Research Article
Liver Transplantation

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Improving outcomes of *in situ* split liver transplantation in Italy over the last 25 years

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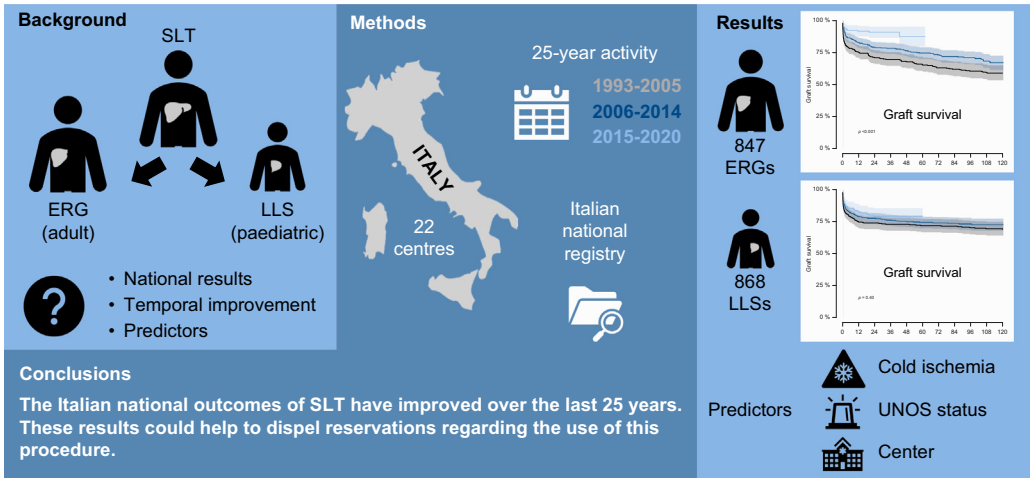
Graphical abstract



Highlights

- SLT is still considered a challenging procedure and is by no means widely accepted.
- Initially poor outcomes for SLT explain the early reluctance to adopt this option.
- Improved results with SLT have been reported recently.
- Sharing experience has been instrumental in improving outcomes.
- SLT is a significant source of paediatric grafts without compromising adults.

Impact and implications

Split liver transplant(ation) (SLT) is still considered a challenging procedure and is by no means widely accepted. This study included all consecutive *in situ* SLTs performed in Italy from May 1993 to December 2019. With more than 1,700 cases, it is one of the largest series, examining long-term national trends in *in situ* SLT since its introduction. The data presented indicate that the outcomes of SLT improved during this 25-year period. Improvements are probably due to better recipient selection, refinements in surgical technique, conservative graft-to-recipient matching, and the continuous, yet carefully managed, expansion of donor selection criteria under a strict mandatory split liver allocation policy. These results could help to dispel reservations regarding the use of this procedure.

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Improving outcomes of *in situ* split liver transplantation in Italy over the last 25 years

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Background & Aims: Split liver transplant(ation) (SLT) is still considered a challenging procedure that is by no means widely accepted. We aimed to present data on 25-year trends in SLT in Italy, and to investigate if, and to what extent, outcomes have improved nationwide during this time.
Methods: The study included all consecutive SLTs performed from May 1993 to December 2019, divided into three consecutive periods: 1993–2005, 2006–2014, and 2015–2019, which match changes in national allocation policies. Primary outcomes were patient and graft survival, and the relative impact of each study period.
Results: SLT accounted for 8.9% of all liver transplants performed in Italy. A total of 1,715 *in situ* split liver grafts were included in the analysis: 868 left lateral segments (LLSs) and 847 extended right grafts (ERGs). A significant improvement in patient and graft survival (p <0.001) was observed with ERGs over the three periods. Predictors of graft survival were cold ischaemia time (CIT) <6 h (p = 0.009), UNOS status 2b (p <0.001), UNOS status 3 (p = 0.009), and transplant centre volumes: 25–50 cases *vs.* <25 cases (p = 0.003). Patient survival was significantly higher with LLS grafts in period 2 *vs.* period 1 (p = 0.008). No significant improvement in graft survival was seen over the three periods, where predictors of graft survival were CIT <6 h (p = 0.007), CIT <6 h *vs.* ≥10 h (p = 0.019), UNOS status 2b (p = 0.038), and UNOS status 3 (p = 0.009). Retransplantation was a risk factor in split liver graft recipients, with significantly worse graft and patient survival for both types of graft (p <0.001).
Conclusions: Our analysis showed Italian SLT outcomes to have improved over the last 25 years. These results could help to dispel reservations regarding the use of this procedure.

Introduction

More than 30 years after the report of the first split liver transplant (SLT), the procedure remains one of the options to overcome the ongoing shortage of liver grafts, expanding the donor pool for both paediatric and adult recipients. In 1988, the first clinical application of SLT was reported by Pichlmayr in Hannover using an *ex vivo* splitting technique that involved dividing the liver in an ice-cold bath.[1] Subsequently, many single-centre series of *ex situ* SLTs have been reported in Europe and the United States, reflecting efforts to extend the clinical application of this surgical technique.[2,3] Simultaneously, the first living donor liver transplantation (LDLT) of the left lateral segments (LLSs) of a Japanese mother to her 18-month-old son, reported in Australia by Strong *et al.*,[4] revealed a further source of potential grafts.

In May 1993, the first successful *ex situ* split liver procedure was performed in Italy and a further four procedures were performed by the summer of 1995 (unpublished data). The so-called "*in situ*" SLT was first introduced by Rogiers *et al.* in 1995[5] and subsequently reported by the UCLA group.[6] The splitting procedure was performed in a heart-beating brain-dead donor before cold organ preservation and was based on a technique already established for living donor LLS procurement.[4]

Keywords: Split liver transplant; pediatric liver transplant; graft; outcomes; organ allocation policy; learning curve; living donor liver transplant.
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In 1998, the first Italian series of four *in situ* SLTs and the outcomes of the eight recipients were reported.[7] This led to the *in situ* split technique quickly becoming the most widely used in all Italian transplant centres.

The advantages of the *in situ* over the *ex vivo* procedure have been amply discussed since its introduction. These are mainly shorter cold ischaemia time (CIT) and the opportunity to better assess the graft under physiological conditions. However, several experienced centres have continued to use the *ex vivo* technique with satisfactory outcomes, so the debate regarding the best option remains open.[8,9]

Splitting one liver between two adult recipients was another strategy to expand the organ donor pool, and was pioneered in 1999 by Italian transplant centres working in close collaboration.[10] However, although meeting with widespread enthusiasm for the paediatric population, SLT has so far had limited use in adult recipients,[11–14] being a more challenging procedure than whole liver transplantation (WLT) and associated with less favourable outcomes, especially in the early postoperative period.[15–17] Despite recent reports showing similar results for SLT and WLT in adult recipients,[18–21] the SLT procedure is far from being generally accepted for the adult population.[15–17]

In recent years, Italy's split liver graft allocation policies have considerably contributed to the development and spread of the SLT surgical technique, as shown by the number of cases.[22–27] However, no extensive review of the national SLT experience has ever been published. This study aims to fill this gap, examining our national registry data and assessing the impact of SLT over time on Italy's liver transplant activity. We look at changes in clinical practice over the years, discuss the development of sequential allocation policies, and assess outcome improvements for both paediatric and adult recipients against the recently reported experience worldwide.

Patients and methods

Study design and data collection

This retrospective, nationwide study includes all consecutive SLTs performed in Italy between May 13, 1993 (*i.e.*, the start of SLT in Italy) and December 31, 2019. Data on patients transplanted between 1993 – 2001 were obtained from the prospective registry of the Nord Italia Transplant program, which initially regulated the national experience and cases shared between centres in northern Italy, while data for the period 2002 – 2019 came from the Centro Nazionale Trapianti. A broader view of SLT evolution over the whole study period was achieved with the inclusion of paediatric transplants from living donors and paediatric WLTs.

In Italy, paediatric LT is currently performed in five centres; one is a paediatric-only LT unit, while the other four perform both adult and paediatric transplantation. The geographical distribution and case volumes of the 22 transplant centres in Italy are reported in Fig. 1. The list of the corresponding centres is reported in the Supplementary Methods.

All 22 Italian transplant centres were included in the study and further categorized into three groups according to overall SLT volumes: low (<25), medium (25-50), and high (>50). To analyse the impact of changes over time on SLT outcomes in paediatric and adult recipients, the observation period was divided into three phases: 1993-2005, 2006-2014, and 2015-2019 to mirror changes in national allocation policies.

The primary study outcomes were: paediatric and adult patient and graft survival, retransplant rate, and the impact of the different eras on clinical results. Based on previous international series, we also analysed the impact of several other variables on adult and paediatric outcomes, such as donor and recipient clinical parameters, donor-to-recipient (D/R) size matching, centre volume, and the use of split liver grafts for retransplantation.

Allocation policy

Deceased donor liver graft selection and split allocation criteria have changed enormously over time, and have already been extensively reported.[22,27,28] The major modifications have concerned donor age; the introduction in 2015 of a mandatory split liver policy, and the adoption of model for end-stage liver disease (MELD) score-based allocation, adjusted for MELD score exceptions.[28] In the most recent allocation policy, all deceased donors aged 18-50 years with standard risk (defined as the absence of potential transmissible infections or neoplastic diseases) are mandatorily offered to paediatric transplant centres according to the national paediatric LT-waiting list unless a United Network for Organ Sharing (UNOS) 1 status or MELD ≥30 adult candidate is on the waiting list. If the deceased donor's liver is "splittable," the LLS graft is allocated to a paediatric recipient. According to the rules applicable to adults, an ERG is then allocated to a recipient not only on the basis of the MELD/ISO score but also taking into account clinical parameters and donor-to-recipient size matching.[27,28]

Surgical technique

The universally accepted definition of *conventional* split liver divides the liver into an ERG (Couinaud's segments 1, 4-8), and an LLS (Couinaud's segments 2-3) graft for one adult and one paediatric recipient. The split liver technique for two adult recipients divides the liver along Cantlie's line to give a right lobe graft (Couinaud's segments 5-8) and a left lobe graft (Couinaud's segments 1-4). Liver splitting was mainly performed *in situ* before cold flush, except in a few sporadic cases, which were excluded from the analysis.

Splitting was not performed in donors after circulatory death, due to the particular features these donors present in Italy.[29] We evaluated paediatric and adult donor-to-recipient (D/R) size matching using the D/R body surface area (BSA) ratio, considered a more accurate predictor of liver size than body weight or height alone.[30]

Since the introduction of the ongoing mandatory split liver allocation policy in 2015, hepatic artery division is decided jointly by paediatric and adult surgeons intraoperatively. The celiac trunk is retained either with the LLS or the ERG according to (1) D/R size matching, (2) donor and recipient's vascular anatomy and size, and (3) recipient's clinical status, such as high-urgency, retransplantation, or previous hepatic artery thrombosis. Only in the event of disagreement on vessel division is the final decision taken by the centre to which the graft was assigned.[27,31]

Statistical analyses and ethical approval

Our retrospective study complies with the Declaration of Helsinki ethical guidelines and was approved by the Centro

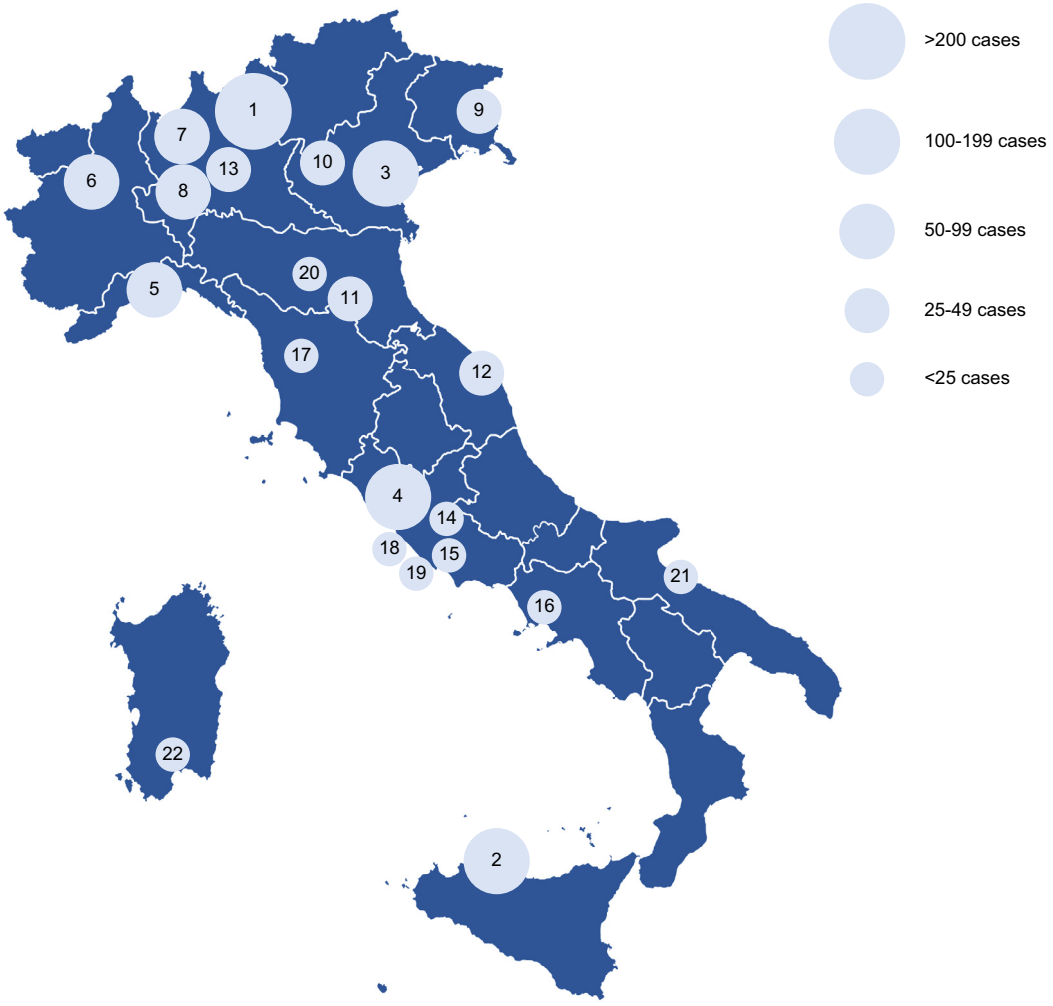


Fig. 1. Geographical distribution of participating centres. The scale proportionally reflects the surgical volume of each centre. The list of the corresponding centres is reported in the supplementary methods.

Nazionale Trapianti review board. Continuous variables were described using median and first-third quartiles (Q1-Q3) while categorical variables were reported as absolute values and relative frequencies.

The three study periods were compared for donor and recipient characteristics in the case of ERG and LLS SLT grafts, considered separately, using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. Pairwise comparisons were performed with the chi-square or Mann-Whitney test with Holm correction respectively. Patient and graft survival was estimated using the Kaplan-Meier method and the curves of the three study periods were compared using the log-rank test.

Finally, multivariable Cox regression models were used to assess the association between study periods and donor and recipient characteristics against patient mortality and graft failure. Covariates were selected based on clinical knowledge. A gamma frailty term was also included in the models to account for the dependency between observations of patients transplanted multiple times.

Results

SLT according to graft type over the three study periods

A total of 21,846 LTs were performed in Italy over the study period, of which 1,945 (8.9%) were deceased donor SLTs. We excluded from our analysis 230 recipients: 84 who received combined transplants; 76 SLTs received by two adults (39 right lobes and 37 left lobes) extensively reported elsewhere;[23–25] 42 recipients lost to follow-up, and 28 recipients of *ex situ* split liver grafts. A total of 1,715 SLTs were included in our analysis: 868 were deceased donor LLSs, and 847 were deceased donor ERGs. In the same period, a further 117 paediatric living donor LTs and 532 paediatric WLTs were performed. The percentage of SLT (ERG and LLS), paediatric LDLTs, and paediatric WLTs performed annually, and the differences over the three periods are reported in Fig. 2. Three centres performed more than 50% of all the SLT procedures during the study period, with over 50% of the deceased donor LLS SLTs carried out by one high-volume SLT centre (501/868; 57.7%).

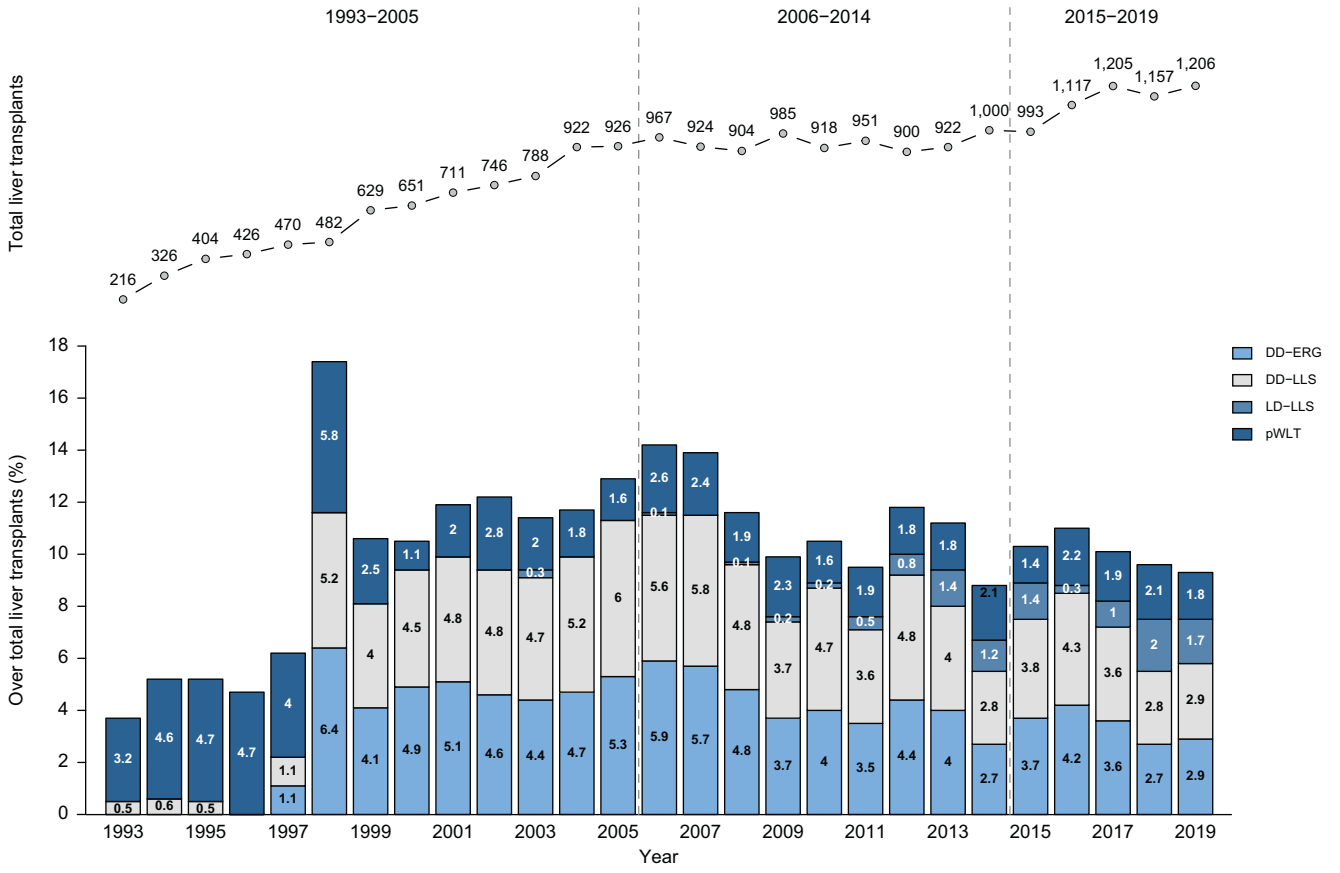


Fig. 2. Overall transplant activity in Italy from 1993 to 2019. The percentage of SLT (ERG and LLS), paediatric LDLT and WLT performed annually are colour-coded in the columns. ERG, extended right graft; LDLT, liver donor liver transplantation; LLS, left lateral segment; pWLT, paediatric whole liver transplantation; SLT, split liver transplantation.

ERG SLT outcomes

The baseline characteristics of ERG donors and recipients during each of the three study periods are reported in Table S1.

Both donor and recipient selection were seen to change over time. Indications for transplantation also changed significantly during the period considered (p <0.001). A significant decrease in the MELD score at transplant was observed between periods 2 and 3 (p = 0.004), and the proportion of ERGs used for retransplantation fell to 1.6% (p <0.001) between 2015-2019. Notably, the median CIT was significantly shorter between 2015-2019 (p <0.001) compared to the other study periods.

Median donor age was significantly lower in the first period (p = 0.048) compared to the later periods, as was the percentage of female donors compared to 2015-2019 (p = 0.01). The D/R BSA ratio showed significant variability in the three periods (p <0.001), with a ratio <0.9 being significantly more frequent between 1993-2005. The median waiting time for ERG SLTs in adult recipients was similar over the three study periods.

Overall patient and graft survival of the ERG SLT cohort are shown in Fig. S1. Patient survival at 1, 3, 5, and 10 years was 79.9%, 73.1%, 70.5%, and 62.1% in period 1, respectively; 89.9%, 86.1%, 82.2%, and 74.6% in period 2, respectively; and 95.9%, 95.1% in period 3, respectively. Patient survival was observed to improve between periods 1 and 2 (p <0.001), and between periods 2 and 3 (p <0.001) (Fig. 3A).

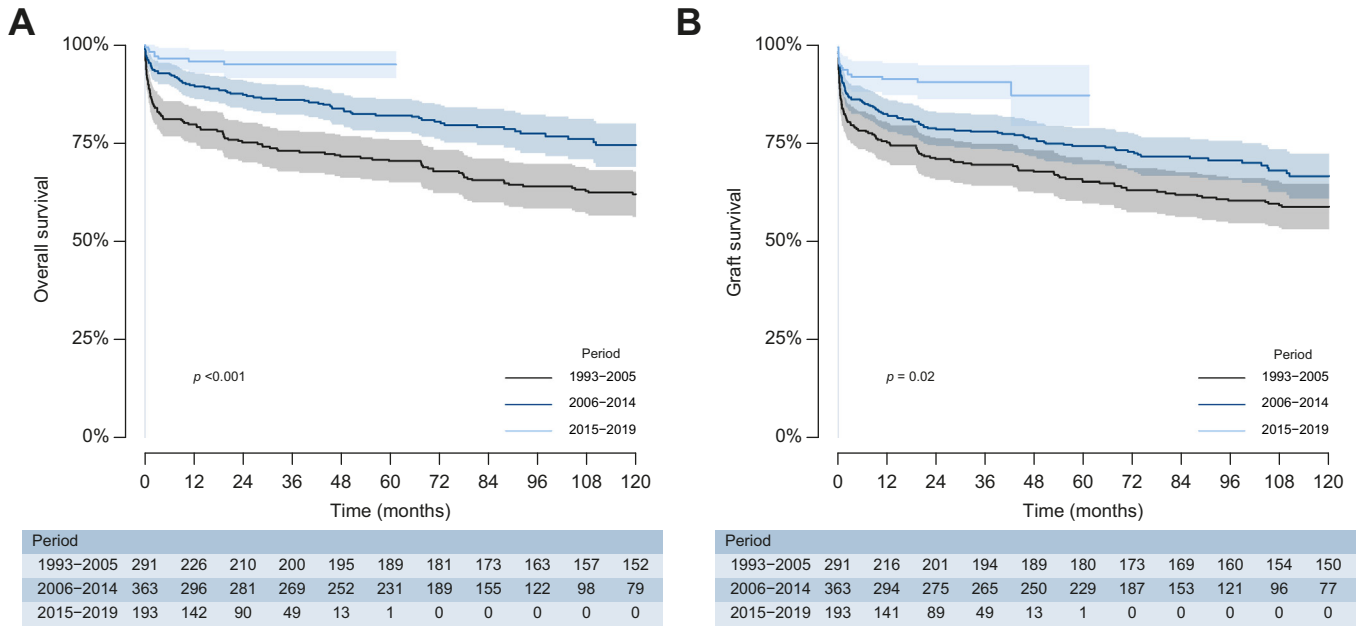
Graft survival at 1, 3, 5, and 10 years was 75.2%, 69.6%, 65.3%, and 58.9% in period 1, respectively; 82.6%, 78%, 74.3%, and 66.7% in period 2, respectively; 91.4%, 90.6% in period 3, respectively. Significant improvement in graft survival was observed between periods 1 and 2 (p <0.001) and between periods 2 and 3 (p = 0.02) (Fig. 3B).

The overall incidence of retransplantation was 9.1% (77/847), falling significantly to 5.2% in the last period (p = 0.05).

Multivariable analysis to assess the association between each study period and patient and graft survival was performed considering as covariates donor age, donor-recipient size matching, CIT, recipient status, centre volume, and split liver graft utilization for retransplantation. Even after adjustment for all the above-mentioned variables, both period 2 (hazard ratio [HR] 0.521; p = 0.002) and period 3 (HR 0.137; p <0.001) were associated with higher patient survival rates compared to period 1.

The following variables showed a significant association with patient survival: UNOS status 2b *vs.* 1 (HR 0.450; p = 0.021); UNOS status 3 *vs.* 1 (HR 0.438; p = 0.045); centre case volumes of 25-50 cases *vs.* <25 cases (HR 0.372; p = 0.007); centre case volumes of ≥50 cases *vs.* <25 cases (HR 0.385; p = 0.005), and ERG utilization for retransplantation (HR 5.585; p <0.001). Period 3 was associated with higher graft survival rates than the other periods (HR 0.294; p <0.001) (Table 1).

The variables significantly associated with graft survival included CIT ≥10 h (HR 2.668; p = 0.009); UNOS status 2b (HR



Period											
1993–2005	291	226	210	200	195	189	181	173	163	157	152
2006–2014	363	296	281	269	252	231	189	155	122	98	79
2015–2019	193	142	90	49	13	1	0	0	0	0	0

Period											
1993–2005	291	216	201	194	189	180	173	169	160	154	150
2006–2014	363	294	275	265	250	229	187	153	121	96	77
2015–2019	193	141	89	49	13	1	0	0	0	0	0

Fig. 3. ERG outcomes by period. (A) Kaplan-Meyer overall patient survival. Period 1 *vs.* period 2 (p <0.001), period 2 *vs.* period 3 (p <0.001). (B) Kaplan-Meyer graft survival. Period 1 *vs.* period 2 (p <0.001), period 2 *vs.* period 3 (p = 0.02). ERG, extended right graft.

Table 1. Univariable and multivariable Cox regression predicting patient mortality after ERG SLT*.

Variables	Univariable HR (95% CI)	p value	Multivariable HR (95% CI)	p value
Study period 2006-2014 *vs.* 1993-2005	0.389 (0.241–0.626)	<0.001	0.521 (0.347–0.782)	0.002
Study period 2015-2019 *vs.* 1993-2005	0.104 (0.046–0.237)	<0.001	0.137 (0.059–0.317)	<0.001
Donor age (50-60) *vs.* <50	1.570 (0.804–3.068)	0.19	1.806 (1.014–3.217)	0.078
Donor age ≥60 years *vs.* <50 years	2.873 (0.739–11.166)	0.13	1.966 (0.604–6.400)	0.26
BSA ratio [0.9-2) *vs.* <0.9	0.721 (0.374–1.392)	0.33	0.850 (0.484–1.490)	0.57
BSA ratio ≥2 *vs.* <0.9	0.936 (0.386–2.265)	0.88	0.884 (0.420–1.863)	0.75
CIT (6-10 h) *vs.* <6 h	3.267 (1.292–8.259)	0.012	1.341 (0.722–2.491)	0.35
CIT ≥10 h *vs.* <6 h	8.261 (2.485–27.468)	<0.001	1.862 (0.891–3.888)	0.098
Status UNOS 2A *vs.* 1	0.409 (0.136–1.233)	0.11	0.867 (0.360–2.088)	0.75
Status UNOS 2B *vs.* 1	0.115 (0.046–0.284)	<0.001	0.450 (0.203–0.997)	0.049
Status UNOS 3 *vs.* 1	0.151 (0.060–0.381)	<0.001	0.438 (0.195–0.983)	0.045
ERG centre volume (25-50 cases) *vs.* <25 cases	0.641 (0.267–1.539)	0.32	0.372 (0.181–0.763)	0.007
ERG centre volume ≥50 cases *vs.* <25 cases	1.003 (0.461–2.186)	0.99	0.385 (0.197–0.752)	0.005
Retransplant *vs.* NO	9.483 (4.856–18.520)	<0.001	5.585 (2.609–11.956)	<0.001

BSA, body surface area; CIT, cold ischaemia time; D/R, donor-to-recipient; ERG, extended right graft; SLT, split liver transplantation; UNOS, united network for organ sharing.
*A gamma frailty term was also included in the models to account for the dependency between observations of patients transplanted multiple times.

0.351; p = 0.003); UNOS status 3 (HR 0.401; p = 0.009); centre case volumes of 25-50 cases *vs.* <25 cases (HR 0.399; p = 0.003); centre case volumes of ≥50 cases *vs.* <25 cases (HR 0.544; p = 0.03), and ERG utilization for retransplantation (HR 4.159; p <0.001) (Table 2).

LLS SLT outcomes

The baseline characteristics of LLS donors and recipients during each of the three periods are reported in Table S2.

Significant variability was observed in the indications for transplantation over the three study periods (p = 0.009), with cholestatic liver disease being the most frequent indication (54.8%). The proportion of LLSs used for retransplantations remained stable over time. Over the three study periods, 71.4% of patients were classified as UNOS >2A, while a significantly higher number of patients (62.8%) were listed as UNOS status 3 (p <0.001) in the last period. Median CIT was significantly shorter in the last period 2015-2019 (p = 0.004) compared to the other study periods. We found no significant difference in waitlist times for LLS SLT in paediatric recipients over the three periods.

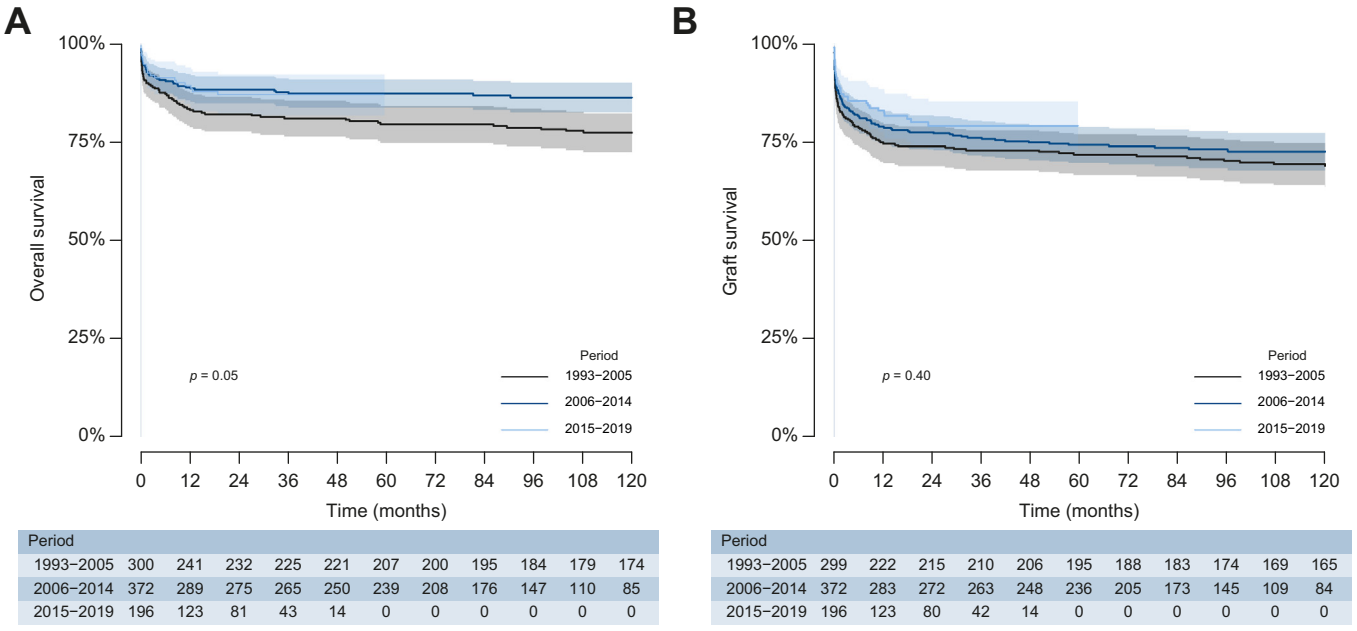
Overall patient and graft survival of the LLS SLT cohort is shown in Fig. S2. Patient survival at 1, 3, 5, and 10 years was 83.1%, 81%, 79.5%, and 77.3% in period 1, respectively; 88.9%, 87.6%, 87.3%, and 86.3% in period 2, respectively; 89.3% and 87% in period 3, respectively, showing improvement only between the first and subsequent periods (p = 0.05) (Fig. 4A).

Graft survival at 1, 3, 5, and 10 years was 74.6%, 72.9%, 71.8%, and 68.9% in period 1, respectively; 78.9%, 76%, 74.2%, and 72.6% in period 2, respectively; 83% and 79.1% in period 3, respectively, interestingly showing no significant improvement over the three periods (p = 0.40) (Fig. 4B).

Table 2. Univariable and multivariable Cox regression predicting graft failure after ERG SLT*.

Variables	Univariable HR (95% CI)	*p* value	Multivariable HR (95% CI)	*p* value
Study period 2006-2014 *vs.* 1993-2005	0.598 (0.404–0.885)	0.01	0.725 (0.511–1.029)	0.072
Study period 2015-2019 *vs.* 1993-2005	0.239 (0.132–0.433)	<0.001	0.294 (0.160–0.539)	<0.001
Donor age (50-60) *vs.* <50	1.602 (0.824–3.112)	0.16	1.802 (0.978–3.319)	0.059
Donor age ≥60 years *vs.* <50 years	1.693 (0.423–6.784)	0.46	1.442 (0.503–4.130)	0.50
BSA ratio [0.9-2) *vs.* <0.9	0.787 (0.404–1.533)	0.48	0.842 (0.517–1.371)	0.49
BSA ratio ≥2 *vs.* <0.9	0.817 (0.334–1.996)	0.66	0.766 (0.396–1.482)	0.43
CIT (6-10 h) *vs.* <6 h	2.029 (0.889–4.629)	0.093	1.263 (0.749–2.133)	0.38
CIT ≥10 h *vs.* <6 h	6.465 (2.279–18.338)	<0.001	2.268 (1.222–4.211)	0.009
Status UNOS 2A *vs.* 1	0.268 (0.093–0.777)	0.015	0.638 (0.297–1.372)	0.25
Status UNOS 2B *vs.* 1	0.095 (0.039–0.234)	<0.001	0.351 (0.178–0.693)	0.003
Status UNOS 3 *vs.* 1	0.141 (0.057–0.350)	<0.001	0.401 (0.201–0.798)	0.009
ERG centre volume (25-50 cases) *vs.* <25 cases	0.466 (0.209–1.039)	0.062	0.399 (0.218–0.731)	0.003
ERG centre volume ≥50 cases *vs.* <25 cases	0.902 (0.445–1.831)	0.78	0.544 (0.313–0.944)	0.03
Retransplant *vs.* NO	6.486 (3.476–12.100)	<0.001	4.159 (2.148–8.051)	<0.001

BSA, body surface area; CIT, cold ischaemia time; D/R, donor-to-recipient; ERG, extended right graft; SLT, split liver transplantation; UNOS, united network for organ sharing.
*A gamma frailty term was also included in the models to account for the dependency between observations of patients transplanted multiple times.



Period											
1993–2005	300	241	232	225	221	207	200	195	184	179	174
2006–2014	372	289	275	265	250	239	208	176	147	110	85
2015–2019	196	123	81	43	14	0	0	0	0	0	0

Period											
1993–2005	299	222	215	210	206	195	188	183	174	169	165
2006–2014	372	283	272	263	248	236	205	173	145	109	84
2015–2019	196	123	80	42	14	0	0	0	0	0	0

Fig. 4. LLS outcomes by period. (A) Kaplan-Meyer overall patient survival. Period 1 *vs.* period 2 ($p = 0.05$), period 2 *vs.* period 3 ($p = 0.05$). (B) Kaplan-Meyer graft survival. Period 1 *vs.* period 2 ($p = 0.4$), period 2 *vs.* period 3 ($p = 0.4$). LLS, left lateral segment.

The overall incidence of retransplantation was 12.5% (109/868) with no significant changes over time.

Even after adjustment for all the above-mentioned variables, period 2 (HR 0.495; $p = 0.008$) showed improved patient survival compared to period 1.

Variables significantly associated with patient survival were: CIT 6-10 h *vs.* <6 (HR 2.534; $p = 0.005$); CIT >10 h *vs.* <6 h (HR 2.911; $p = 0.034$); UNOS status 2b *vs.* 1 (HR 0.365; $p = 0.006$); UNOS status 3 *vs.* 1 (HR 0.461; $p = 0.022$), and LLS utilization for retransplantation (HR 4.959; p <0.001) (Table 3).

Variables associated with graft survival included: CIT 6-10 h *vs.* <6 h (HR 1.669; $p = 0.007$); CIT ≥ 10 h *vs.* <6 h (HR 1.946; $p = 0.019$); UNOS status 2b *vs.* 1 (HR 0.623; $p = 0.038$); and UNOS status 3 *vs.* 1 (HR 0.570; $p = 0.009$), and LLS utilization for retransplantation (HR 2.737; p <0.001) (Table 4).

Discussion

With more than 1,700 cases, this is one of the largest series examining long-term national trends in *in situ* SLT since its introduction. Hopefully, it will contribute to achieving consensus on this procedure.

The initially poor outcomes for SLT explain the early reluctance to adopt this transplant option worldwide. However, more recently and despite some authors still claiming that SLT is more hazardous in the early post-transplant period,[15,17,20] several single- and multi-centre studies have reported similar graft and patient survival rates for SLT and WLT in adult recipients.[11,13,18,19,22,26,27] Despite improvements in survival and the new SLT regulations applied worldwide, the use of SLT is still suboptimal, accounting for only approximately 5% of LTs

Table 3. Univariable and multivariable Cox regression predicting patient mortality after LLS SLT*.

Variables	Univariable HR (95% CI)	*p* value	Multivariable HR (95% CI)	*p* value
Study period 2006-2014 *vs.* 1993-2005	0.553 (0.341–0.899)	0.017	0.495 (0.293–0.835)	0.008
Study period 2015-2019 *vs.* 1993-2005	0.602 (0.326–1.112)	0.10	0.696 (0.358–1.355)	0.29
Recipient weight (5-10 kg) *vs.* <5 kg	0.456 (0.223–0.931)	0.031	0.59 (0.246–1.416)	0.24
Recipient weight ≥10 kg *vs.* <5 kg	0.707 (0.348–1.439)	0.34	0.772 (0.32–1.863)	0.57
Donor age (50-60 years) *vs.* <50 years	1.625 (0.818–3.228)	0.17	1.354 (0.645–2.841)	0.42
Donor age >60 age *vs.* <50	2.021 (0.588–6.944)	0.26	0.762 (0.2–2.903)	0.69
BSA ratio ≥2 *vs.* <2	0.370 (0.191–0.715)	0.003	0.542 (0.234–1.258)	0.15
CIT (6-10 h) *vs.* <6 h	1.912 (1.067–3.426)	0.029	2.534 (1.326–4.843)	0.005
CIT ≥10 h *vs.* <6 h	1.810 (0.757–4.325)	0.18	2.911 (1.082–7.835)	0.034
Status UNOS 2A *vs.* 1	0.588 (0.280–1.231)	0.16	0.866 (0.392–1.911)	0.72
Status UNOS 2B *vs.* 1	0.220 (0.120–0.406)	<0.001	0.365 (0.178–0.748)	0.006
Status UNOS 3 *vs.* 1	0.246 (0.142–0.427)	<0.001	0.461 (0.238–0.893)	0.022
LLS centre volume ≥50 cases *vs.* <50 cases	0.161 (0.035–0.739)	0.019	0.226 (0.038–1.332)	0.10
Retransplantation *vs.* NO	6.699 (3.871–11.590)	<0.001	4.959 (2.583–9.524)	<0.001

BSA, body surface area; CIT, cold ischaemia time; D/R, donor-to-recipient; LLS, left lateral segment; SLT, split liver transplantation; UNOS, united network for organ sharing.
*A gamma frailty term was also included in the models to account for the dependency between observations of patients transplanted multiple times.

Table 4. Univariable and multivariable Cox regression predicting graft failure after LLS SLT*.

Variables	Univariable HR (95% CI)	*p* value	Multivariable HR (95% CI)	*p* value
Study period 2006-2014 *vs.* 1993-2005	0.828 (0.566–1.211)	0.33	0.836 (0.619–1.130)	0.24
Study period 2015-2019 *vs.* 1993-2005	0.678 (0.416–1.105)	0.12	0.809 (0.535–1.223)	0.31
Recipient weight (5-10 kg) *vs.* <5 kg	0.620 (0.336–1.143)	0.13	0.794 (0.481–1.310)	0.37
Recipient weight ≥10 kg *vs.* <5 kg	0.948 (0.515–1.744)	0.86	1.068 (0.644–1.773)	0.80
Donor age (50-60 years) *vs.* <50 years	1.208 (0.725–2.013)	0.47	1.138 (0.750–1.726)	0.55
Donor age >60 age *vs.* <50	1.794 (0.660–4.878)	0.25	1.424 (0.663–3.060)	0.36
BSA ratio ≥2 *vs.* <2	0.386 (0.224–0.664)	<0.001	0.658 (0.408–1.060)	0.085
CIT (6-10 h) *vs.* <6 h	1.807 (1.157–2.822)	0.009	1.669 (1.149–2.426)	0.007
CIT ≥10 h *vs.* <6 h	2.248 (1.135–4.451)	0.020	1.946 (1.118–3.389)	0.019
Status UNOS 2A *vs.* 1	0.663 (0.377–1.167)	0.15	0.803 (0.488–1.322)	0.39
Status UNOS 2B *vs.* 1	0.686 (0.449–1.051)	0.083	0.623 (0.399–0.974)	0.038
Status UNOS 3 *vs.* 1	0.557 (0.373–0.832)	0.004	0.570 (0.374–0.870)	0.009
LLS centre volume ≥50 cases *vs.* <50 cases	0.185 (0.053–0.646)	0.008	0.436 (0.177–1.073)	0.071
Retransplantation *vs.* NO	2.834 (2.071–3.877)	<0.001	2.737 (1.907–3.930)	<0.001

BSA, body surface area; CIT, cold ischaemia time; D/R, donor-to-recipient; LLS, left lateral segment; SLT, split liver transplantation; UNOS, united network for organ sharing.
*A gamma frailty term was also included in the models to account for the dependency between observations of patients transplanted multiple times.

across different countries.[15,18,32–34] Various reports indicate that SLT grafts are not frequently utilized in the United States, with no appreciable increase in the number of cases observed over time.[35–37]

A total of 1,945 deceased donor SLTs were performed in Italy over the study period, *i.e.* 8.9% of all transplantation procedures (1,945/21,846). Since Italy introduced a mandatory SLT policy in 2015, waiting list mortality has fallen significantly for both paediatric and adult patients (from 4.5% to 2.5% and from 9.7% to 5.2%, respectively).[27,31] Interestingly, although our analysis shows similar median waitlist times over the period for both adult and paediatric populations, preliminary paediatric waitlist data indicate a significant reduction soon after the new regulation was enforced.[27] The number of SLTs performed dropped in the two-year period 2018-2019 (Fig. 2), returning to 2016 figures in 2020, despite the COVID-19 pandemic.[38,39]

Over the last decade, there has been some shift from deceased donor LLS SLT to LDLT in paediatric recipients. Living donation increased over the last decade, with 41.8% (23/55) of all paediatric LTs coming from living donors in 2018, and 36.4% (20/55) in 2019. We believe the benefits of minimally invasive surgery may help to counter some of the disincentives and thereby increase donation rates.

Our registry data analysis shows a significant countrywide improvement in patient and graft survival with ERG over the years (Fig. 3), and a significant drop in retransplantation rates. The improvement in outcomes was seen to be largely due to the change in recipient selection policy (absence of high MELD and fewer retransplant candidates), but also to greater centre experience (higher volumes, shorter CIT, and standardized surgical technique). Undoubtedly, split graft allocation and utilization have been impacted by the surgical learning curve. Our analysis also confirms refinements in graft-to-recipient matching. In addition, the laboratory MELD score at transplant declined over time as more attention was paid to D/R size match, as demonstrated by the higher frequency of a D/R BSA ratio <0.9 in the first study period.

We have used SLT for several indications, including retransplant procedures. In our experience, however, split liver grafts for retransplantation are a risk factor for significantly worse graft and patient survival in both the paediatric and adult populations (p <0.001). In fact, split liver grafts for acute liver failure and retransplantation remain controversial.[40–42] Of note is the recent dramatic fall in the percentage of ERGs used for retransplantation in Italy (1.6%; 2015-2019) due to poor outcomes, which may be partly explained by the challenge of arterial reconstruction during retransplantation when it was mandatory to maintain the celiac trunk with the paediatric graft. The change over time in the division of the arteries during the splitting procedure from a child-favouring policy to a more

liberal arterial division has facilitated transplant procedures and increased acceptance of ERGs by adult-only transplant centres.[21,27,43,44] We believe that maintaining the celiac trunk with a split liver graft destined for retransplantation will increase and optimize the number of liver grafts available for these high-risk recipients.

Most of our splitting procedures were performed *in situ*. Since the introduction of the *in situ* option, the advantages of *in situ* and *ex vivo* procedures have been widely discussed.[5,8,9,21,44] *In situ* splitting clearly abolishes *ex vivo* benching and prolonged ischaemia times, allowing better definition of the transection plane, and providing two grafts in which haemostasis has been accomplished. However, this procedure requires a surgical team with extensive split liver experience. In addition, logistical requirements may lead to the application of the *ex situ* split technique only in selected cases. We agree, however, that these techniques are interchangeable and should be applied where most appropriate and not according to operator preference as both can give equally good results, provided optimal technique and D/R matching are ensured.

Our experience nonetheless suggests that the systematic adoption and standardization of the *in situ* procedure has facilitated split graft sharing between centres, favoured expansion of donor selection criteria, and reduced CIT.[22,27] As demonstrated by other studies,[15,30] our registry data analysis confirmed CIT to increase the risk of graft failure. CIT >6 h was associated with decreased graft survival with LLS SLT, while CIT >10 h decreased graft survival for both types of graft in the paediatric and adult populations. Prolonged CIT is often due to logistical and/or technical issues, increasing ischaemia/reperfusion injury and negatively impacting the outcomes of split liver grafts. As recently reported, splitting the liver during machine perfusion could potentially combine the advantages of both *in situ* and *ex vivo* techniques, especially when prolonged CIT or graft complexity are likely.[45,46]

One of the variables reported as strongly associated with SLT outcomes is donor age, with 40 years still a UNOS cut-off criterion for liver graft splitting.[30,47] We observed that although donor criteria expansion significantly increased our median donor age, this did not affect long-term outcomes. Moreover, while donor age >50 years was seen to be negatively associated with patient and graft survival in this study, it was not a significant predictor of patient and graft survival at multivariable analysis. We agree, however, that the decision to split a donor liver is complex, requiring accurate risk assessment.[27,30]

Our current national mandatory split liver policy considers 50 years as the cut-off for liver splitting.[27] However, these indications are meant as guidelines. The final decision is taken in light of each transplant centre's criteria and expertise.

Finally, we found that centres transplanting <25 split liver grafts during the study period reported higher graft failure rates for ERG SLT. In contrast to other reports,[26] our data suggest that experience-gaining programs spanning several years would contribute to better results.

We confirm that paediatric transplant outcomes have remained largely unchanged over the years considered, with the learning curve plateauing more rapidly than for ERG procedures in adults.

No experience-based difference in deceased donor LLS graft survival was observed in any of the transplant centres. In fact, deceased donor LLS graft survival showed no significant improvement over time despite the significantly higher patient survival in the last two periods compared to the first. The significant decrease in primary non function after the first period, due to better D/R matching and improvements in surgical technique, is reflected in the rapid learning curve. The reason is probably that in Italy, most paediatric SLTs have been performed consecutively over a short period of time in just a few centres by the same surgical teams.[48,49] In addition, we believe that the deceased donor LLS graft is at lower surgical risk of arterial complications compared to ERG procedures, especially since the lifting of the previous mandatory child-favouring assignment of the celiac tripod. While there are numerous reports of short- and mid-term survival after SLT, very few studies consider long-term (25 years) outcomes. The long-term outcomes of this Italy-wide study are similar to other recently published reports.[18,19,30,33–35,42,50–53]

As a registry data analysis, our study has the limitations of self-reported data. In addition, as recipient surgical complications were not precisely reported, graft survival is the only accurately measurable outcome. No analysis was possible of the impact of SLT in the perioperative period.

The advancements achieved in *in situ* SLT probably reflect the confidence and skill gained in complex hepatobiliary surgery by those centres most actively involved in SLT and LDLT. Our data analysis would indicate the benefits for less experienced transplant centres of liaising with more experienced units on key issues such as recipient selection and conservative graft-to-recipient matching. Indeed, we believe that the sharing in recent years of clinical experience by more experienced centres has been instrumental in improving outcomes, and beneficial for the transplant community as a whole. Our community should continue to identify new strategies to expand the donor pool and utilize SLT to reduce, and even possibly eliminate, paediatric waitlist mortality.

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Abbreviations

CIT, cold ischaemia time; BSA, body surface area; D/R, donor-to-recipient; ERG, extended right graft; HCC, hepatocellular carcinoma; LDLT, liver donor liver transplant(ation); LLS, left lateral segment; MELD, model for end-stage liver disease; SLT, split liver transplant(ation); UNOS, United Network for Organ Sharing; WLT, whole liver transplantation.

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Conflict of interest

All the authors declare no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

AL, UC, LDC, MC and EA designed and conceived this project. AL wrote the manuscript. AL, ST, TDF, CS, MC, DB and MGV summarized data obtained from the two registries. All coauthors obtained approvals, collected and provided clinical data. AL, ST, TDF, DB, MGV and UC analysed and interpreted data. AL, RDC, UC, LDC, MC and EA revised the manuscript. All authors contributed to and approved the manuscript.

Data availability statement

Study data are available from the corresponding author upon reasonable request.

Supplementary data

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