Transplant International

META-ANALYSIS

Survival following right lobe split graft, living- and deceased-donor liver transplantation in adult patients: a systematic review and network meta-analysis

Paschalis Gavriilidis[1], Aurelio Tobias[2], Robert P. Sutcliffe[1] & Keith J. Roberts[1]

1 Department of Hepato-Pancreato-Biliary and Liver Transplant Surgery, Queen Elizabeth University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

2 Biostatistician in Tommy's National Centre for Miscarriage Research, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK

Correspondence
Paschalis Gavriilidis PhD, Queen Elizabeth University Hospitals Birmingham NHS Foundation Trust, Mindelsohn Way, B15 2TH, Birmingham, UK.
Tel.: +447553949678;
e-mail: pgavrielidis@yahoo.com

SUMMARY

Graft and patient survival outcomes following split liver transplantation (SLT), living-donor liver transplantation (LDLT) and deceased-donor liver transplantation (DDLT) were estimated using Bayesian network meta-analysis. Databases were searched for relevant articles over the previous 20 years (MEDLINE, Embase, Cochrane Library and Google Scholar). Systematic review, pairwise meta-analysis and Bayesian network meta-analysis were performed. Pairwise meta-analysis demonstrated that there were no significant differences in graft and patient survival outcomes. Consequently, Bayesian network meta-analysis demonstrated no significant differences in 1-, 3- and 5-year graft and patient survival between the three alternative liver transplantations. No discrepancies were demonstrated after comparisons of direct and indirect evidence of 1-, 3- and 5-year patient and graft survival of the three node-split models namely SLT, LDLT and DDLT. The 1-, 3- and 5-year graft and patient survival of the SLT and LDLT cohorts compared to the DDLT cohort demonstrated no significant differences. The direct and indirect evidence of this study can serve as comparator for future studies.

Transplant International 2018; 31: 1071–1082

Key words
living-donor liver transplantation, right lobe split liver transplantation, whole-liver transplantation

Received: 15 May 2018; Revision requested: 18 June 2018; Accepted: 11 July 2018; Published online: 12 August 2018

Introduction

The need for potential recipients for liver transplantation has always exceeded the size of the donor pool. The waiting list mortality among patients waiting for liver transplantation is 10–20% [1]. It has been reported that split liver transplantation (SLT) involves only 1.3% of the deceased-donor liver transplantation (DDLT) [2]. Development of SLT was associated with significantly reduced waiting list times among paediatric recipients older than 1 year, ranging from 192 to 30 days [3]. In countries, where DDLT is prohibited or limited, living-donor liver transplantation (LDLT) has become the standard for liver transplantation. However, in countries where both SLT and LDLT are possible, there is debate over the appropriateness of these techniques.

Both SLT and LDLT present some form of compromise over DDLT. Developing LDLT programmes among those countries where SLT is practiced raises ethical issues due to the inherent risk to the living donors.

doi:10.1111/tri.13317

However, given the shortage of donor organs among adult and paediatric recipients, these techniques remain viable ways to increase the donor pool.

Consequently, comparing outcomes between recipients of SLT, LDLT and DDLT is therefore necessary to form an argument for or against these procedures. To date, there are data of direct comparisons of SLT versus DDLT and LDLT versus DDLT mainly from retrospective studies [4–28]. However, there is a clear paucity of data with limited direct comparisons between recipients of SLT and LDLT. Only one retrospective study reported on the 1-, 3- and 5-year graft and patient survival of SLT versus LDLT [25]. This paucity of direct evidence can be tackled with the estimation of the indirect evidence using the methods of the network meta-analysis [29,30]. Thus, the estimated indirect evidence can be compared with the existing and future direct evidence [29,30].

The aim of this study was to compare the survival benefit between adult recipients of SLT, LDLT and DDLT using Bayesian network meta-analysis.

Methods

The PRISMA Statement checklist for reporting systematic review and meta-analysis was followed in this study.

Literature search

Using both free text and MESH terms (right lobe split liver transplantation; living-donor liver transplantation; deceased-donor liver transplantation; whole-liver transplantation), a systematic search of the literature was performed in MEDLINE, Embase, PubMed and Google Scholar databases from their inception up to February 2018 [Appendix 1]. Abstracts were selected. References of the retrieved articles were checked manually for further studies. Any discrepancies regarding the study selection were resolved by discussion between the authors.

Study selection, and inclusion and exclusion criteria

Only studies that compared (i) right lobe SLT versus whole-liver transplantation (WLT), (ii) right lobe SLT versus LDLT and (iii) LDLT versus DDLT were included in the review. Excluded studies were studies with less than 12 patients in each arm and studies that did not accurately describe the splitting method. The most recent publication was chosen from the overlapped studies. Time, language and region restrictions were not applied to the systematic review.

Data extraction and outcomes

Two researchers (PG and KR) independently extracted the following summary data for the included studies: name of authors; country; number of patients included in SLT, LDLT and DDLT; age of recipient; sex of recipient; model for end-stage liver disease (MELD) score; and 1-, 3- and 5-year patient and graft survival rates. Patient and graft survival rates were the primary outcome measures for the three procedures.

Statistical analysis

The methodological quality of all included studies was assessed using the validated Newcastle–Ottawa scale (NOS) [31]. Studies scoring ≥7 were considered of high quality.

First, a pairwise meta-analysis was performed for studies that compared two transplantation approaches. Subsequently, a Bayesian network meta-analysis was conducted to compare SLT, LDLT and DDLT. Statistical analysis was conducted using both Stata software (version 15; Stata Corp LP, College Station, TX, USA) and General mixed treatments comparisons (GeMTC) software [32,33]. Dichotomous variables were analysed based on odds ratios (ORs) with 95% confidence intervals (CI). Analysis of long-term survival was performed by combining the hazard ratios (HRs) and 95% CIs from the included studies. These were rarely reported and thus were estimated using the method described by Parmar *et al.* [34], where possible. For studies that reported the numbers at risk, these were combined with either the quoted survival rates or values read from enlarged plots of the Kaplan–Meier curves to produce the estimates. Where numbers at risk were not quoted, constant censoring over the period of follow-up was assumed in the estimation.

For all analyses, the point estimate was considered significant at $P < 0.05$.

Bayesian network meta-analysis was performed using hierarchical random-effects models [30]. A fixed-effects model was also used to estimate whether any discrepancy could be demonstrated between the results of the two models. Quantitative data synthesis of the connected network of the studies was conducted using the software package WinBUGS (version 1.4.3; MRC Biostatistics Unit, Cambridge, UK) [33,35]. The pooled estimates were obtained using the Markov chain

Monte Carlo method. Minimally informative priors with vague normal prior distributions were used [35]. For each model, 200 000 simulations were generated for the two sets of different initial values, and the first 5000 were discarded as the burn-in period. The Brooks–Gelman–Rubin statistic was used for the assessment of convergence [35]. The point estimate was defined as the median of the posterior distribution based on 200,000 simulations; the corresponding 95% credible intervals (CrIs) were obtained using the 2.5th and 97.5th percentiles of the posterior distribution, which can be interpreted in a similar way as 95% CIs [35]. Inconsistency and heterogeneity of the direct and indirect evidence for the three surgical approaches were estimated.

The node-splitting method was used to calculate the inconsistency of the model, which separated evidence into direct and indirect; then, the agreement between the two was evaluated and reported with Bayesian values [33,36,37]. The diagnostic information criterion (DIC), random-effects standard deviation (RESD) and effect estimates from direct and indirect evidence were displayed for convenient assessment.

Results

Search strategy and study characteristics

Twenty-six studies, which included 13 374 patients, were selected from a pool of 739 studies [4–28]. Among these, patients that underwent liver transplantation were distributed as follows: SLT 1329 (10%), LDLT 3469 (26%) and DDLT 8576 (64%). From the 43 full-text assessed papers, 17 were excluded for the following reasons; three articles overlapped with the previous publications; and 14 did not clearly describe the splitting graft types (Fig. 1). Thirteen studies compared RLSG to DDLT [4–16], eleven studies compared LDLT to DDLT [17–24,26–28] and two studies compared SLT to LDLT [19,25]. Twenty-two studies (88%) had an NOS score of ≥7 [4–25] (Tables 1–4).

Patient and donor demographics

No differences were observed in the demographic characteristics of the recipients between the SLT, LDLT and DDLT cohort. However, the donors for SLT were significantly younger by 12 years [mean difference (MD) −12.06 years, 95% CI −16.29 to −7.83, $P < 0.001$, $I^2 = 91\%$] (Table 1).

Results from pairwise meta-analysis

Graft survival

There were no significant differences between the SLT and DDLT cohorts in terms of 1-, 3- and 5-year graft survival (HR 0.98, 95% CI 0.93–1.03, $P = 0.42$, $I^2 = 22\%$), (HR 1.05, 95% CI 0.79–1.38, $P = 0.74$, $I^2 = 95\%$), (HR 1.04, 95% CI, 0.98–1.11, $P = 0.20$, $I^2 = 12\%$), respectively (Fig. S1).

Similarly, there was no significant difference between the LDLT cohort and DDLT cohort in 1-, 3- and 5-year graft survival (HR 0.92, 95% CI 0.44–1.94, $P = 0.83$, $I^2 = 89\%$; HR 0.98, 95% CI 0.61–1.39, $P = 0.94$, $I^2 = 65\%$; and HR 1.01, 95% CI 0.80–1.28, $P = 0.93$, $I^2 = 0\%$), respectively (Fig. S1).

Furthermore, there was no significant difference in 1-year graft survival between the SLT and LDLT cohorts (HR 0.94, 95% CI, 0.23–3.79, $P = 0.93$, $I^2 = 0\%$) (Fig. S1).

Patient survival

No significant differences were demonstrated in 1-, 3- and 5-year patient survival between the SLT and DDLT cohorts (HR 1.00, 95% CI 0.93–1.09, $P = 0.92$, $I^2 = 54\%$; HR 0.95, 95% CI 0.89–1.01, $P = 0.12$, $I^2 = 0\%$; and HR 1.02, 95% CI 0.96–1.09, $P = 0.48$, $I^2 = 0\%$), respectively.

Similarly, no significant differences were demonstrated in 1-, 3- and 5-year patient survival between the LDLT and DDLT cohorts (HR 1.12, 95% CI, 0.96–1.31, $P = 0.14$, $I^2 = 4\%$; HR 0.90, 95% CI 0.68–1.20, $P = 0.48$, $I^2 = 45\%$; and HR 0.86, 95% CI 0.72–1.03, $P = 0.10$, $I^2 = 19\%$), respectively.

There was no significant difference in 1-year patient survival between the SLT and LDLT cohorts (HR 1.06, 95% CI 0.87–1.28, $P = 0.59$, $I^2 = 0\%$) (Fig. S2).

Fitness of the model, node-splitting analysis

The network of evidence of the three liver transplantations was demonstrated with a closed loop (triangle) (Fig. S7). Evaluation of inconsistency using loop-specific heterogeneity was estimated to be nonsignificant [relative odds ratio (ROR) 1.15, 95% CI 1.00–1.69; heterogeneity $\tau^2 = 0.005$] (Fig. S3). In addition, the random-effects standard deviation = 0.0592 and time-series standard error = 0.0004 supported the consistency of the model. First, the arbitrary starting values did not have an undue influence on the sampling process and

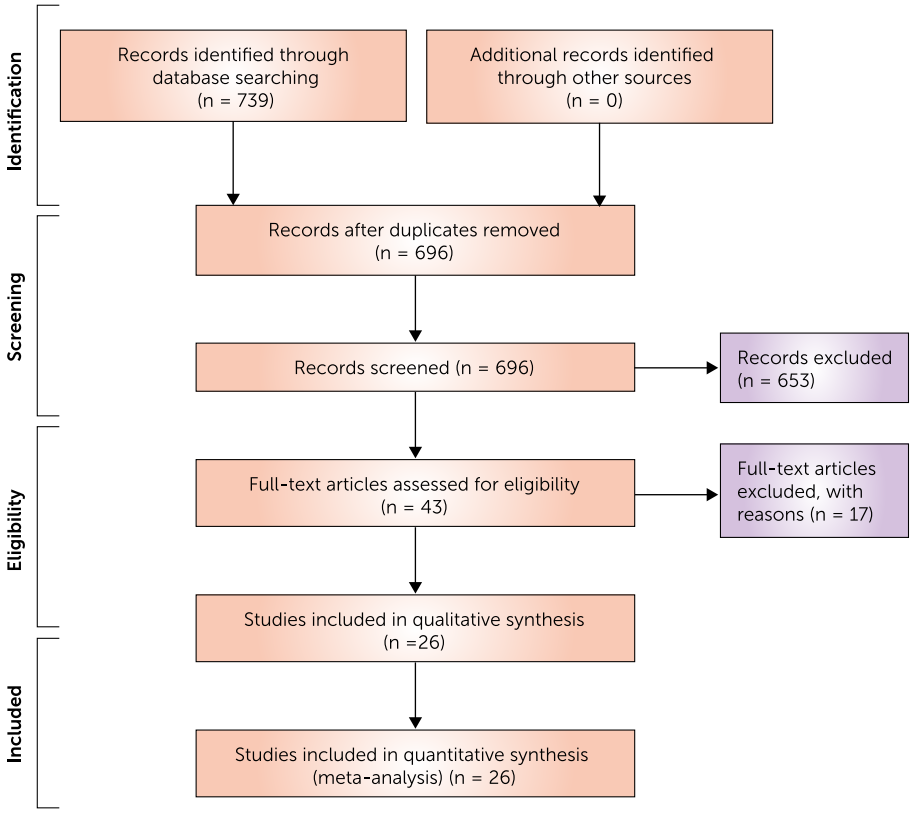

Figure 1 Flow diagram of the search strategy.

secondly, the quantities of interest had been estimated to sufficient accuracy. The time-series plot demonstrated a converged chain that contained sufficient information for accurate inferences; the potential scale reduction factor (PSRF) reached stable values below 1.01 and the series plot of the estimation accuracy showed density and tapering of the extreme values in the tails (Fig. S4). Furthermore, no inconsistency of the model was found using the node-splitting method. An agreement between direct and indirect evidence among the three node-split models was found (Figs S5 and S6).

Results from network meta-analysis

Graft survival

There were no significant differences in 1-year graft survival between SLT, LDLT and DDLT, SLT versus DDLT (HR 1.02, 95% CrI 0.72–1.47); LDLT versus DDLT (HR 0.93, 95% CrI 0.64–1.42); and SLT versus LDLT (HR 0.97, 95% CrI 0.56–1.52).

Similarly, there were no significant differences in the 3-year graft survival between SLT, LDLT and DDLT: SLT versus DDLT (HR 1.08, 95% CrI 0.74–1.59); SLT versus DDLT (HR 0.92, 95% CrI 0.57–1.41); and LDLT versus DDLT (HR 0.85, 95% CrI 0.50–1.38).

In addition, there was no significant difference in the 5-year graft survival between SLT, LDLT and DDLT: SLT versus DDLT (HR 1.04, 95% CrI 0.95–1.14), LDLT versus DDLT (HR 1.03, 95% CrI 0.87–1.22) and SLT versus LDLT (HR 0.98; CrI 0.83–1.16), (Fig. 2).

Indirect evidence for graft survival

There was no significant difference between the direct and indirect evidence in 1-, 3- and 5-year survival based on the node-split models for SLT versus DDLT, SLT versus LDLT and LDLT versus DDLT (Fig. S5).

Patient survival

There was no difference in 1-year patient survival between SLT, LDLT and DDLT: SLT versus DDLT (HR 1.01, 95% CrI 0.91–1.13), LDLT versus DDLT (HR 1.05, 95% CrI 0.89–1.2) and SLT versus LDLT (HR 1.03, 95% CrI 0.86–1.22), respectively.

Similarly, there was no difference in the 3-year patient survival between SLT, LDLT, and DDLT, SLT

Table 1. Split liver transplantation versus whole-liver transplantation study characteristics.

Author, study period, country	Number of patients, SLT–WLT	Age of donor, SLT–WLT, mean ± SD	Sex of donor, SLT–WLT, male (%)	Age of recipient, SLT–WLT, mean, SD	Sex of recipient, SLT–WLT, male (%)	MELD score, SLT–WLT	Split method	Cold ischaemia time SLT-WLT (min)	NOS
Mourad MM, 2015, the UK	171–1412	29 ± 10 46 ± 10 *P* = 0.001	110 (64) 748 (53) *P* = 0.52	50 ± 13 51 ± 12 *P* = 0.43	77 (45) 734 (52) *P* = 0.09	13 ± 3.5 13 ± 4.1 *P* = 0.61	98% *ex situ*	578 ± 8 545 ± 10.5 *P* = 0.07	8
Mallik M, 2012, the UK	17–32	23 ± 12 34 ± 11.5 *P* = 0.014	12(70) 21 (66) *P* = 1.00	50 ± 10.25 58 ± 5.75 *P* = 0.021	4 (24) 24 (75) *P* < 0.001	14 ± 5.75 19 ± 6.5 *P* = 0.058	*Ex situ*	655 ± 109.5 363 ± 87.25 *P* < 0.001	7
Takebe A, 2009, Japan	80–80	33 ± 13.25 38 ± 12.5 *P* = ns	NR	42 ± 12.5 43 ± 11.5 *P* = ns	NR	16 ± 8.5 17 ± 8.5 *P* = ns	*Ex situ*	747 ± 172 662 ± 173 *P* = 0.006	8
Sandroussi C, 2009, Australia	43–182	39 ± 12 47 ± 16.75 *P* < 0.001	22 (51) 106 (58) *P* = 0.238	53 ± 12.5 52 ± 13 *P* = 0.560	29 (67) 141 (77) *P* = 0.169	13 ± 4 18 ± 11 *P* < 0.001	88% *in situ*	494 ± 139 535 ± 138 *P* = 0.09	7
Hong JC, 2008, the USA	72–2433	35–37 *P* = 0.520	NR	52–52 *P* = 0.501	27 (66) 1465 (61)	NR	*In situ*	45–402 *P* < 0.001	7
Sainz-Barriga, 2008, Belgium	12–12	33.3 ± 13 43.8 ± 10.25 *P* = 0.06	8 (67) 7 (58) *P* = 1.00	52 ± 11.6 55.3 ± 6.5 *P* = 0.20	8(66) 11(92) *P* = 0.19	17.1 ± 8.5 20.7 ± 9.5 *P* = 0.18	75% *ex situ*	NR	8
Bonney GK, 2008, the UK	27–27	40 ± 9.75 46.7 ± 15 *P* = 0.08	NR	52 ± 11.5 53 ± 10 *P* = 0.76	16 (59) 12 (44) *P* = 0.41	16 ± 6 16.4 ± 6 *P* = 0.83	*Ex situ*	675 ± 108 602 ± 222 *P* = 0.09	8
Wilms C, 2006, Germany	70–70	33.5 ± 12.25 38 ± 12.16 *P* = ns	46 (66) 45 (64) *P* = ns	51 ± 13.25 51 ± 13.25 *P* = ns	38 (54) 46 (66)	14 ± 7.5 13 ± 6.75 *P* = ns	53% *ex situ*	570 ± 171.25 566 ± 124.75	8
Corno V, 2006, Italy	22–48	22 ± 12.25 54 ± 15.5 *P* = ns	NR	49.9 ± 9.97 54.8 ± 11.52 *P* = ns	16 (73) 40 (83)	17 ± 5.5 24 ± 5.75 *P* = ns	*In situ*	480 ± 14.1 432 ± 121.5 *P* = ns	8
Maggi U, 2005, Italy	20–261	31 ± 14 41 ± 17 *P* = 0.01	10 (50) 161 (60) *P* = ns	46 ± 12 45 ± 10 *P* = ns	12 (60) 185 (71) *P* = ns	NR	*In situ*	527 ± 123.79 541 ± 146.57 *P* = ns	8
Spada M, 2005, Italy	15–87	26 ± 11.75 53 ± 18.25 *P* = 0.001	11 (73) 47(52) *P* = 0.16	51 ± 9.5 52 ± 11.5 *P* = 0.74	12 (80) 58 (67)	NR	*In situ*	540 ± 128.75 408 ± 123.75	8
Cardillo, 2005, Italy	154–1126	31 ± 15 44 ± 20	NR	48 ± 13 46 ± 15	NR	NR	*In situ*	492 ± 150 486 ± 156	8
Broering 2002, Germany	40–40	32 ± 11.5 33.5 ± 12.25 *P* = 0.57	24 (60) 24(60) *P* = 1.00	51 ± 11.25 51 ± 11.25 *P* = 0.78	25 (62) 22(55) *P* = 0.65	NR	68% *ex situ*	NR	8

Table 1. Continued.

Author, study period, country	Number of patients, SLT–WLT	Age of donor, SLT–WLT, mean ± SD	Sex of donor, SLT–WLT, male (%)	Age of recipient, SLT–WLT, mean, SD	Sex of recipient, SLT–WLT, male (%)	MELD score, SLT–WLT	Split method	Cold ischaemia time SLT-WLT (min)	NOS
Pooled 6553	743 (11%)–5810 (89%)	MD = −12.06 (−16.29 to −7.83) $P < 0.001$	OR = 1.25 (0.99–1.58) $P = 0.06$	MD = −0.81 (−2.30 to 0.68) $P = 0.28$	OR = 0.70 (0.47–1.05) $P = 0.08$	MD = −2.45 (−4.61 to −0.28) $P = 0.03$	374 (51%) *ex situ*	MD = 56.68 (20.6–92.7) $P = 0.002$	

MD, mean difference; MELD, model for end-stage liver disease; NOS, Newcastle–Ottawa scale; NR, nonreported; ns, nonsignificant; OR, odds ratio; SD, standard deviation; SLT, split liver transplant; WLT, whole-liver transplant.

versus DDLT (HR 0.96, 95% CrI: 0.82–1.14), LDLT versus DDLT (HR 0.92, 95% CrI 0.75–1.14) and SLT versus LDLT (HR 0.95, 95% CrI 0.76–1.21).

In addition, there was no difference in 5-year patient survival between SLT, LDLT and DDLT, SLT versus WLT (HR 1.02, 95% CrI 0.94–1.10), LDLT versus DDLT (HR 0.97, 95% CrI 0.83–1.12) and SLT versus LDLT (HR 0.95, 95% CrI 0.81–1.10), (Fig. 3).

Indirect evidence of patient survival

There was no significant difference between direct and indirect evidence for 1-, 3- and 5-year survival based on the three node-split models of the SLT versus DDLT, SLT versus LDLT and LDLT versus DDLT (Fig. S6).

Discussion

The present study compared survival outcomes among adult patients who underwent SLT, LDLT and DDLT. The survival outcomes were first estimated and compared with pairwise meta-analysis, and then with network meta-analysis using Bayesian statistics, and finally using effect estimates of direct and indirect evidence.

The pairwise meta-analysis demonstrated that there were no significant differences in graft and patient survival between the three head to head comparisons. So far, there is a paucity of studies comparing SLT versus LDLT. Only two studies have provided data about this comparison, and the estimated direct evidence demonstrated no significant differences [19,25]. In the current study, for the first time to our knowledge, the indirect evidence of the three alternative liver transplantations was estimated using Bayesian network meta-analysis. Noteworthy, the indirect evidence for the node-split model comparing SLT versus LDLT showed no significant differences. Moreover, comparison of the direct and indirect evidence for graft and patient survival did not demonstrate any discrepancy. In addition, comparison of the Bayesian values, DIC and RESD, demonstrated consistency of the model.

Similarly, the model evaluating the SLT versus DDLT and LDLT versus DDLT did not demonstrate any significant discrepancies between direct and indirect evidence for graft and patient survival.

Many factors have been suggested to be associated with recipient survival after SLT; these include recipient health status at transplantation, elevated donor gamma glutamyl transferase (GGT) level, graft steatosis, graft-

Table 2. Living-donor liver transplantation versus deceased-donor liver transplantation study characteristics.

Author, year, country	Number of patients, LDLT-DDLT	Age of recipient, LDLT-DDLT, mean ± SD	Gender of recipient, LDLT-DDLT, male (%)	MELD score, LDLT-DDLT, mean, SD	NOS, max = 9
Reichman T, 2013, Canada	145–145	54 ± 7.5 53.9 ± 7.7 $P = 0.764$	117 (80) 117 (80) $P = 1.00$	14.4 ± 5.75 14 ± 6.75 $P = 0.976$	9
Sandhu L, 2012, Canada	58–287	54.5 ± 8.8 55.8 ± 7.1 $P = 0.30$	46 (79) 246 (86) $P = 0.23$	12.5 ± 6.5 11 ± 10.25 $P = 0.23$	8
Bhangui P, 2011, France	36–120	54 ± 7 56 ± 8 $P = 0.45$	32 (89) 100 (83) $P = 0.42$	13.5 ± 5.9 14.5 ± 5.9 $P = 0.35$	7
Fisher R, 2007, USA	58–34	54.5 ± 8.9 51.7 ± 9.6 $P = 0.21$	45 (78) 25 (74) $P = 0.66$	NR	6
Humar A, 2007, USA	69–284	49.7 ± 11.5 51 ± 13.75 $P = 0.69$	34 (50) 96 (34) $P = 0.004$	17 ± 4 26 ± 6.5 $P < 0.001$	8
Lo CM, 2007, Hong Kong, China	43–17	52 ± 13.25 49 ± 5.75 $P = 0.599$	39 (91) 15 (88) $P = 0.959$	15 ± 13.25 16 ± 5.25 $P = 0.168$	7
Terrault NA, 2006, USA	181–94	50.5 ± 10.5 52.3 ± 11 $P = 0.17$	119 (66) 68 (72) $P = 0.27$	14 ± 8.5 18 ± 8.25 $P < 0.001$	6
Sebagh M, 2006, France	38–38	43 ± 14 48 ± 13 $P =$ ns	29 (76) 23 (61) $P =$ ns	NR	8
Maluf D, 2005, USA	69–202	46 ± 12 49.6 ± 17 $P = 0.01$	57 (82) 156 (77) $P =$ ns	13.2 ± 1.1 21 ± 0.8 $P = 0.001$	8
Hwang SH, 2005, Korea	237–75	50 ± 8 49 ± 7 $P = 0.599$	196 (83) 60 (80) $P = 0.595$	NR	6
Thuluvath P, 2004, USA	764–1470	49.7 ± 5.2 49.8 ± 10.8 $P = 0.969$	512 (67) 985 (67) $P = 1.00$	NR	8
Pooled differences 4464	1698 (33) 2766 (67)	MD-80 (−1.91 to 0.32), $P = 0.16$, $I^2 = 57\%$	OR = 1.06 (0.94–1.19), $P = 0.33$, $I^2 = 5\%$	MD = −3.10 (−6.37, 0.16), $P = 0.06$, $I^2 = 98\%$	HQ = 8

DDLT, deceased-donor liver transplantation; LDLT, living-donor liver transplantation; MD, mean difference; MELD, model for end-stage liver disease; NOS, Newcastle–Ottawa scale; NR, nonreported; ns, nonsignificant; OR, odds ratio; SD, standard deviation.

to-recipient body weight ratio, intensive care unit stay and total hospital stay [38].

Given the risk profile of transplanting split grafts, previous studies have attempted to define splitting criteria involving donors for one adult and one paediatric recipient. These include age between 14 and 50 years, weight over 45 kg, BMI ≤26, intensive care unit stay ≤3 days, mean arterial pressure ≥60 mmHg, sodium levels ≤160 mmol/l, serum glutamic transaminase (SGPT) ≤60, GGT ≤50; of note, when the donor weight exceeded 70 kg, two adult recipients were preferred. Modelling demonstrated that if splitting criteria applied only to optimal donors, there would be an increase in the number of paediatric donors by 15% and adults by 8.6%. Within the same model, if donor age was increased to 60 years, then the additional increase would be 6% and 2.4% for paediatrics and adult donors, respectively [39].

Table 3. Split liver transplantation versus living-donor liver transplantation study characteristics.

Author, year, country	Number of patients, SLT-LDLT	Donor age, SLT-LDLT	Donor gender male, SLT-LDLT (%)	Recipient age, SLT-LDLT	Recipient gender male, SLT-LDLT (%)	MELD score, SLT-LDLT	CIT, SLT-LDLT	Splitting method in SLT	Used lobe in SLT right-left (%)	Lobe in LDLT, right-left (%)	NOS, max = 9
Saidi RF, 2011, USA	557–1715	23 ± 9.4	384 (69)	52.8 ± 10	250 (45)	20.9 ± 9.2	8.2 ± 3.7	223 (40) *in-situ*	457 (82)	1646 (96)	7
		37.3 ± 10	1218 (71)	50.7 ± 11	943 (55)	14.5 ± 5.6	3.1 ± 5.9	110 (20) *ex-situ*	100 (18)	69 (4)	
		P < 0.001	*P* < 0.001	*P* < 0.001	*P* < 0.001	*P* < 0.001	*P* < 0.001	224 (40) NR	*P* < 0.001	*P* < 0.001	
Sebagh M, 2006, France	20–38	36 ± 11	14 (68)	43 ± 16	12 (60)	NR	550 ± 180	NR	17 (85)	38 (100)	9
		39 ± 13	15 (39)	43 ± 14	29 (76)		185 ± 132		3 (15)		
		P = 0.003	*P* = ns	*P* = ns	*P* = ns		*P* < 0.001		*P* < 0.001		
Pooled differences 2357 patients	586 (25) 1771 (75)	MD = −9.10 (−20.14, 1.93) *P* = 0.11	OR = 1.59 (0.42, 5.99) *P* = 0.49	MD = 2.07 (1.10, 3.04) *P* < 0.001	OR = 0.66 (0.55, 0.80) *P* < 0.001	MD = 5.99 (5.21, 6.76) *P* < 0.001	MD = 6.09 (3.98,8.20) *P* < 0.001	254 (40) *in-situ* 110 (20) *ex-situ* 224 (40) NR	499 (81) 118 (19) *P* < 0.001	1753 (96) 69 (4) *P* < 0.001	HQ = 2

CIT, cold ischaemia time; LDLT, live donor liver transplant; MELD, model for end-stage liver disease; NOS, Newcastle–Ottawa scale; NR, nonreported; ns, nonsignificant; SLT, split liver transplant.

Limitations

The results of this study should be interpreted cautiously because the included studies are all retrospective analyses from single centres and a heterogeneous splitting procedure was used in SLT. Moreover, the results may be influenced by national and institutional characteristics and practice. Furthermore, this study only estimated the survival outcomes because of the lack of data on postoperative complications that could have been used for meta-analysis.

Many centres, especially those without high volume of patients, were more likely to be cautious with patient selection of for SLT and LDLT. The new Italian allocation criteria allowed for the potential allocation of partial grafts to less acutely ill patients [39]. The aetiologies of hepatic diseases and the definitions of the complications may vary across the different studies because no international validated classification tool like Clavien-Dindo has been used by the authors of the included studies. Therefore, all of these may have added bias to our outcomes. Risk adjustment of donor and recipient factors is needed to accurately determine benefit, harm or equivalence of one technique over another. Various factors related to reduced graft and recipient survival of split grafts have been reported [40]. Modelling based upon this data has been used to estimate changes to the size of the donor pool based upon changes in definitions of SLT criteria. An international registry of SLT and LDLT could serve a similar purpose to better define donor and recipient cohorts in detail and permit an in-depth assessment of outcomes. Until then, this network meta-analysis presents the most thorough assessment of survival outcomes to date.

Conclusions

In conclusion, SLT and LDLT cohorts demonstrated equivalent graft and recipient survival compared to DDLT. The direct and indirect evidence of this study can serve as comparator for findings of future studies.

Funding

The authors have declared no funding.

Conflicts of interest

The authors have declared no conflicts of interest.

Table 4. Newcastle–Ottawa scale star template for risk of bias.

Newcastle–Ottawa star template of studies of split liver versus whole-liver transplantation					Living-and deceased-donor liver transplantation and split liver versus living-donor liver transplantation†				
Author, study period, country	Selection, max = 4	Comparability, max = 2	Outcome, max = 3	NOS, max = 9	Author, year, country	Selection, max = 4	Comparability, max = 2	Outcome, max = 3	NOS, max = 9
Mourad MM, 2015, the UK	****	*	***	8	Reichman T, 2013, Canada	****	**	***	9
Mallik M, 2012, the UK	***	*	***	7	Sandhu L, 2012, Canada	****	*	***	8
Takebe A, 2009, Japan	****	*	***	8	Bhangui P, 2011, France	***	*	***	7
Sandroussi C, 2009, Australia	***	*	***	7	Fisher R, 2007, USA	**	*	***	6
Hong JC, 2008, the USA	***	*	***	7	Humar A, 2007, USA	****	*	***	8
Sainz-Barriga, 2008, Belgium	****	*	****	8	Lo CM, 2007, Hong Kong, China	***	*	***	7
Bonney GK, 2008, the UK	****	*	****	8	Terrault NA, 2006, USA	***	*	**	6
Wilms C, 2006, Germany	****	*	****	8	Sebagh M, 2006, France	****	*	***	8
Corno V, 2006, Italy	****	*	****	8	Maluf D, 2005, USA	****	*	***	8
Maggi U, 2005, Italy	****	*	****	8	Hwang SH, 2005, Korea	***	*	**	6
Spada M, 2005, Italy	****	*	****	8	Thuluvath P, 2004, USA	****	*	***	8
Cardillo, 2005, Italy	****	*	****	8	Sebagh M, 2009, France†	****	**	***	9
Broering 2002, Germany	****	*	****	8	Saidi RF, 2011, USA†	***	*	***	7

†This symbol indicates studies which compare Split liver versus living-donor liver transplantation. In the horizontal line it is demonstrated selection maximum stars are 4, comparison 2 and outcome 3. In NOS, we assess each domain and according to findings in the papers we give the adequate number of stars. Less stars higher the possibility of bias.

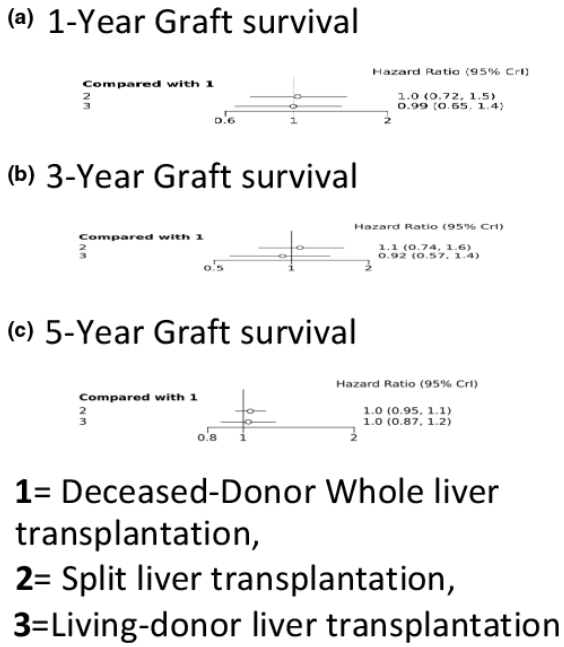

Figure 2 Graft survival. (a) 1-year graft survival. (b) 3-year graft survival. (c) 5-year graft survival. 1 = deceased-donor whole liver transplantation; 2 = split liver transplantation; and 3 = living-donor liver transplantation.

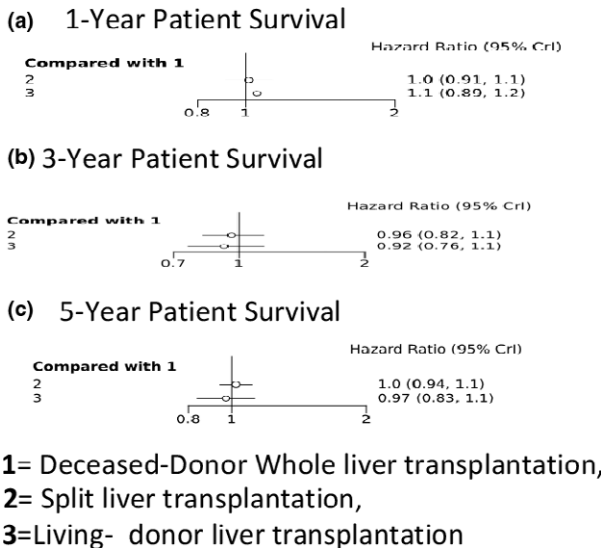

Figure 3 Patient survival. (a) 1-year patient survival. (b) 3-year patient survival. (c) 5-year patient survival. 1 = deceased-donor whole liver transplantation; 2 = split liver transplantation; and 3 = living-donor liver transplantation.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Graft survival of pairwise meta-analysis.

Figure S2. Patient survival of pairwise meta-analysis.

Figure S3. Evaluation of inconsistency using loop-specific heterogeneity.

Figure S4. Convergence diagnostics.

Figure S5. Consistency/inconsistency comparisons of graft survival.

Figure S6. Consistency/inconsistency comparisons of patient survival.

Figure S7. Network of evidence.

REFERENCES

1. Clavien PA, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. *N Engl J Med* 2007; **356**: 1545.
2. Washburn K, Halff G, Mieles L, Goldstein R, Goss JA. Split-liver transplantation: results of state-wide usage of the right trisegmental graft. *Am J Transplant* 2005; **5**: 1652.
3. Busuttil RM, Goss JA. Split liver transplantation. *Ann Surg* 1999; **229**: 313.
4. Broering DC, Topp S, Schaefer U, *et al.* Split liver transplantation and risk to the adult recipient: analysis using matched pairs. *J Am Coll Surg* 2002; **195**: 648.
5. Cardillo M, De Fazio N, Pedotti P, *et al.* Split and whole liver transplantation outcomes: a comparative study. *Liver Transpl* 2006; **12**: 402.
6. Spada M, Cescon M, Aluffi A, *et al.* use of extended right grafts from in situ split livers in adult liver transplantation: a comparison with whole-liver transplants. *Transplant Proc* 2005; **37**: 1164.
7. Maggi U, Caccano L, Melada T, *et al.* Long-term outcome of right split in situ grafts in adults. *Transpl Proc* 2005; **37**: 1170.
8. Corno V, Colledan M, Dezza MC, *et al.* Extended right split liver graft for primary transplantation in children and adults. *Transpl Int* 2006; **19**: 492.
9. Wilms C, Walter J, Kaptein M, *et al.* Long-term outcome of split liver transplantation using right extended grafts in adulthood: a matched pair analysis. *Ann Surg* 2006; **244**: 665.
10. Bonney GK, Aldouri A, Attia M, *et al.* Outcomes in right liver lobe transplantation: a matched paired analysis. *Transpl Int* 2006; **21**: 1045.
11. Sainz-Barriga M, Ricciardi S, Haentjens I, *et al.* Split liver transplantation with extended right grafts under patient-oriented allocation policy. Single centre watched-pair outcome analysis. *Clin Transplant* 2008; **22**: 447.
12. Hong JC, Yersiz H, Farmer DG, *et al.* Longterm outcomes for whole and segmental liver grafts in adult and

paediatric liver transplant recipients: a 10-year comparative analysis of 2.988 cases. *J Am Coll Surg* 2009; **208**: 682.
13. Sandroussi C, Crawford M, Lockwood DS, *et al.* Donor and recipient selection leads to good patient and graft outcomes for right lobe split transplantation versus whole liver transplantation in adult recipients. *Liver Transpl* 2009; **15**: 1586.
14. Takebe A, Schrem H, Ringe B, *et al.* Extended right liver grafts obtained by an ex-situ split can be used safely for primary and secondary transplantation with acceptable biliary morbidity. *Liver Transpl* 2009; **15**: 730.
15. Mallik M, Callaghan CJ, Hope M, *et al.* Comparison of liver transplantation outcomes from adult split liver and circulatory death donors. *Br J Surg* 2012; **99**: 839.
16. Mabrouk Mourad M, Liossis C, Kumar S, *et al.* Vasculobiliary complications following adult right lobe split liver transplantation from the perspective of reconstruction techniques. *Liver Transpl* 2015; **21**: 63.
17. Thuluvath PJ, Yoo HY. Graft and patient survival after adult live donor liver transplantation compared to a matched cohort who received a deceased donor transplantation. *Liver Transplant* 2004; **10**: 1263.
18. Maluf DG, Stravitz RT, Cotterell AH, *et al.* Adult living donor versus deceased donor liver transplantation: a 6-year single centre experience. *Am J Transplant* 2005; **5**: 149.
19. Sebagh M, Yilmaz F, Karam V, *et al.* Cadaveric full-size liver transplantation and the graft alternatives in adults: a comparative study from a single centre. *J Hepatol* 2006; **44**: 118.
20. Lo CM, Fan ST, Liu CL, Chan SC, Ng IO, Wong J. Living donor versus deceased donor liver transplantation for early irresectable hepatocellular carcinoma. *Br J Surg* 2007; **94**: 78.
21. Humar A, Beissel J, Crotteau S, Kandaswamy R, Lake J, Payne W. Whole liver versus split liver versus living donor in the adult recipient: an analysis of outcomes by graft type. *Transplantation* 2008; **85**: 1420.
22. Bhangui P, Vibert E, Majno P, *et al.* Intention-to-treat analysis of liver transplantation for hepatocellular carcinoma: living versus deceased donor transplantation. *Hepatology* 2001; **53**: 1570.
23. Sandhu L, Sandroussi C, Guba M, *et al.* Living donor liver transplantation versus deceased donor liver transplantation for hepatocellular carcinoma: comparable survival and recurrence. *Liver Transplant* 2012; **18**: 315.
24. Reichman TW, Katchman H, Tanaka T, *et al.* Living donor versus deceased donor liver transplantation: a surgeon-matched comparison of recipient morbidity and outcomes. *Transplant Int* 2013; **26**: 780.
25. Saidi RF, Jabbour N, Li YF, Shah SA, Bozorgzadeh A. Outcomes in partial liver transplantation: deceased donor split-liver vs live donor liver transplantation. *HPB (Oxford)* 2011; **13**: 797.
26. Fisher RA, Kulik LM, Freise CE, *et al.* Hepatocellular carcinoma recurrence and death following living and deceased donor liver transplantation. *Am J Transplant* 2007; **7**: 1601.
27. Terrault NA, Shiffman ML, Lok AS, *et al.* Outcomes in hepatitis C virus-infected recipients of living donor vs. deceased donor liver transplantation. *Liver Transplant* 2007; **13**: 122.
28. Hwang S, Lee SG, Joh JW, Suh KS, Kim DG. Liver transplantation for adult patients with hepatocellular carcinoma in Korea: comparison between cadaveric donor and living donor liver transplantations. *Liver Transplant* 2005; **11**: 1265.
29. Dias S, Welton NJ, Cadwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010; **29**: 932.
30. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004; **23**: 3105.
31. Wells GA, Shea B, O'Connell D, *et al.* The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_ epidemiology/oxford.asp
32. Van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NS. Automating network meta-analysis. *Res Synth Meth* 2012; **3**: 285.
33. Van Valkenhoef G, Bujkiewicz S, Efthimiou O, Reid D, Stroomberg C, de Keijser J. GeMTC Manual. https://gemtc.drugis.org
34. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998; **17**: 2815.
35. Ades AE, Sculper M, Sutton A, *et al.* Bayesian methods for evidence synthesis in cost-effectiveness analysis. *Pharmacoeconomics* 2006; **25**: 1.
36. Wandel J, Juni P, Tendal B, *et al.* Effects of glucosamine, chondrotin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ* 2010; **341**: c4675.
37. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity: subgroups, meta-regresion, bias, and bias adjustment. *Med Decis Making* 2013; **33**: 618.
38. Azoulay D, Castaing D, Adam R, *et al.* Split-transplantation for two adult recipients: feasibility and long-term outcomes. *Ann Surg* 2001; **233**: 565.
39. Cillo U, Burra P, Mazzafero V, *et al.* A multistep, consensus-based approach to organ allocation in liver transplantation: toward a "blended principle model". *Am J Transplant* 2015; **15**: 2552.
40. Toso C, Ris F, Mentha G, *et al.* Potential impact of in situ liver splitting on the number of available grafts. *Transplantation* 2002; **74**: 222.

APPENDIX 1

Search terms for literature search

Search free terms and MeSH terms

right[All Fields] AND lobe[All Fields] AND split[All Fields] AND ("liver transplantation"[MeSH Terms] OR ("liver"[All Fields] AND "transplantation"[All Fields]) OR "liver transplantation"[All Fields]) AND ("living donors"[MeSH Terms] OR ("living"[All Fields] AND "donors"[All Fields]) OR "living donors"[All Fields] OR ("living"[All Fields] AND "donor"[All Fields]) OR "living donor"[All Fields]) AND ("liver transplantation"[MeSH Terms] OR ("liver"[All Fields] AND "transplantation"[All Fields]) OR "liver transplantation"[All Fields]) AND deceased-donor[All Fields] AND ("liver transplantation"[MeSH Terms] OR ("liver"[All Fields] AND "transplantation"[All Fields]) OR "liver transplantation"[All Fields]) AND whole[All Fields] AND ("liver transplantation"[MeSH Terms] OR ("liver"[All Fields] AND "transplantation"[All Fields]) OR "liver transplantation"[All Fields]).

Transplant International 2018; 31: 1071–1082