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SYSTEMATIC REVIEWS AND META-ANALYSIS

Split versus living-related adult liver transplantation: a systematic review and meta-analysis

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Abstract

Background-objective The outcomes of split liver transplantation between recipients of deceased donor split liver transplant (SLT) or live donor liver transplants (LDLT) have never been compared in meta-analysis. It is important to understand graft and recipient survival between recipients of these grafts.

Methods Databases were searched for relevant articles over the previous 20 years (MEDLINE, Embase, Cochrane Library and Google Scholar). Meta-analyses were performed using both fixed- and random-effects models. Patient survival and graft survival were obtained using the inverse variance hazard ratio method.

Results There were differences in the characteristics of the donors and recipients. Donors of the SLT were younger compared to LDLT cohort [mean difference (MD) = − 11.12 years (− 15.41 to − 6.84), $p < 0.001$] whilst recipients of LDLT were younger [MD = − 2.06 years (− 1.12 to − 3.01), $p < 0.001$]. Significantly fewer men received grafts after SLT, 45%, compared to those receiving LDLT, 55%, [OR = 0.66 (0.55 to 0.80), $p < 0.001$]. There were no significant differences detected in postoperative complications, graft and patient 1-, 3- and 5-year survival between the SLT and LDLT cohorts.

Conclusions There is no apparent difference in overall survival, graft survival or complications between recipients of SLT or LDLT. However, characteristics of the donor and recipients differed suggesting the need for adequate risk-adjusted assessment of outcomes.

Keywords Deceased donor · Split liver transplant · Live donor liver transplant

Introduction

The needs of potential recipients for liver transplantation have always exceeded the size of the donor pool. Transplantation of reduced liver grafts evolved primarily to increase the donor pool for paediatric and adult recipients [1, 2]. Initially, grafts were reduced to suit the size of the recipient, but with evolution and careful selection, grafts were split to benefit two recipients. Cadaveric grafts were used for split liver transplantation (SLT), but living donor transplantation (LDLT) was the natural evolution of the technique. In July 1989, in Brisbane Australia, Russel Strong performed the first successful LDLT in a child with biliary atresia [3]. In countries, where deceased donor transplantation is prohibited or limited, LDLT has become the standard for liver transplantation. However, among 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 deceased donor liver transplantation. Developing LDLT programmes among those countries where SLT is practiced raises ethical issues due to the inherent risk to the living donors. 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 and LDLT is therefore desirable to inform the argument for or against these procedures. However, there is a clearly paucity of data with limited direct comparisons between recipients of SLT and LDLT.

The aim of this study is to compare outcomes and estimate the survival benefit between adult recipients of DD-SLT or LDLT using meta-analysis.

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Methods

The PRISMA statement was used in reporting systematic review and meta-analysis results.

Literature search

A systematic database search (Embase, MEDLINE [PubMed], Cochrane Library and Google Scholar) of literature was performed using both free texts and MeSH terms (split liver graft or transplant, split liver transplantation, live donor liver transplant or graft, living donor liver transplantation) over the past 20 years (1998–2018). A grey literature search in the clinicaltrials.gov website was also performed. References of the retrieved articles were checked manually for further studies.

Study selection and inclusion and exclusion criteria

Only studies that compared SLT and LDLT were included in the study. In cases, wherein two studies were conducted by the same authors, the most recent was selected. From studies comparing more than two graft types, SLT and LDLT were selected.

Data extraction and outcomes

Two reviewers (PG and KR) independently extracted the following data: name of authors, number of patients included in SLT and LDLT, age of donor and recipient, gender of donor and recipient, MELD score, split method, cold ischaemia time (CIT), overall biliary complications, hepatic artery thrombosis and 1-, 3- and 5-year patient and graft survival.

Patient survival and graft survival were the primary outcome measures of the two procedures.

Secondary outcomes were MELD score, cold ischaemia time, overall biliary complications and hepatic artery thrombosis.

Statistical analysis

The methodological quality of the studies was assessed with the validated Newcastle–Ottawa scale (NOS) [4]. Studies with an NOS score of ≥ 7 were considered to be high quality.

Statistical analysis was conducted using Review Manager 5.3 software (Cochrane Collaboration, Oxford, England) that was used for all statistical analyses. Heterogeneity was assessed via I^2 test, and values that are more than 30% indicated potentially important heterogeneity. In this case, both fixed- and random-effects models were produced. The results were compared, and the latter was used if there were discrepancies. In cases, wherein I^2 values are less than 30%, fixed effects models were used [4].

Dichotomous variables were analysed and assessed by calculating odds ratios (OR) with 95% confidence intervals (CI). An OR < 1 was observed in DD-SLT transplantation. The studies were then combined using the Mantel–Haenszel method during the first instance, and the Peto approach was used for rare outcomes [5]. Continuous variables were combined based on both the mean difference (MD) and the standardised mean difference (SMD). For studies that did not report the means and variances of the two groups, these values were estimated based on the median, range and size of the sample, using the technique described by Hozo et al. [6] if possible.

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 then estimated using the method described by Parmar et al. [7] if possible. For studies that reported the numbers at risk, these were combined with either the quoted survival rates or values read from the enlarged plots of the Kaplan–Meier curves to produce the estimates. When the numbers at risk were not quoted, constant censoring over the follow-up period was assumed during the estimate. The studies were weighted using an inverse variance approach, and HRs < 1 favoured SLT transplantation.

In all analyses, a p value < 0.05 was considered statistically significant.

Sensitivity analysis

The analyses of both the primary and secondary outcomes were performed using the random and fixed effect models to assess the effect of heterogeneity on the conclusions. Publication bias was not investigated because less than 10 studies were included in the present study [8].

Results

Search strategy and study characteristics

Four studies, which included 2457 patients, were selected from a pool of 2003 studies. Of these patients, 617 (25%) and 1840 (75%) underwent SLT and LDLT, respectively. Of the 12 full-text papers assessed, nine were excluded for the following reasons: six studies compared LDLT to whole transplantation and three compared split transplant to whole transplant (Fig. 1) [9–12]. Three out of four studies had an NOS score of ≥ 7 (Table 1) [10–12].

Recipient and donor demographics

Donors among the SLT cohort were significantly younger by 11 years compared to LDLT cohort [MD = − 11.12 (−

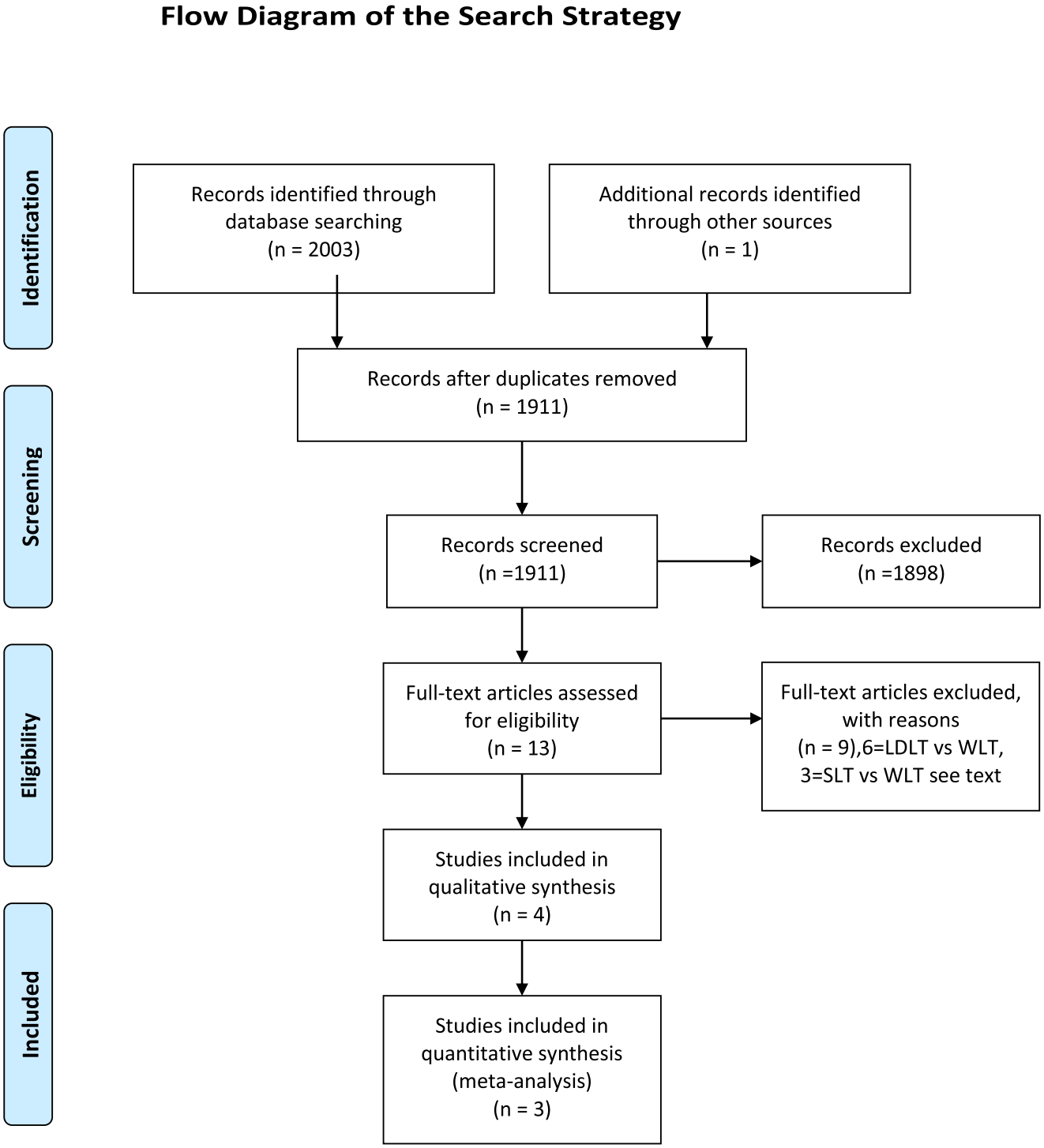

Fig. 1 Flow diagram of the search strategy

15.41 to −6.84), $p < 0.001$, $I^2 = 85\%$]. There was no significant difference in the gender of donors between the two cohorts. On the other hand, there was evidence that the LDLT recipients were younger by 2 years compared to SLT recipients [MD = 2.06 (1.12 to 3.01), $p < 0.001$, $I^2 = 0\%$] (Fig. 2). There was evidence of significant difference in the gender of recipients between the two cohorts; in the SLT cohort, the men were 45% and in LDLT 55% [OR = 0.66 to 0.80, $p < 0.001$, $I^2 = 0\%$] (Table 2). In the SLT cohort, 254 (40%) procedures were performed in situ, 110 (20%) were ex situ splitting whilst in 224 (40%) cases, the splitting method was not reported. Among the LDLT graft, the right lobe was used in 96% of procedures compared with 81% in SLT (Table 1). The most common aetiology of

Table 1 Comparison of donor and recipient variables and complications among the SLT and LDLT cohorts. Data is presented as mean ± standard deviation or *n* and %. Results are presented as the mean difference (MD) and 95% confidence intervals (CIs) or odds ratio (OR) and 95% (CIs)

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 (%)	Biliary complications, SLT-LDLT (%)	Hepatic artery thrombosis, SLT-LDLT (%)	NOS Max = 9
Saidi 2011, USA	557–1715	23 ± 9.4 37.3 ± 10 $p < 0.001$	384 (69) 1218 (71) $p < 0.001$	52.8 ± 10 50.7 ± 11 $p < 0.001$	250 (45) 943 (55) $p < 0.001$	20.9 ± 9.2 14.5 ± 5.6 $p < 0.001$	8.2 ± 3.7 3.1 ± 5.9 $p < 0.001$	223 (40) in situ 110 (20) ex situ 224 (40) NR	457 (82) 100 (18) $p < 0.001$	1646 (96) 69 (4) $p < 0.001$	NR	NR	7
Sebagh, 2006, France	20–38	36 ± 11 39 ± 13 $p = 0.003$	14 (68) 15 (39) p = ns	43 ± 16 43 ± 14 p = ns	12 (60) 29 (76) p = ns	NR	550 ± 180, 185 ± 132 $p < 0.001$	NR	17 (85) 3 (15) $p < 0.001$	38 (100)	8 (40) 10 (26) $p = 0.006$	2 (10) 4 (10) p = ns	9
Giacomoni, 2005, Italy	9–18	NR	NR	38, Median	NR	NR	NR	NR	NR	NR	3–4	1–1	4
Pooled differences 2357 patients	586 (25) 1771 (75)	MD = − 11.12 (15.4, 6.8)	OR = 3.56 (0.60, 2.10)	MD = 2.06 (1.12, 3.01)	OR = 0.66 (0.55, 0.80)	MD = 3.87 (− 1.4, 9.1)	MD = 6.09 (3.98, 8.20	254 (40) in situ 110 (20) ex situ 224 (40) NR	499 (81) 118 (19)	1753 (96) 69 (4)	OR = 1.71 (0.70, 4.18)	OR = 1.67 (0.46, 6.13)	HQ = 3

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

liver disease was hepatitis C accounting for about half of the patients in both cohorts (Table 3).

MELD score and cold ischaemia time

Using the random-effects model, there was no significant difference in MELD score between the cohorts [MD = 3.87 (− 1.41 to 9.15), $p = 0.15$, $I^2 = 92\%$]. On the contrary, fixed-effects model produced significant difference [MD = 5.99 (5.21 to 6.76), $p < 0.001$] (Fig. 3, Table 2).

The cold ischaemic time was significantly shorter by 6 h in LDLT cohort compared to SLT cohort [MD = 6.09 (3.98 to 8.20), $p < 0.001$, $I^2 = 99\%$] (Table 2).

Complications

There was no statistically significant difference in biliary complications and hepatic artery thrombosis rate between the two cohorts (Table 2).

Primary outcomes: 1-, 3- and 5-year graft and recipient survival

Nonsignificant differences were detected in 1-, 3- and 5-year graft and recipient survival between the SLT and LDLT cohorts (Figs. 4 and 5, Table 2).

Sensitivity analysis

Because the study by Humar may overlap with Saidi, subgroup analysis was performed and the results of both were compared to estimate the robustness of the conclusions. The results of the 3- and 5-year patient and graft survival remained the same in both main and subgroup analysis (Figs. 4 and 5).

In the MELD score analysis, the result of the outcome remains the same in main and subgroup analysis under fixed-effects model. However, under random-effects model, the result became nonsignificant because the model gives similar importance in small and large studies.

Discussion

This was a meta-analysis of studies comparing outcomes among adult recipients of SLT or LDLT. The main finding of the study was that there was equivalent graft and recipient survival at key time points and no difference in major complications. There was however discrepancy between the characteristics of the donors and recipients. Donors of SLT and recipients of LDLT were younger. There was also a gender difference among recipients where there were fewer male recipients of SLT but more of LDLT. Naturally, the CIT was longer among SLT. Given that there is no suitable method of risk

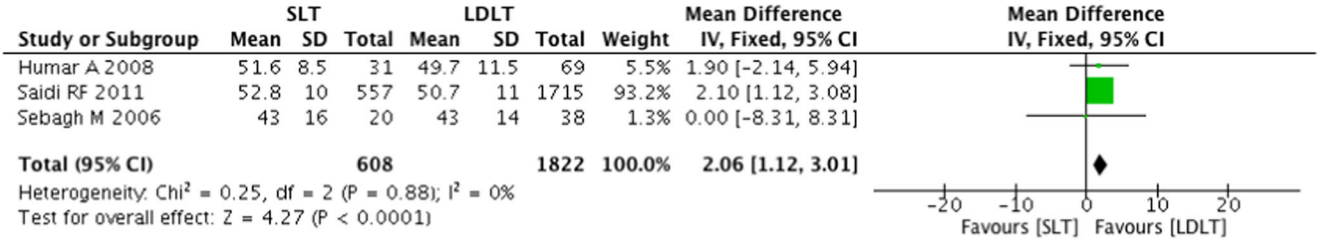

Fig. 2 Meta-analysis describing the age of the included patient cohorts. SLT split liver transplantation, LDLT live donor liver transplant

adjusting these cohorts, it is not possible to define whether one presented a higher risk profile than the other.

The waiting list mortality among patients waiting for liver transplantation is 10 to 20% [13]. It is reported that SLT involves only 1.3% of deceased donor liver transplantations [14]. Moreover, there are increased risks of biliary and arterial complications and reduced graft survival among recipients of split liver grafts when compared to those receiving whole graft transplantation [15]. Given the issues surrounding complications with recipients of split grafts, waiting list mortality and of risks to potential live liver donors, it is essential to understand the outcomes among recipients of living and deceased split liver grafts.

It is necessary to consider the differences between the cohorts. The difference in donor age reflects the bias to select younger deceased donors for SLT and presumably the demographic profile of living donors for adult recipients where these are likely to be partners, siblings or parents.

It is unclear whether there was a difference in severity of underlying liver disease. There was discrepancy when the MELD score was studied using fixed- and random-effects models. The fixed effect model, which weighs larger studies, was influenced by the study by Saidi [12] demonstrating significant lower MELD among LDLT recipients. However, due to variation among the study cohorts, the random-effects method was used for this study and produced a result that was nonsignificant. It therefore seems most likely that there was no meaningful difference in MELD scores between recipients though this represents a potential weakness of the study and demonstrates the need for a suitable method of risk adjustment.

The lack of difference in occurrence of biliary complications or hepatic artery thrombosis between recipients of SLT or LDLT should be interpreted cautiously because results from the meta-analysis were produced by a relatively small sample size [9–11]. Given the nature of arterial reconstruction at SLT and LDLT, it is perhaps unsurprising that there was no difference in occurrence of hepatic artery thrombosis; however, biliary reconstruction is more complex at LDLT where the first-order bile duct, sometimes with accessory ducts, are anastomosed, compared to SLT where the main duct is anastomosed.

Table 2 Outcome of interests describing the estimated effects of all variables, their *p* values and heterogeneity I^2

Outcome of interests	Number of studies and patients	Statistical method, estimated effect, 95% CIs	*p* value	I^2 (%)
Age of donor [9–12]	3, 2340	MD = − 11.12 years (− 15.41 to − 6.84) (RE)	< 0.001	85
Gender of donor [9–12]	3, 2340	OR = 3.56 (0.60 to 21.03) (RE)	0.16	90
Age of recipient [9–12]	3, 2340	MD = 2.06 years (1.12 to 3.01) (RE)	< 0.001	0
Gender of recipient [9–12]	3, 2340	OR = 0.66 (0.55 to 0.80) (RE)	< 0.001	0
MELD score [11, 12]	2, 2372	MD = 3.87 (− 1.41 to 9.15) (RE) MD = 5.99 (5.21, 6.76) (FE)	0.15 < 0.001	92
CIT [10–12]	3, 2340	MD = 6.09 h (3.98 to 8.20) (RE)	< 0.001	99
Biliary complications [9–11]	3, 185	OR = 1.71 (0.70 to 4.18) (RE)	0.24	0
Arterial thrombosis [9–11]	3, 185	OR = 1.67 (0.46 to 6.13) (RE)	0.44	0
1-year graft survival [10–12]	3, 2340	HR = 1.79 (0.52 to 6.17) (RE)	0.36	16
3-year graft survival [11, 12]	2, 2372	HR = 1.39 (0.64 to 2.98) (RE)	0.40	67
5-year graft survival [11, 12]	2, 2372	HR = 1.40 (0.59 to 3.35) (RE)	0.45	75
1-year patient survival [11, 12]	3, 2340	HR = 2.08 (0.51 to 8.58) (RE)	0.31	50
3-year patient survival [11, 12]	2, 2372	HR = 1.50 (0.67 to 3.36) (RE)	0.32	69
5-year patient survival [11, 12]	2, 2372	HR = 1.41 (0.61 to 3.30) (RE)	0.42	71

MD mean difference, *OR* odds ratio, *RE* random effects, *FE* fixed effects, *CIs* confidence intervals, *MELD* model for end-stage liver disease, *CIT* cold ischaemia time

Table 3 Most common diagnosis

Author country, year	Hepatitis C SLT-LDLT (%)	HCC SLT-LDLT (%)	Alcohol SLT-LDLT (%)	Cholestatic SLT-LDLT (%)	Cryptogenic SLT-LDLT (%)
Saidi, 2011, USA	48–47	15–16	14–15	19–18	12–13
Humar, 2008, USA	29–42	NR	NR	NR	NR
Sebagh, 2006, France	5–5	50–10	5–20	1–1	0–1
Giacomoni, 2005, Italy	NR	NR	NR	NR	NR

Numbers represent percentages of patients included in each diagnosis

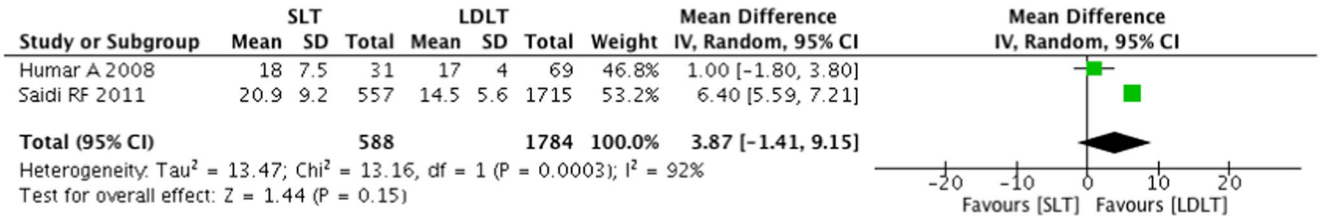

Fig. 3 Meta-analysis describing the MELD score

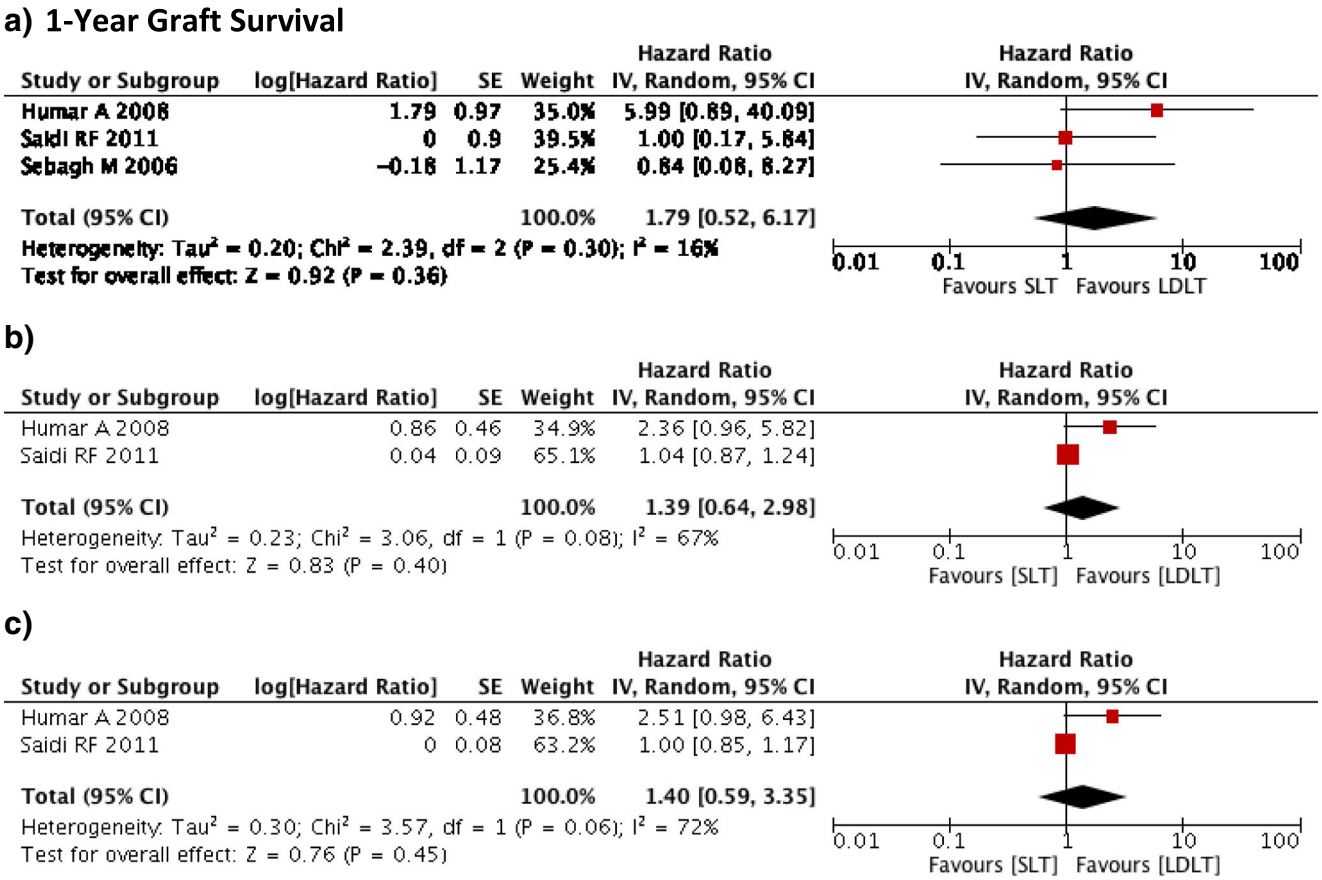

Fig. 4 Meta-analysis describing the graft survival at 1-, 3- and 5-year points of the included patient cohorts. SLT split liver transplantation, LDLT live donor liver transplant

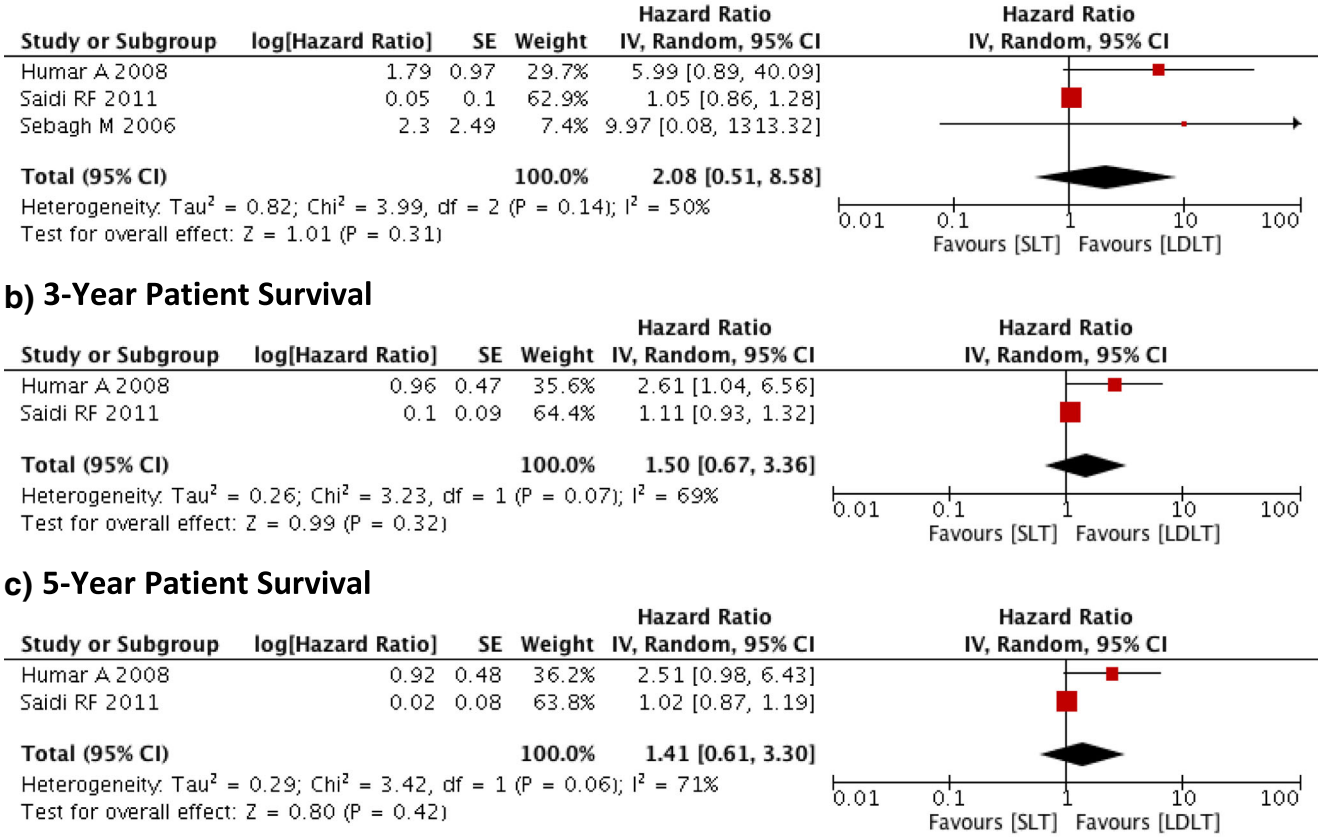

Fig. 5 Meta-analysis describing the recipient survival at 1-, 3- and 5-year of the included patient cohorts. SLT split liver transplantation, LDLT live donor liver transplant

Many factors have been related to recipient survival after SLT; these include recipient health status at transplantation, elevated donor GGT level, graft steatosis, graft-to-recipient body weight ratio, intensive care unit stay and total hospital stay [16].

Given the profile of risk of transplanting split grafts, researchers have attempted to define splitting criteria of the donor for one adult and one paediatric recipient. These include age between 14 and 50, weight more than 45 kg, BMI ≤ 26, intensive care unit stay ≤ 3 days, mean arterial pressure ≥ 60 mmHg, Na ≤ 160 mmol/L, SGPT ≤ 60 and GGT ≤ 50; 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 model, if donor age were increased to 60 years, then the additional increase would be 6% and 2.4% for paediatric and adult donors, respectively [17].

Limitations

The results of this meta-analysis should be interpreted cautiously due to the small number of retrospective analyses from single centres and heterogeneous splitting technique used in SLT. Therefore, underpowered studies and heterogeneous samples may have influenced the results. Furthermore, results may be influenced by national and institutional characteristics and practice. Risk adjustment of donor and recipient factors is needed to accurately determine benefit, harm or equivalence of one technique over the other. Various factors related to reduced graft and recipient survival of split grafts have been reported [17]. Modelling based upon this data has been used to estimate changes to the size of the donor pool based upon changes to criteria for SLT. An international registry of SLT and LDLT could serve a similar purpose to define donor and recipient cohorts in detail and permit an in-depth assessment of outcomes. Until that time, this meta-analysis presents the most thorough assessment of outcomes.

Based on Grading of Recommendations Assessment, Development, and Evaluation (GRADE) considerations, such as risk of bias, imprecision, inconsistency and indirectness [5], the quality of findings of the present study ranks from moderate to low across the outcomes. The main limiting factor, which was the reason for a decrease in quality, was the heterogeneity across the small number of included studies. With only three studies included in the analyses, it is important to

acknowledge the large impact of the average effect if one study differs in size or direction.

Recently, Goossen et al. [18], based on the assumption of recall (%), precision (%), unique contribution (%) and the number needed to read (%), estimated the performance of literature databases when conducting surgical systematic reviews. For nonrandomised studies, a combination of Medline/Web of Science databases demonstrated the best performance (recall: 99.5%, number needed to read: 60) [18]. In the future, the above methodological tool will make the systematic search of surgical literature more efficient by using an adequate combination of databases and consequently reducing the number of papers needed to be read.

Conclusions

In conclusion, LDLT results in equivalent graft and recipient survival compared to recipients of SLT. In itself, this observation supports the continued use of LDLT among populations where deceased donation is possible when donor mortality continues to be prevalent.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study does not contain any studies with human participants or animals performed by any of the authors.

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