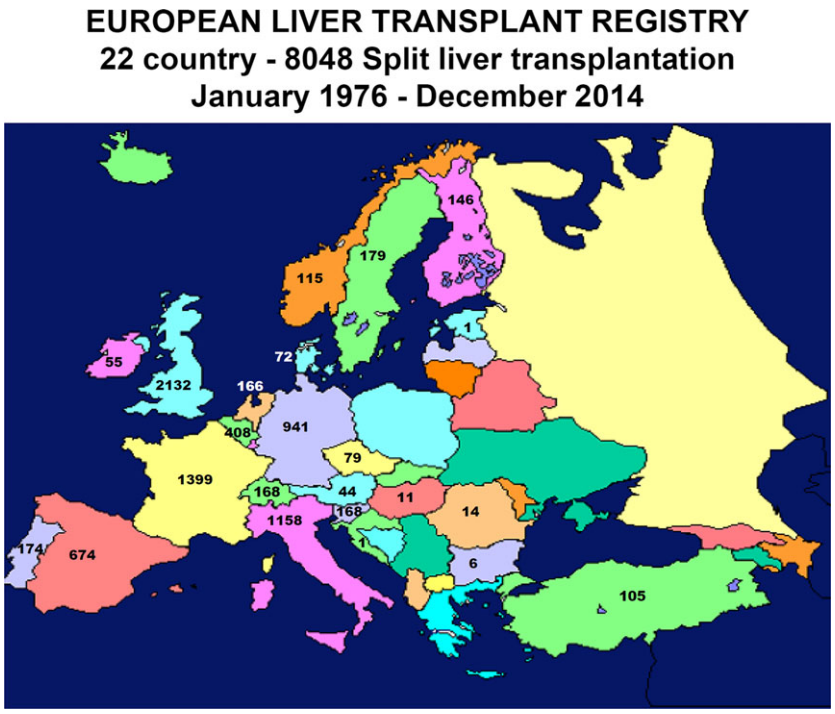

Figure 2 Number of Split Liver Transplant performed in each country (January 1976–December 2014).

statistics. Associations between categorical variables were evaluated by chi-square test; Fisher's exact test was preferred in case of sparse tables. Continuous covariates were compared by *t*-test or Wilcoxon rank sum test when a significant departure from normality was detected.

The outcomes in the survival analysis were the patient and the graft survival. The latter was defined as time from transplant to either graft failure or patient death, whichever occurred first. Kaplan–Meier estimator was used to estimate the post-transplant patient and graft survival probability. The log-rank test was used to compare groups.

At multivariable analysis, the effect of patient and donor variables on graft survival was evaluated by the Cox's model, considering all variables with missing data rate <20%. These variables included age, gender, weight

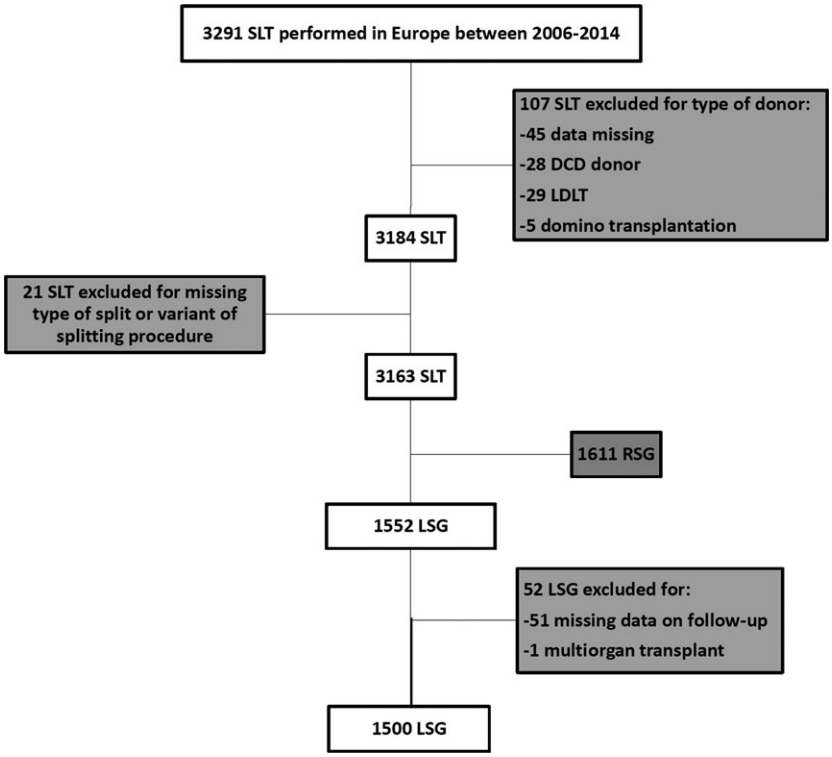

Figure 3 Selection of the study population from the European Liver Transplant Registry (ELTR). SLT, split liver transplant; LSG, left split graft; RSG, right split graft; DCD, donation after cardiac death; LDLT, living donor living transplant.

and urgency among recipient data; age, gender, weight, height and BMI among donor data; and CIT and fluid preservation recipient/donor weight ratio as surgical variables.

A preliminary analysis showed the presence of several time-depending effects, with different covariates having diverse impact on the risk of early and late graft loss. Therefore, we separately investigated short- and mid-term graft survival. Based on clinical motivations, the former was limited at 90 days of follow-up from SLT, considering patients alive at this date as censored. The mid-term analysis started at 90 days after SLT and was conditioned on being alive with functioning graft at this time to avoid the carry-over effect of early mortality.

Predictors of graft loss were identified by a nonautomate backward selection, taking correlation structure among covariates and clinical interpretation of their effects into account. Possible time-dependent effects were evaluated by plots and test statistics based on Schoenfeld residuals. No evidence of significant departures from proportionality was observed in short- and mid-term models. The effects of continuous variables in the Cox model were initially modelled as linear. This assumption was verified by plots of martingale residuals against covariate values. A nonlinear effect was detected for donor age and recipient weight. For these variables, suitable cut-off values were chosen, based on prior clinical hypotheses to be tested and preserving a sufficient sample size within each class. Because these choices were arbitrary, nonlinear effect was also modelled in continuous, using restricted cubic spline functions [12]. All analyses were performed using SAS version 9.4 and R version 3.4.

Results

Demographics

A total of 1500 patients [median age, 1.8 years (IQR, 0.9–4.8); male, 50.6%] receiving a LSG were analysed. Features of the recipients, donor and surgical characteristics are summarized in Table 1. Recipients included 76.3% children younger than 5 years and 44.5% with a weight <10 kg. Hundred and twenty-two (9.0%) children were <6 kg [median weight, 5.0 kg (IQR, 4.0–5.0); median age, 0.5 years (IQR, 0.3–0.8)]. The median PELD at the time of transplant was 25 (IQR, 18–31).

The primary indication for SLT was chronic liver disease (61.9%), of which cholestatic cirrhosis was observed in 14.4% cases. Other indications included acute liver failure (22.6%), metabolic disorders (10.3%) and tumours (5.2%). Urgent SLT was performed in 21.1% of cases, and 20.1% were defined as status UNOS 1. Combined LSG–kidney transplantation was performed in 2.9% of cases.

Table 1. Recipient, donor and surgical characteristics of the study cohort (n = 1500).

Variables	Median or n	Q1–Q3 or %
Recipient variables		
Age (years)	1.8	0.9–4.8
Gender (male)	755	50.6
Weight (kg)	10.2	7.0–16.0
Height (cm)	78.0	66.0–100.0
BMI (kg/m^2)	16.4	14.9–18.3
Creatinine at SLT (mg/dl)	0.3	0.2–0.5
Bilirubin at SLT (mg/dl)	13.4	2.9–22.9
INR at SLT	1.4	1.1–2.1
PELD at SLT	25	18–31
Indication to SLT		
Acute	256	22.6
Chronic	700	61.9
Tumour	59	5.2
Metabolic	116	10.3
Urgency	315	21.1
Status UNOS		
1	191	20.1
2	240	25.2
3	355	37.3
4	165	17.4
Combined SLT–kidney transplant	35	2.9
Donor variables		
Age (years)	26.2	18.5–39.6
Male gender	849	57.1
Weight (kg)	68.0	59.0–75.0
Height (cm)	170.0	163.0–180.0
BMI	22.9	20.8–25.0
Cause of death		
Stroke	860	60.0
Trauma	429	29.9
Anoxia	56	3.9
Others	89	6.2
Surgical variables		
Graft weight (g)	310	262–370
Recipient/donor weight ratio	1.1	0.8–1.6
CIT (h)	9.1	7.4–10.6
Fluid preservation		
Collins	1	0.1
UW	788	61.8
Belzer	35	2.8
Celsior	225	17.7
Custiodiol (HTK)	171	13.4
IGL-1	50	3.9
SCOT	5	0.4
Graft biopsy at reperfusion	847	56.5
Microsteatosis		
Absent	734	88.66
Mild	96	11.3
Moderate	17	2.0
Severe	0	0.0
Macrosteatosis		
Absent	281	91.8
Mild	23	7.5
Moderate	2	0.7
Severe	0	0.0

BMI, body mass index; CIT, cold ischaemia time; IGL-1, Institut Georges Lopez-1; INR, international normalized ratio; HTK, Histidine–tryptophan–ketoglutarate; PELD, paediatric end-stage liver disease; SCOT, Solution de conservation des organes et tissus; SLT, split liver transplant; UNOS, United Network of Organ Sharing; UW, University of Wisconsin.

The median donor age was 26.2 years (IQR, 18.5–39.6), 23.7% of LSG donors being older than 40 years. Seventy-one (4.8%) split grafts were from donors <10 years old [median age, 6.0 years (IQR, 3.2–7.8); male, 51.4%], and of these, 53.5% were transplanted in children <6 kg [median recipient weight, 4.0 kg (IQR, 3.0–5.0)] with a median age of 0.4 years (IQR, 0.2–0.7). LSG from small donors (<10 years old) was used in children with a median PELD of 20 (IQR, 11–28) and for acute liver failure in 26.4% cases.

The median donor BMI was 22.9 (IQR, 20.8–25.0), and the median weight of LSG was 310 g (IQR, 262–370). Donor BMI >25.0 was present in 24.6% of LSG. The median recipients/donor weight ratio was 1.1 (IQR, 0.8–1.6), in 29.5% of cases being >1.5. Causes of donor death included stroke (60.0%), trauma (29.9%), anoxia (3.9%) and others (6.2%).

The median CIT was 9.1 h (IQR, 7.4–10.6), and the University of Wisconsin (UW) solution was the mostly used preservation fluid (61.8%). Graft biopsy after reperfusion was performed in 847 (56.5%) cases: microsteatosis was evident in 113 cases, while macrosteatosis in 25 biopsies.

Graft/patient survivals, cause of deaths and re-transplantation rate

The median follow-up after SLT was 2.98 years, with 21.3% of cases having a follow-up >5 years. The overall graft survival was 83.3% [standard error (SE), 0.98%] at 90 days and 73.9% (SE, 1.29%) at 5 years (Fig. 4a). Of note, of a total of 343 graft loss events, 240 (70.0%) occurred within the first 90 days post-transplant.

The overall patient survival was 89.1% (SE, 0.82%) at 90 days and 82.9% (SE, 1.08%) at 5 years (Fig. 4b).

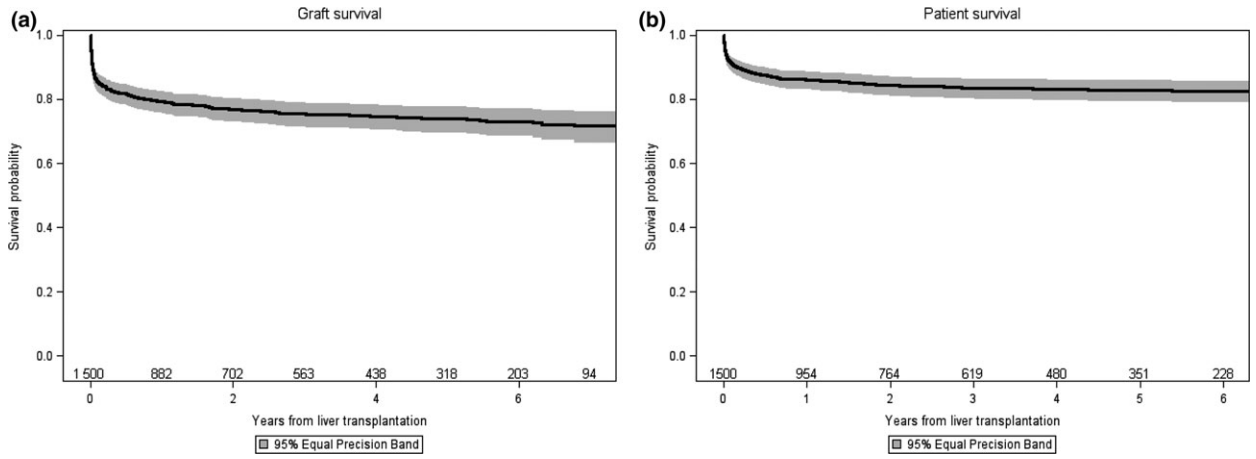

Figure 4 Graft (a) and patient (b) survival of the left split grafts between January 2006 and December 2014.

Table 2. Causes of death after left split graft transplantation in the study population.

Cause of death	Within 90 days from SLT *n* (%)*	After 90 days from SLT *n* (%)*
Infections	43 (30.9)	27 (48.2)
Cardiovascular complications	14 (10.1)	–
Cerebrovascular accidents	8 (5.8)	1 (1.8)
Gastrointestinal complications	11 (7.9)	5 (8.9)
Primary non function (re-LT or death within 7 days)	14 (10.1)	–
Primary liver dysfunction (re-LT or death >7 days)	4 (2.9)	–
Bleeding	3 (2.2)	–
Hepatic artery thrombosis	4 (2.9)	2 (3.6)
Hepatic vein thrombosis	2 (1.4)	–
Portal vein thrombosis	1 (0.7)	–
Biliary complications	1 (0.7)	1 (1.8)
Liver disease recurrence	1 (0.7)	1 (1.8)
Tumour recurrence	–	5 (8.9)
Chronic rejection	2 (1.4)	3 (5.4)
Kidney failure	1 (0.7)	–
Intraoperative death	3 (2.2)	–
Other	27 (19.4)	11 (19.6)
Data not available	17	13
Total number of deaths	156	69

LT, liver transplantation; SLT, split liver transplantation.

*Percentage is computed considering available data.

Causes of recipients' death are reported in Table 2. Infections represented the major causes of recipients' death both at 90 days from LT (30.9%) and after the first 3 months from transplantation (48.2%).

Of 172 (11.5%) children who were re-transplanted, 112 (65.1%) SLT recipients underwent re-transplantation within 90 days. After the second transplant 54 (31.4%) recipients died.

Of 122 recipients <6 kg, we observed 39 graft losses (32.0%) vs. 259 graft losses out of 1229 recipients ≥6 kg (21.1%). The estimated graft–survival probability was 85% (SE, 1.0%) at 90 days and 78% (SE, 1.3%) at 3 years in recipients ≥6 kg vs. 75% (SE 3.9%) at 90 days and 66% (SE, 4.6%) at 3 years in recipients with body weight <6 kg. In this subgroup, graft losses were due to sepsis (34.6%), primary liver nonfunction – within 7 days from LT – (15.4%), primary liver dysfunction – after 7 days from LT – (11.5%), gastrointestinal complications (11.5%), hepatic artery thrombosis (7.8%), kidney failure (3.8%) and other causes (15.4%). In 13 (33.3%) patients, the cause of graft loss was not available.

For urgent transplantation, we observed 105 graft losses (33.3%), while 230 graft losses for nonurgent cases (20.2%). The estimated survival probability was 85% (SE, 1.1%) at 90 days and 79% (SE, 1.3%) at 3 years in nonurgent cases vs. 77% (SE, 2.4%) at 90 days and 63% (SE, 3.0%) at 3 years in urgent cases. Causes of graft loss for urgent transplantation included the following: sepsis (41.8%), cardiovascular accident (10.8%), primary liver nonfunction – within 7 days from LT – (4.1%), primary liver dysfunction – after 7 days from LT – (2.7%), hepatic artery thrombosis (4.1%), hepatic vein thrombosis (2.7%), tumour recurrence (5.4%), chronic rejection (4.1%), gastrointestinal complications (4.1%) and others (20.2%). In 31 (29.5%) cases, the cause of graft loss was not available.

Risk factors affecting graft survival

At univariate marginal analysis, a significant effect of recipient body weight on risk of graft failure was observed ($P = 0.0075$): very small children with body weight <6 kg showed an increased risk of early graft failure as compared to children with weight between 6 and 20 kg and a moderate increased risk was observed also in recipient with body weight >20 kg (Fig. 5a). Acute liver failure as indication for SLT was associated with an inferior outcome ($P < 0.0001$). Donor age was significantly related to graft loss ($P < 0.0001$) with a worse outcome for donor younger than 10 years and older than 50 years old (Fig. 6a).

Data on surgical technique of splitting were available on 380 cases: 221 (58.2%) *in situ* and 159 (41.8%) *ex situ* SLT were performed. The median CIT was 7.2 h (IQR, 6.1–8.8) for *in situ* procedures, while 9.3 h (IQR, 8.3–11.3) for *ex situ* splitting technique ($P < 0.0001$). *Ex situ* SLT was associated with an increased risk of early graft failure ($P < 0.0001$).

Table 3 shows risk factors affecting graft survival at Cox multivariable analysis. Risk factors for graft failure within the first 90 days after LT were urgent LSG transplantation, recipient body weight, donor age and CIT. Estimated HR for urgency was 1.73, and recipients with a weight ≤6 kg had an estimated HR of 1.91 as compared to the others. Increasing risk of graft failure was associated with every additional hour of CIT (HR = 1.07), rising up to 1.33 every 4 h. Grafts from donors older than 50 years had worse outcome as compared with those younger than 40 years (HR = 1.87), while a donor age between 40 and 50 years was not apparently associated with greater risk of early graft failure. As departures from linearity were detected for the effect of donor age and recipient weight, the HR was modelled in continuous age (Fig. 6b): risk of early graft loss starts to gradually increase from 45 years, reaching about 1.30 at 50 years and rising steeply afterwards. An analogous plot in Fig. 5b shows that estimated HR for recipient weight increased sharply for values lower than 6 kg. The inclusion of recipient/donor weight ratio did not add any significant contribution to the final model.

In long-term survival, only urgent transplantation was correlated with an increased risk of graft failure (HR = 2.60),

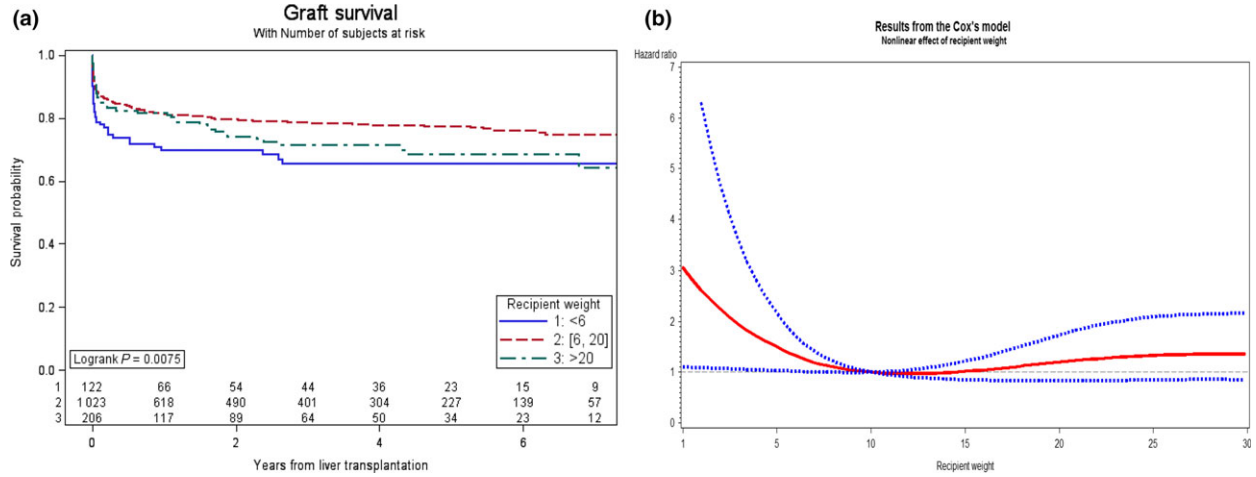

Figure 5 Left split graft survival and estimated hazard ratio according to recipient body weight. Recipient body weight was associated with increased risk of graft failure: (a) at the univariate analysis, recipient body weight <6 kg showed an increased risk of early graft failure when compared to children with weight between 6 and 20 kg, while moderate increasing risk of graft failure is observed for recipient body weight >20 kg; (b) the Cox multivariable analysis confirmed that recipient body weight <10 kg is independently associated with increase in estimated hazard ratio.

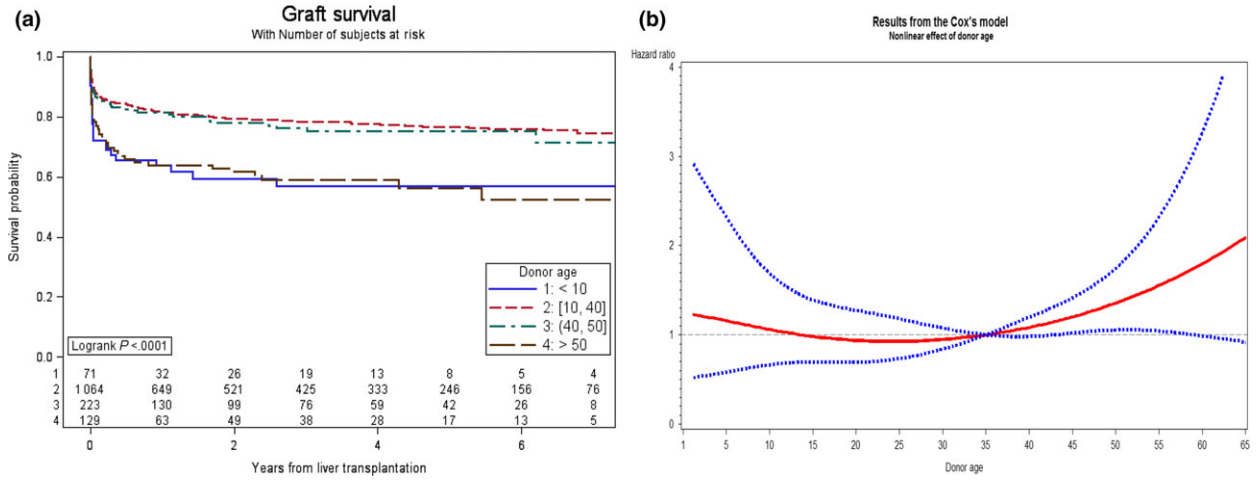

Figure 6 Left split graft survival and estimated hazard ratio according to donor age. (a) Shows that donor age was significantly related with graft loss with a worse outcome for donor younger than 10 years and older than 50 years old ($P < 0.0001$). The Cox multivariable analysis (b) confirms that the risk of graft loss starts to gradually increase from 45 years, reaching about 1.25 at 50 years and sharply increasing thereafter. The risk associated with donor age lower than 10 years is only slightly increased at multivariable analysis probably because this effect is mitigated by fact that grafts from donor <10 years are mainly transplanted in recipients with very low weight, which is another significant risk factor.

Table 3. Predictors of graft failure in left split graft recipients at Cox analysis.

	90-day graft survival			Long-term graft survival		
Variable	HR	95% CI	*P* value	HR	95% CI	*P* value
Urgency (yes versus no)	1.73	(1.24, 2.41)	**0.0012**	2.60	(1.61, 4.17)	**<0.0001**
Recipient weight						
(<6 kg) vs. (≥6 kg)	1.91	(1.25, 2.93)	**0.0029**	1.21	(0.55, 2.67)	**0.6389**
Donor age			**0.0151**			**0.5769**
(>40 and ≤50 years) vs. (≤40 years)	1.19	(0.78, 1.83)	0.4190	1.17	(0.62, 2.20)	0.6233
(>50 years) vs. (≤40 years)	1.87	(1.22, 2.87)	0.0039	1.42	(0.71, 2.85)	0.3201
CIT (×1 h)	1.07	(1.01, 1.14)	**0.0227**	1.02	(0.93, 1.12)	**0.6186**

LSG, left split graft; HR, hazard ratio; CI, confidence interval; CIT, cold ischaemia time. Bold p-values refer to the global effect of the covariate; light p-values provide details about the internal levels of the covariate (if more than 2).

showing that the effects of the other risk factors disappear as patients overcome the transplant related risk.

To illustrate the risk of graft failure associated with different combination of donor and recipients characteristics, probability of graft survival was calculated based on the fitted Cox model (Table 4). The impact of donor age between 40 and 50 years on graft survival was negligible for nonurgent recipients with body weight ≥6 kg and CIT about 6 h and was still acceptable when recipient's body weight <6 kg was the only risk factor associated. LSG from donor age >50 years showed a reduced survival probability in all association of risk factors, in particular for low recipient body weight and prolonged CIT. The urgency status, as indication for transplantation, had inferior graft outcome for all recipient body weight, with decreased survival for prolonged CIT. Moreover, in low recipient's body weight without additional risk factors, the survival probability at 90 days was 84%, but it significantly reduced in case of urgency or long CIT.

Missing data

At the multivariable analysis, 340 (22.7%) patients were excluded because of missing data on at least one of the considered explanatory variables. Characteristics of this subgroup were investigated in detail (Table S1). Higher risk of early graft failure was detected as compared to the corresponding group of patients with complete data: estimated survival probability at 90 days was 79% in incomplete data and 85% in complete data ($P = 0.0085$). SLT with incomplete data was performed

Table 4. Adjusted left split graft-estimated survival according to recipient, donor and surgical variables.

Recipient body weight (kg)	Urgency	Donor age (years)	CIT (h)	Estimated survival probability at 90 days (SE)	Estimated survival probability at 3 years (SE)
≥6	No	≤40	6	91% (1.3%)	85% (1.7%)
≥6	No	>40 & ≤50	6	89% (2.3%)	82% (3.0%)
≥6	No	>50	6	83% (3.7%)	75% (4.5%)
<6	No	≤40	6	84% (3.8%)	76% (4.4%)
<6	No	>40 & ≤50	6	83% (5.1%)	74% (6.2%)
<6	No	>50	6	75% (7.4%)	64% (8.2%)
<6	No	>50	10	63% (8.4%)	55% (8.7%)
≥6	Yes	≤40	6	84% (2.7%)	73% (3.6%)
<6	Yes	≤40	6	78% (6.0%)	61% (7.3%)
<6	Yes	>50	6	54% (9.5%)	39% (10.1%)
<6	Yes	>50	10	45% (10.1%)	31% (10.8%)

CIT, cold ischaemia time; SE, standard error.

at the beginning of the observational period, with higher proportion of urgent transplants and with worse recipient clinical status, in which associated factors may explain the inferior outcome. As multivariable analysis was adjusted for urgency, exclusion of incomplete cases should not result in any severe bias, but only in increased standard errors of parameter estimators.

Discussion

Because of the discrepancy between liver graft demand and supply, surgeons and physicians have been innovative in making the best use of available organs [13]. The split technique generally provides the smaller part to a child and the larger to an adult [14,15]. Despite the growing popularity of this approach, there is limited evidence of the overall performance of SLT. Most of the current knowledge on outcomes of both left and right split liver grafts is based on the analysis of small series from single centres [6,16,17]. The largest study is a retrospective analysis of the UNOS database published in 2008, which reported the outcome of right and left SLT in 568 adults and 508 children, respectively, transplanted between 1996 and 2006 [18].

In the present study, we analysed the ELTR records to reassess the performance of LSG in paediatric recipients transplanted from 2006 to 2014. We selected from the registry all consecutive LSGs with a minimum follow-up of 12 months (n = 1500) performed from 2006 onwards. This period corresponds to the most recent split experience and overlaps with the introduction of PELD/MELD scores as tools for recipient prioritization in many European countries [11].

In our series, graft failures occurred in 70% of cases within the first 3 months from SLT. Thus, after the first early post-transplant period, graft and patient outcomes are satisfactory. When compared to the American data, the 5-year graft survival of LSG was superior to those from the UNOS data (74.0% vs. 64.5%, respectively) [18]. However, the discrepancy is probably related to the fact that our study analysed SLT performed in a more recent period.

In the ELTR database, the risk factors for early graft failure differed from those for long-term outcomes, showing that risk factors are time-related in young recipients. Low recipient weight, high donor age and prolonged CIT negatively influence mainly the early postoperative period, while urgent transplantation is associated with short- and long-term negative outcome.

Our results confirm that very small LSG recipient presents an 'innate' problem related to both the graft/recipient size-matching and technical difficulties due to small structures. A greater risk of failure was found in very small recipients as well as using donors younger than 10 years of age. Note that the effects of these two risk factors tend to overlap as LSGs from young donors were transplanted mostly in very small recipients. As a consequence, donor age <10 years was not associated with significant increments of risk in the Cox model despite the fact that unadjusted survival probability appeared significantly reduced at univariate analysis. This effect likely reflects the known technical difficulties of neonatal transplantation (such as small-diameter vascular anastomoses) as well as a theoretical 'immaturity' of livers from young donors. These results are in accordance with those reported in 2007 by the Studies of Paediatric Liver

Transplantation (SPLIT) group [19]. In this series, young donor age was a significant risk factor for graft failure: the relative risk of graft failure in donor age <5 months was 2.54 (CI 1.59–4.05) and 1.67 (CI 0.89–3.15) for donor age between 6 and 11 months when compared to donor age between 1 and 17 years. The analysis also showed that the 30-day surgical morbidity (such as vascular and biliary complications) was increased for each type of technical variant compared to whole liver (45.1% whole, 66.7% split, 65.5% reduced, 51.9% live donor) with a high occurrence of vascular complications of 23.8% and 23.5% for split and reduced grafts, respectively.

Out of the rare studies regarding children transplanted with young donors, the Hamburg group also reported their experience with 53 paediatric donors younger than 6 years of age [20]. In this series, the outcome of children receiving grafts from young donors was comparable to those receiving a graft from older donors; however, no liver from <6-year-old donors was split and the majority was used as whole (72%) or reduced (28%) organ.

Hence, over the past decades, there has been a reduction in vascular complications of SLT in small recipients due to the implementation of thorough anticoagulation protocols and perfected surgical techniques [21–25]. Moreover, the use of living donor liver transplantation (LDLT) has been expanded also for very small recipients. Recently, the Japanese Liver Transplantation Society [26] reported the largest experience of LDLT in children with biliary atresia (n = 2085), out of which children with body weight <5 kg (9.3% of the population) showed excellent graft survival (85.1% at 1 year and 82.6% at 15 years of follow-up), which was comparable with children with body weight >6 kg. Thus, in the Japanese experience, good outcomes of small recipients seem related to novel surgical techniques to further reduce the LLS graft, thus avoiding the large-for-size graft syndrome. Kasahara *et al.* [27] also proposed an algorithm for graft type selection in LDLT for very small children based on GRWR and the ratio of the thickness of the LLS to the anteroposterior diameter in the recipient's abdominal cavity. Despite the issues associated with further reduction in the LLS graft in the cadaveric split donor setting, monosegment grafts showed good outcomes when performed by expert surgeons and should be considered in recipients with body weight <6 kg [28].

In urgent transplantation, the risk of large-for-size graft syndrome is even more consistent, as children usually present very small abdominal cavity (i.e. acute liver failure), requiring the use of prosthetic abdominal closure and the need for reoperations. Thus, in our analysis, the inferior outcome of urgent transplantation seems to be related mainly to the very sick status of the recipients at the time of SLT, causing more susceptibility to infection and comorbidities. Therefore, the meticulous clinical management before SLT is crucial for good outcomes in urgency.

In agreement with the UNOS database analysis, we found that prolongation of CIT was associated with an increase in the risk of early graft failure: we estimated that increasing the CIT from 6 to 10 h corresponds to an HR of 1.33. The susceptibility of LSG to prolonged CIT seems to be confirmed by the fact that, in our subanalysis, the *ex situ* splitting technique, characterized by longer CIT, is associated with inferior graft survival compared to the *in situ* splitting. Interestingly, prolonged CIT enhances slightly the risk of graft failure in LSG from older donors, but produces a sharp increase in risk in very small recipients, resulting in a reduction in the estimated survival probability at 90 days post-SLT from 83% to 75%.

The ELTR data show also that the risk associated with donor age smoothly increases above 40 years of age, without any evidence of a clear cut-off level. Donor age up to 50 years appears acceptable in paediatric recipients, although donors of about 50 years of age and older should be considered with caution, taking other risk factors into account. Currently, the maximum donor age recommended for SLT differs across Europe. For example, the British Transplant Society guidelines suggest splitting grafts from donors less the 40 years old [29], whilst in Italy, this limit has been recently extended to 50 years of age [30]. Notably, at Cox multivariable analysis, donor age was a risk factor for graft failure in short-term outcomes. This has been noted in several previous studies and attributed to a reduced capacity of hepatocytes from aged donors to recover from ischaemic–reperfusion injury. In addition, urgent SLT in children is associated with a high risk of graft failure.

Despite the risk groups described above, which involved less than 25% of patients, the vast majority of recipients achieved good long-term survival. Our results suggest that the current splitting criteria might be successfully expanded in many countries by extending donor age up to 50 years, but a careful recipient selection is crucial to avoid concomitant risk factors.

Some European countries have implemented specific allocation policies to facilitate splitting programmes, aiming to minimize the paediatric waiting-list mortality and the need of LDLT [31–34]. However, so far, the long-term results of LSG from living-related donors are superior when compared to those using graft from

deceased donors probably because of donor selection, shorter CIT, technical variables and timely planned procedures [26]. Moreover, the implementation of splitting allocation policy implicates the increasing of adult patients receiving the extended right grafts, whose outcome has been reported to be similar to those receiving whole livers [5,10,35]. Despite the fact that the use of partial graft has been associated with augmented risk of biliary and vascular complications, this was reported mainly in *ex situ* splitting technique, in which the identification of structures might be more challenging and the CIT is prolonged [10]. In SLT, early biliary complications, such as biliary leak, might occur from unrecognized bile ducts on the cut surface of the partial graft, which might be avoided performing intraoperative cholangiography during the split procedure.

This study has several limitations, mainly related to its retrospective nature, being based on registry data. The expected lack of granularity of split-specific information of the registry (i.e. donor ICU stay, use of vasopressors in donors, organ location, trans-hilar or trans-umbilical split technique for parenchymal transection) limited potential further analyses of SLT-relevant data. Similarly, due to a high proportion of missing registry data on the weight of split grafts, it was not possible to calculate the graft-to-recipient-weight ratio, which is associated with increased risk of graft loss in SLT in paediatric recipients [36,37], as well as the donor risk index. Another potential weakness is the lack of a LDLT control group. Finally, the median current follow-up is approximately 3 years.

In conclusion, the present study, which analysed the largest cohort of LSG reported so far, has confirmed that SLT is associated with a good outcome for paediatric recipients. LSG from deceased donor is a valuable procedure and is an excellent option in the current organ shortage era.

In LSG recipients, the early post-transplant period remains the most critical phase. Graft from donors up to 50 years of age may be safely used if multiple risk factors are avoided. Yet, prolonged CIT increases the risk of graft failure for every hour of ischaemia, especially in very small recipients and urgent SLT. Therefore, the presence of concomitant risk factors needs to be avoided and adequate donor/recipient matching is essential for LSG good outcomes.

Authorship

RA and AN: involved in data collection, analysis and interpretation and wrote the manuscript. RA (Custodian of the European Liver Transplant Registry) and PT: involved in data collection, analysis and interpretation and revised the manuscript for intellectual content. SN and WGP: involved in analysis and interpretation and revised the manuscript for intellectual content. VK: involved in data collection, analysis and interpretation. PM: designed the study, involved in data analysis and interpretation and revised the manuscript for intellectual content.

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Conflict of interests

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Recipient, donor and surgical characteristics' of left split graft comparing compete and incomplete cases.

Appendix S1. List of the European Liver and Intestine Transplant Association (ELITA) centres which contributed with data.

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